Physician's Guide to the Treatment and Follow-Up of Metabolic Diseases

Nenad Blau
Georg F. Hoffmann
James Leonard
Joe T. R. Clarke *Editors*

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Nenad Blau · Georg F. Hoffmann
James Leonard · Joe T. R. Clarke
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Physician's Guide to the Treatment and Follow-Up of Metabolic Diseases

Foreword by C. R. Scriver

With 12 Figures and 267 Tables

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Nenad Blau
Division of Clinical Chemistry
and Biochemistry
University Children's Hospital
Steinwiesstrasse 75
8032 Zurich
Switzerland
e-mail: nenad.blau@kispi.unizh.ch

Georg F. Hoffmann
Universitätsklinik für Kinder-
und Jugendmedizin
Im Neuenheimer Feld 150
D-69120 Heidelberg
Germany
e-mail:
Georg_Hoffmann
@med.uni-heidelberg.de

James Leonard
Biochemistry, Endocrinology
and Metabolism Unit
Institute of Child Health
30, Guilford Street
London, WC1N 1EH
UK
e-mail: j.leonard@ich.ucl.ac.uk

Joe T. R. Clarke
Division of Clinical
& Metabolic Genetics
Hospital for Sick Children
555 University Avenue
Toronto, Ontario, M5G 1X8
Canada
e-mail: jtrc@sickkids.ca

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Foreword

The greatest difficulty in life is to make knowledge effective, to convert it into practical wisdom. Sir William Osler.

The inborn errors of metabolism, as a group of metabolic diseases, are relatively rare and are sometimes called "orphan diseases." As a group, they account for about 1 in 2,500 births (Applegarth et al. 2000) and, as a cumulative group reaching 20 years of age, their prevalence is about 40 cases per 100,000 population. In terms of patient days of continuous supervision and care, hundreds of thousands of such days are involved per generation of these patients. Although experience with these diseases as a class may be small and people expert in their management may be relatively few, in the years to come many caregivers will become involved. This book offers help to them.

Until the mid-twentieth century, hereditary metabolic and other genetic diseases were considered to be purely "genetic" problems. Destiny would take its course, treatment did not exist, and genetic counseling about recurrence risks was virtually all that could be offered. Phenylketonuria (PKU) was then shown to be a treatable genetic disease in which early diagnosis and effective treatment prevented the disease (mental retardation) in PKU. Other genetic diseases for which an environmental experience was an essential component of cause (e. g., exposure to a dietary component or a drug) were then seen to yield to treatment. Combinations of early diagnosis and access to treatment began to change our outlook. Accordingly, diagnosis is the natural focus of our companion book (*The Physician's Guide to the Laboratory Diagnosis of Metabolic Disease*); the present volume focuses on treatment and follow-up.

Over the past two decades, systematic analyses of treatment outcomes for genetic disease have been attempted (Hayes et al. 1985; Treacy et al. 1995, 2001). There has been slow but significant progress overall, reflecting improvements in treatment protocols, in the therapeutic agents (drugs and foods, for example), in tissue transplantation, and in enzyme replacement by other means.

Now there is another problem. Patients with treatable hereditary metabolic disease grow up and become adult-age subjects. For them, treatment continues but under new auspices. The net result is an ever-growing community of persons in need of continuing care (Lee 2002, 2003). This book also addresses that challenge.

The Physician's Guide to the Treatment and Follow-up of Metabolic Disease is not an in-depth reference resource such as may be found elsewhere. This new book is concise, its information is succinct, and it describes procedures of assistance to patients in need of continuous care and support. Approximately 300 different disorders are identified for which a documented therapeutic modality is available. How to monitor the therapeutic effect is described.

One of the legacies of the Human Genome Project is ignorance; we know so little about our genome and how it works. On the other hand, the project is a significant beginning of new knowledge from which new forms of treatment, to neutralize the effect of mutant disease-causing alleles, will emerge. Accordingly one can anticipate a long life for *The Physician's Guide to the Treatment and Follow-up of Metabolic Disease* as it evolves and incorporates new information, knowledge, and wisdom.

Charles R. Scriver, MDCM FRS
Alva Professor Emeritus of Human Genetics. McGill University

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Preface

You may ask whether there is a need for another book about metabolic disorders. Although there are a number of good books dealing with both the diagnosis and treatment of inborn errors of metabolism, many of them are rather complex and detailed. *This* book starts where the previous one, *Physician's Guide to the Laboratory Diagnosis of Metabolic Diseases*, leaves off: what to do after the laboratory reports arrive, and how to proceed once the final diagnosis is made. In contrast to diagnostic procedures, which are today fairly straightforward, treatment and follow-up of inherited metabolic disorders are more complex. Appropriate treatment depends not only on the exact diagnosis, but the management may differ from one country to another to meet local circumstances.

This book is divided into two parts: the first part deals with initial management (emergency treatment of hypoglycemia, hyperammonemia, ketoacidosis, lactic acidemia, liver failure, acute encephalopathy, effect of anesthesia) while awaiting final diagnosis; the second part describes the treatment of groups of disorders. Each chapters starts with a list of disorders, which are numbered the same way as in the first book, *Physician's Guide to the Laboratory Diagnosis of Metabolic Diseases*, followed by simple protocols for the treatment and follow-up.

Although this book reflects as much as possible current knowledge of the treatment of inherited metabolic disorders, written by experts in this field, medicine is constantly advancing. The application of this information in daily practice remains the responsibility of the attending physician. The details have been checked, but the authors, editors, and publisher can take no responsibility for any consequences arising from the application of the information in the management of any patients. Drug doses, particularly those used rarely, should always be checked meticulously.

Nenad Blau
Georg F. Hoffmann
James Leonard
Joe T. R. Clarke

List of Contributors

Generoso Andria
Dipartimento di Pediatria
Università Federico II
Via S. Pansini 5
80131 Napoli
Italy
e-mail: andria@unina.it

Bruce A. Barshop
UCSD Biochemical Genetics
Department of Pediatrics
La Jolla, CA 92093
USA
e-mail: bbarshop@UCSD.Edu

Roberta Battini
Division of Child Neurology and Psychiatry
University of Pisa
Stella Maris Scientific Institute
Via dei Giacinti 1
56018 Calambrone, Pisa
Italy
e-mail: roberta.battini@inpe.unipi.it

Anna Biason-Lauber
Dept. of Pediatrics
Division of Clinical Chemistry and Biochemistry
and Endocrinology/Diabetology
University of Zurich
Steinwiesstrasse 75
8032 Zurich
Switzerland
e-mail: anna.lauber@kispi.unizh.ch

Jörgen Bierau
Academic Hospital Maastricht
Department of Clinical Genetics
Laboratory for Genetic Metabolic Diseases
3-X Building
PO Box 2500
6202 AZ Maastricht
The Netherlands
e-mail: Jorgen.Bierau@GEN.unimaas.nl

Nenad Blau
Division of Clinical Chemistry and Biochemistry
University Children's Hospital
Steinwiesstrasse 75
8032 Zurich
Switzerland
e-mail: nenad.blau@kispi.unizh.ch

Carolien Boelen
University Medical Center Sint Radboud
CAKN
Huispostnummer 435
Geert Grooteplein 10
PO Box 9101
6500 HB Nijmegen
The Netherlands
e-mail: c.boelen@cukz.umcn.nl

Peter Burgard
Universitätsklinik für Kinder-
und Jugendmedizin
Im Neuenheimer Feld 150
D-69120 Heidelberg
Germany
e-mail: peter.burgard@t-online.de

Alberto Burlina
Universita degli Studi di Padova
Department of Pediatrics
Via Giustiniani 3
35123 Padova
Italy
e-mail: burlina@child.pedi.unipd.it

Peter T. Clayton
Institute of Child Health
Division of Biochemistry & Genetics
30 Guilford Street
London WC1N 1EH
UK
e-mail: pclayton@ich.ucl.ac.uk

Joe T.R. Clarke
Division of Clinical & Metabolic Genetics
Hospital for Sick Children
555 University Avenue
Toronto, Ontario, M5G 1X8
Canada
e-mail: jtrc@sickkids.ca

Ton De Grauw
Division of Neurology
CHMC
3333 Burnet Ave.
Cincinnati, OH 45229
USA
e-mail: t.degrauw@chmcc.org

Tom J. de Koning
Department of Paediatric Metabolic Diseases
University Medical Center Utrecht
PO Box 85090
3508 AB Utrecht
The Netherlands
e-mail: T.deKoning@wkz.azu.nl

Katrina Dipple
Department of Pediatrics
David Geffen School of Medicine at UCLA
10833 LeConte Ave.
Los Angeles, CA 90095
USA
e-mail: kdipple@ucla.edu

Mike Gibson
Department of Molecular and Medical Genetics
Oregon Health & Science University
2525 SW 3rd Avenue
Mail Code MP-350
Portland, OR 97201
USA
e-mail: gibsonm@ohsu.edu

Erik Harms
Universitäts-Kinderklinik
Albert Schweizer-Strasse 33
48129 Münster
Germany
e-mail: harms@uni-muenster.de

Dorothea Haas
Universitätsklinik für Kinder-
und Jugendmedizin
Department of Metabolic Diseases
Im Neuenheimer Feld 150
D-69120 Heidelberg
Germany
e-mail: Dorothea.Haas@med.uni-heidelberg.de

Georg F. Hoffmann
Universitätsklinik für Kinder-
und Jugendmedizin
Im Neuenheimer Feld 150
D-69120 Heidelberg
Germany
e-mail: Georg_Hoffmann@med.uni-heidelberg.de

Elisabeth Holme
Department of Clinical Chemistry
Sahlgrenska University Hospital
41345 Gothenburg
Sweden
e-mail: Elisabeth.Holme@clinchem.gu.se

Bernd Hoppe
Division of Pediatric Neprology
University Children's Hospital
Josef-Stelzmann-Strasse 9
50924 Cologne
Germany
e-mail: bernd.hoppe@medizin.uni-koeln.de

Khalid Hussain
Institute of Child Health
Great Ormond Street
Children's Hospital
London WC1N 1EH
UK
e-mail: K.Hussain@ich.ucl.ac.uk

Jaak Jaeken
University Hospital Gasthuisberg
Department of Pediatrics
Division of Metabolic Diseases
3000 Leuven
Belgium
e-mail: jaak.jaeken@uz.kuleuven.ac.be

Richard I. Kelley
Kennedy Krieger Institute
707 N Broadway
Baltimore, MD 21205
USA
e-mail: rkelley3@jhmi.edu

Jörg Klepper
Department of Pediatric Neurology
University of Essen
Hufelandstr. 55
45122 Essen
Germany
e-mail: joerg.klepper@uni-essen.de

Agne Larsson
Department of Pediatrics
Karolinska Institute
Huddinge University
Hospital
14186 Stockholm
Sweden
e-mail: agne.larsson@klinvet.ki.se

James Leonard
Biochemistry, Endocrinology and Metabolism Unit
Institute of Child Health
30, Guilford Street
London, WC1N 1EH
UK
e-mail: j.leonard@ich.ucl.ac.uk

Ernst Leumann
Segetenweg 3
8053 Zurich
e-mail: e.leumann@swissonline.ch

Hanna Mandel
Metabolic Unit
Department of Pediatrics
Rambam Medical Centre
Haifa
Israel
e-mail: h_mandel@rambam.health.gov.il

Ertan Mayatepek
Klinik für Allgemeine Pädiatrie
Zentrum für Kinder- und Jugendmedizin
Moorenstr. 5
40225 Düsseldorf
Germany
e-mail: mayatepek@uni-duesseldorf.de

Edward R.B. McCabe
Department of Pediatrics
David Geffen School of Medicine at UCLA
10833 LeConte Ave.
Los Angeles, CA 90095
USA
e-mail: emccabe@mednet.ucla.edu

Brian McCrindle
Department of Pediatrics
The Hospital of Sick Children
Toronto, Ontario
Canada
e-mail: brianmccrindle@sickkids.ca

Elisabeth Minder
Stadtspital Triemli
Chemie Zentrallabor
8000 Zurich
Switzerland
e-mail: eminder@swissonline.ch

William L. Nyhan
Department of Pediatrics
Division of Biochemical genetics
UCSD
9500 Gilman Drive
La Jolla, CA 92093
USA
e-mail: wnyhan@pedsmail.ucsd.edu

Hélène Ogier de Baulny
Hôpital Robert Debré
Service de Neurologie Pediatrique, et des Maladies Metaboliques
48, boulevard Sérurier
75019 Paris
France
e-mail: helene.ogier@rdb.ap-hop-paris.fr

Giancarlo Parenti
Dipartimento di Pediatria
Università Federico II
Via S. Pansini 5
80131 Napoli
Italy
e-mail: parenti@unina.it

Jan Peter Rake
Department of Metabolic Diseases
Beatrix Children's Hospital
University
Medical Centre Groningen
9700 RB Groningen
The Netherlands
e-mail: j.p.rake@bkk.azg.ne

Ellinor Ristoff
Department of Pediatrics
Karolinska Institute
Huddinge University
Hospital
14186 Stockholm
Sweden
e-mail: ellinor.ristoff@klinvet.ki.se

Eve A. Roberts
Division of Gastroenterology and Nutrition
Hospital for Sick Children
555 University Avenue
Toronto, Ontario M5G 1X8
Canada
e-mail: eve.roberts@sickkids.ca

René Santer
Universitäts-Kinderklinik
Martinistr. 52
20246 Hamburg
Germany
e-mail: r.santer@uke.uni-hamburg.de

Charles R. Scriver
McGill University Health Center
Montreal Children's Hospital
DeBelle Laboratory, A717
2300 Tupper Street
Montreal, Quebec, H3H 1P3
Canada
e-mail: charles.scriver@mcgill.ca

Andreas Schulze
Universitätsklinik für Kinder- und Jugendmedizin
Department of Pediatrics I
Division of Metabolic and Endocrine Diseases
Im Neuenheimer Feld 150
D-69120 Heidelberg
Germany
e-mail: andreas_schulze@med.uni-heidelberg.de

Susanne Schweitzer-Krantz
Evangelisches Krankenhaus Düsseldorf
Postfach 102254
40013 Düsseldorf
Germany
e-mail: Schweitzer-Krantz@t-online.de

Jan Smeitink
Nijmegen Center for Mitochondrial Disorders
Department of Pediatrics
University Medical Center Nijmegen
Geert Grooteplein 10
PO Box 9101
6500 HB Nijmegen
The Netherlands
e-mail: J.Smeitink@cukz.umcn.nl

G. Peter A. Smit
Department of Metabolic Diseases
Beatrix Children's Hospital
PO Box 30.001
9700 RB Groningen
The Netherlands
e-mail: g.p.a.smit@bkk.azg.nl

Sylvia Stöckler-Ipsiroglu
Universitäts-Kinderklinik
Department of Pediatrics and National Newborn Screening Laboratory
Währinger Gürtel 18–20
1090 Wien
Austria
e-mail: stoeckler@metabolic-screening.at

Andrea Superti-Furga
Centre for Pediatrics and Adolescent Medicine
Freiburg University Hospital
Mathildenstr. 1
79106 Freiburg
Germany
e-mail: asuperti@uniklini-freiburg.de

Robert Surtees
Institute of Child Health
Neurosciences Unit
The Wolfson Centre
Meckleburgh Square
London, WC1N 2AP
UK
e-mail: r.surtees@ich.ucl.ac.uk

Serena Tonstad
Preventive Cardiology
Ullevål University Hospital
0407 Oslo
Norway
e-mail: serena.tonstad@ulleval.no

Albert H. van Gennip
Academic Hospital Maastricht
Clinical Genetics Center
Tripple-X-building
PO Box 1475
6201BL Maastricht
The Netherlands
e-mail: albert.vangennip@gen.unimaas.nl

Gepke Visser
Department Metabolic Diseases
Wilhelmina Children's Hospital
University Medical Centre Utrecht
Utrecht
The Netherlands

John Walter
Willink Biochemical Genetics Unit
Royal Manchester Children's Hospital
Manchester M27 4HA
UK
e-mail: john.walter@cmmc.nhs.uk

Rebecca S. Wappner
Riley Hospital
Room 0907
702 Barnhill Drive
Indianapolis, IN 46202–5225
USA
e-mail: BeckyWappner@aol.com

Udo Wendel
Department of Pediatrics
University of Düsseldorf
Moorenstr. 5
40225 Düsseldorf
Germany
e-mail: wendelu@uni-duesseldorf.de

Bridget Wilcken
Children's Hospital at Westmead
Locked Bag 4001
Sydney, Westmead, NSW 2145
Australia
e-mail: bridgetw@chw.edu.au

J. Edward Wraith
Royal Manchester Children's Hospital
Pendlebury
Manchester, M27 4HA
UK
e-mail: Ed.wraith@cmmc.nhs.uk

Contents

Part One
Initial Approaches

A Emergency Management of Metabolic Diseases

Georg F. Hoffmann, Joe T.R. Clarke, James V. Leonard

A.1 Emergency Management (While Awaiting Diagnosis)

Metabolic diseases often present with life-threatening decompensation requiring prompt and deliberate action. This often occurs in the neonatal period or in infancy, but sometimes not until adulthood. There is only a limited repertoire of pathophysiological sequences and consequently only a small number of clinical presentations in response to metabolic illness (Nyhan and Ozand 1998; Fernandes et al. 2000; Scriver et al. 2001; Hoffmann et al. 2002; Prietsch et al. 2002). Therefore only a limited number of therapeutic measures are needed immediately (Dixon and Leonard 1992; Hoffmann et al. 2002; Prietsch et al. 2002).

First of all, adequate samples for basic as well as special metabolic investigations (Table A.1) must be obtained to cover all differential diagnoses. This is the basis for rational therapy. Basic laboratory investigations must be available in all hospitals offering emergency treatment for children 24 h/day, 7 days/week, and results should be available at latest within 30 min. Guidelines for interpretation are described in metabolic reference textbooks (Fernandes et al. 2000; Hoffmann et al. 2002; Zschocke and Hoffmann 2004). The results of the special metabolic investigations relevant to the diagnosis of potentially treatable metabolic disorders should be available within 24 h, the latest within 48 h. Further investigations may have to be performed depending on the clinical picture

Table A.1. Laboratory evaluation of a suspected acutely presenting metabolic disease

Basic metabolic investigation[a]	Special metabolic investigation
Bood gases and plasma electrolytes	Acylcarnitines (dried blood spots)
Plasma glucose	Plasma amino acids
Plasma lactate	Urinary organic acids
Plasma ammonium	
Urinary ketones (Ketostix)	Plasma (5 ml) and urine (5–20 ml) stored frozen, and dried blood spots stored with dessicant at 4 °C, for further investigations, e. g., in the event of death

[a] In addition to complete blood count, liver function tests (bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and International Normalized Ratio, INR, of prothrombin time), CK, creatinine, plasma urea, and urate

and the results of the basic investigations; these may include serum or plasma levels of insulin, carnitine in plasma and/or urine, plasma total homocysteine, urine orotic acid, and urine-reducing substances.

Dangers/Pitfalls

- In a healthy, full-term neonate, acute sepsis, often the initial diagnosis, is also uncommon; and inherited metabolic disease should always be investigated in parallel from the beginning with basic as well as special metabolic investigations.
- Ammonia must be assayed, whenever a septic screen is considered.

Indispensable for early diagnosis are ammonia, pH, electrolytes, glucose, and ketonuria (Hoffmann et al. 2002; Prietsch et al. 2002). Any child admitted to an intensive care unit with a life threatening, nonsurgical illness should be tested for these. Especially important is the early recognition of metabolic diseases resulting in elevated ammonia and no acidosis, most of which are urea cycle defects. Similarly, those in whom the ammonia is elevated or normal but in whom there is metabolic acidosis and massive ketosis usually have organic aciduria. The occurrence of acidosis and ketonuria in the neonatal period is an almost certain indicator of metabolic disease, as ketonuria is otherwise rare even in sick newborns. Hypoglycemia along with an elevation of CK is seen in disorders of fatty acid oxidation. These disorders are likely if, in older children, ketones are absent from the urine. The definitive diagnoses of these disorders is made by measuring acylcarnitines in blood spots, amino acids in blood, organic acids, and orotic acid in urine.

Lactic acidemia is an important indicator of metabolic diseases and the hallmark of mitochondriopathies as well as of disorders of defects in gluconeogenesis. Many laboratory abnormalities such as metabolic acidosis, lactic acidemia, hyperammonemia, and signs of liver failure may be secondary consequences of hemodynamic shock.

With the help of the history, clinical findings, and the initial laboratory values, four presentations should be delineated which require different, although overlapping, approaches (Table A.2).

Table A.2. Principles of emergency management of acute metabolic decompensation

Disorder	Initial management
Hypoglycemia[a]	Administer glucose at up to 10 mg/kg per min, monitoring plasma glucose frequently. If requirements exceed 12 mg/kg per min, suspect hyperinsulinism and administer glucagon as constant intravenous infusion at 1 mg/24 h
Ketoacidosis[b]	Administer glucose at up to 10 mg/kg per min If the plasma bicarbonate is < 10 mmol/l, treat acidosis by administration of sodium bicarbonate: administer an amount sufficient to half correct the calculated base deficit. This may be repeated whilst taking care not to overcorrect, causing metabolic alkalosis
Lactic acidosis	In the case of secondary lactic acidosis, caused by hypoxemia, major organ failure, or intoxication, by treating the underlying disorder In the case of primary lactic acidosis, caused by pyruvate carboxylase deficiency, pyruvate dehydrogenase deficiency, or mitochondrial respiratory chain defects, treat acidosis by administration of sodium bicarbonate, giving an amount sufficient to maintain the plasma bicarbonate > 10 mmol/l. The hypernatremia caused by the need to administer large amounts of sodium bicarbonate is treated by: (a) concomitant administration of furosemide, up to 2 mg/kg per dose, along with sufficient potassium to prevent life-threatening hypokalemia[c]; (b) hemodialysis, continuous venous-venous hemofiltration, or peritoneal dialysis; (c) use of THAM as buffer[d] Consider administration of sodium dichloroacetate, 50 mg/kg, intravenously initially
Hyperammonemia[e]	Stop all protein intake Administer intravenous fluids at 1.5 times the calculated maintenance to accelerate ammonium excretion by water diuresis Administer glucose, 10 mg/kg per min, to minimize endogenous protein breakdown and reliance on amino acid oxidation for energy Administer nitrogen wasting drugs: (a) sodium benzoate, 250 mg/kg initially, then 250 mg/kg per 24 h; (b) sodium phenylacetate or phenylbutyrate, 250 mg/kg initially, then 250 mg/kg per 24 h Consider hemodialysis or continuous venous-venous hemofiltration/dialysis[f]
Intractable seizures	Administer pyridoxine, 100 mg, intravenously to start, then 30 mg/kg per 24 h given orally[g] Administer folinic acid, 5 mg/kg, intravenously to start, then 5 mg/kg per 24 h, orally or intravenously, divided into 3 equal doses Administer pyridoxal phosphate, 30 mg/kg per 24 h, orally divided into 3 equal doses
Acute metabolic encephalopathy	Removal of endogenous toxins, such as accumulate in maple syrup urine disease, organic acidurias, urea cycle enzyme defects, etc.[h] Ventilatory support, avoidance of overhydration, administration of mannitol for treatment of cerebral edema, ionotropic drugs, etc.
Acute liver failure	Removal of endogenous toxins, such as accumulate in hereditary tyrosinemia type I[h] Ventilatory support, replacement of essential products of liver metabolism (e. g., fresh frozen plasma, albumin, etc.), ionotropic drugs, diuretics, etc.

[a] Caused either by impaired glucose production, i. e., glycogen storage diseases or disorders of gluconeogenesis (generally associated with ketosis) or increased glucose utilization, i. e., either hyperinsulinism or fatty acid oxidation defects (see Chaps. 15 and 35)

[b] Ketosis is generally an indication of impaired production or utilization of glucose

[c] This must be done with a central venous line in place and constant monitoring by electrocardiogram and serial plasma electrolyte measurements

[d] The use of THAM for the correction of metabolic acidosis is controversial

[e] See Chap. 11

[f] Peritoneal dialysis is slow and relatively ineffective compared with hemodialysis, but it may be the only approach that is technically feasible in very small newborn infants

[g] There is no universal protocol for a pyridoxine challenge. The dose of pyridoxine required is variable and higher doses may be necessary to control seizures, at least initially (see text)

[h] This includes measures to decrease production and to accelerate removal of endogenous toxins, which are covered in chapters dealing with specific diseases

It is probable that many metabolic patients who present in the first days of life with catastrophic illness die undiagnosed. Characteristically, there is an asymptomatic interval in which toxic metabolites accumulate. In protein-dependent metabolic disorders (aminoacidopathies, organic acidurias, urea cycle disorders) and long-chain fatty acid oxidation defects, there is exogenous as well as endogenous intoxication. Exogenous intoxication results from the intake of specific substrates, and endogenous intoxication results from breakdown of muscle protein or body fat during episodes of catabolism such as prolonged fasting or intercurrent infections. If defects of the pyruvate dehydrogenase complex (PDHC), the Krebs cycle, and the respiratory electron transport chain present with catastrophic illness at birth or during infections or minor illnesses, there is mostly not a symptom-free interval. However, these disorders present more commonly as chronic progressive disease or with episodic deterioration.

By proposing the classification of clinical conditions and institution of rational therapy in a suspected metabolic emergency in Table A.2, we are well aware that different metabolic centers may treat differently and that evidence base is lacking in several therapeutic strategies. Doses of drugs that are essential in the acute emergency treatment and therefore should be available in every intensive care unit are listed in Table A.3.

Table A.3. Metabolic emergency drugs

Drug	Indication	Dose	i.v.	p.o.	Application[a]
L-Carnitine	Organic acidurias; carnitine transporter defect; MCAD deficiency; mitochondrial disorders	Bolus (only with org. acid.): 100 mg/kg, then CI: 50–100–200 mg/kg per day	x		Bolus; CI
L-Arginine HCl	Hyperammonemia	SI: 2 mmol (350 mg)/kg over 90 min; after that, CI: 2–4 mmol (350–700 mg)/kg per day	x		SI; CI
Na-Benzoate	Hyperammonemia	SI: 250 mg/kg over 90 min, then CI: 250 mg/kg per day	x	x	SI; CI
Na-Phenylbutyrate	Hyperammonemia	250 mg/kg per day	x	x	3 SD
Na-Phenylacetate	Hyperammonemia	250 mg/kg per day	x		3 SD
Na-Dichloracetate	Lactic acidosis	50 mg/kg per dose	x	x	Bolus; CI
Carbamylglutamate	Hyperammonemia	100 mg/kg per day		x	3 SD
Hydroxocobalamin (B_{12})	Methylmalonic acidurias; disorders of cobalamin metabolism; transcobalamin II deficiency; disorders of homocysteine metabolism	1 (−5) mg/day i.m. or i.v.	x		1 SD

Table A.3. (continued)

Drug	Indication	Dose	i.v.	p.o.	Application[a]
Biotin (H)	Biotinidase deficiency Holocarboxylase synthetase deficiency Lactic acidosis	10–15 mg/d		x	3 SD
Riboflavin (B_2)	Glutaric aciduria type II	150 mg/d	x		3 SD
Thiamine (B_1)	Lactic acidosis	150 mg/d, > 3 year 300 mg/d	x		3 SD
Pyridoxine (B_6)	B_6-responsive seizures	100 mg	x	x	Bolus
	Disorders of homocysteine metabolism	100–500 mg/d			3 SD
Pyridoxal-phosphate	Pyridoxal phosphate-responsive seizures	30 mg/kg per day for 3 days		x	3 SD
Folinic acid 10 ml	Folinic acid-responsive seizures	3–5 mg/kg per day for 3 days	x		3 SD
Folic acid 2 × 10 ml	Disorders of homocysteine metabolism	15 mg/kg per day	x		3 SD
Betaine	Disorders of homocysteine metabolism	250 mg/kg per day		x	3 SD
NTBC	Tyrosinemia type I	1–2 mg/kg per day		x	2–3 SD
Glucagon	Hyperinsulinism	Bolus: 30–100 µg/kg (max. 1 mg)	x		Bolus
		CI: 5–10 µg/kg per h			CI
Diazoxide	Hyperinsulinism	15 mg/kg per day		x	3 SD
Insulin	All disorders with endogenous intoxication	Start with 0.05–0.1 U/kg h	x		CI
L-Isoleucine	Maple syrup urine disease	5–20 mg/kg per day		x	3–5 SD
L-Valine	Maple syrup urine disease	5–20 mg/kg per day		x	3–5 SD
Methionine	Disorders of remethylation	100 mg/kg per day		x	3–5 SD

SI short

[a] Dilute drugs for SI and CI each in 30 ml/kg glucose 10%, apply by bypass (to be included in the calculation of calories + fluids). L-carnitine, L-arginine and Na-benzoate may be mixed

In all instances symptomatic treatment has to be continued. Ventilator or circulatory support may be required as well as anticonvulsive medication. Antibiotic therapy is recommended in every patient, because sepsis is an important consideration in differential diagnosis and may be present, leading to further catabolism. Provision of ample quantities and control of fluid and electrolytes is indispensable and can be started before any laboratory results are available. Glucose should be started via a peripheral i.v. line at 150 ml/kg per day of a 10% solution ($\sim$ 10 mg glucose/kg per min, providing an energy supply of $\sim$ 60 kcal/kg per day) in a neonate or infant. Overhydration is rarely a problem in metabolic crises, as they are mostly accompanied by some degree of dehydration. Electrolytes and acid-base balance are checked every 6 h. Serum sodium should be $\geq$ 138 mmol/l.

This approach, providing glucose above the rate of hepatic glucose production (7–8 mg/kg per min in the newborn) is already the definitive treatment in

patients presenting with hypoglycemia due to a reduced fasting tolerance. However, in patients with congenital hyperinsulinism, the glucose requirement may be much higher and must be adjusted individually. The initial treatment of hyperinsulinism requires drug therapy with glucagon and/or diazoxide (Table A.3) in addition to the high-glucose supply (10–30 mg/kg min). As a rule of thumb, glucagon should be started if the a patient is still hypoglycemic despite a glucose infusion of $\geq$ 15 mg glucose/kg per min. Frequent monitoring of blood glucose is essential if symptomatic hypoglycemia is to be avoided.

The intake of all potentially toxic compounds (protein, fat, galactose, fructose) must be stopped. In disorders of amino acid catabolism, such as maple syrup urine disease, the classic organic acidurias, or the urea-cycle defects, toxic compounds are derived from exogenous as well as from endogenous sources. In addition to stopping the intake of natural protein until the crisis is over (but no longer than 24–48 h), reversal of catabolism to anabolism and consequently reversal of the breakdown of endogenous protein is the major goal. High amounts of energy are needed, e. g., in neonates > 100 kcal/kg per day. In a sick baby this can only be accomplished by hyperosmolar infusions of glucose together with fat through a central venous line. Insulin should be started early, especially in the presence of significant ketosis or in maple syrup urine disease, to enhance anabolism and prevent hyperglycemia (Wendel et al. 1982; Biggemann et al. 1993). One approach is to use a fixed combination of insulin to glucose (a useful combination is 1 U of insulin/8 g of glucose). The administration of i.v. lipids can often be increased up to 3 g/kg, provided serum triglycerides are monitored.

Carnitine is valuable for the elimination of toxic metabolites and the restoration of intramitochondrial-free acyl-CoA in organic acidurias (Chalmers et al. 1984). The dose is 100–200 mg/kg per day. However, supplementation of carnitine in suspected or proven defects of fatty acid oxidation is controversial, i. e., in the presence of significant cardiomyopathy or elevated levels of CK. The restoration of levels of free carnitine appears indicated in medium-chain acyl-CoA dehydrogenase deficiency (MCAD).

Pharmacological detoxification must be immediately initiated in hyperammonemia, which is a major emergency. Before the diagnosis is known, carnitine (for organic acidurias) and arginine (for urea cycle disorders) may be given. The use of sodium benzoate and sodium phenylacetate or phenylbutyrate in these circumstances is controversial. If the response to these medicines is poor, if ammonia concentration exceeds 400 µmol/l, or the patient is deteriorating then hemofiltration or hemodialysis needs to be considered urgently. In any case of a neonate with hyperammonemic coma, the dialysis team should be informed immediately. For more details please see Chap. 11.

Defects of the PDHC, the Krebs cycle, and the respiratory electron transport chain may have occasional life threatening episodes of acidosis and lactic acidemia. Therapy in this situation calls for vigorous treatment of the acid-base balance. However, patients with PDHC deficiency are glucose-sensitive

and glucose infusions can result in a further increase in lactate. The correction of metabolic acidosis may require large amounts of sodium bicarbonate. In as many as 20% of children with mitochondrial disease, the acute decompensation may be complicated by renal tubular acidosis, and this may increase the requirement for sodium bicarbonate or trometamol (THAM).

In patients with mitochondrial disease, replacement of cofactors is commonly undertaken. The only documented evidence in support is the positive response to biotin in multiple carboxylase deficiency and to riboflavin in some patients with multiple acyl-CoA dehydrogenase deficiency. In severe lactic acidemia and a history of insufficient food intake, a trial with thiamine should be performed (Mayatepek and Schulze 1999).

If liver failure is the presenting feature, enteral feeding should be discontinued, and glucose should be started via a peripheral i.v. line at 150 ml/kg per day of a 10% solution in a neonate or infant while awaiting the results of specific metabolic investigations, i. e., reducing substances, succinylacetone and bile acids in urine, amino acids and galactose in plasma, and the enzyme activity of galactose-1-phosphate uridyltransferase as well as acylcarnitines in blood spots. Two diagnostic pitfalls must be remembered. Galactose is cleared rapidly in a few hours from the body after discontinuation of enteral feeds, and the determination of galactose-1-phosphate uridyltransferase activity is falsely negative after a blood transfusion.

In summary a suspected metabolic emergency calls for prompt diagnostic and therapeutic measures, giving a generous energy supply, promotion of anabolism, and the use of pharmacological, and if necessary extracorporeal detoxification. Early intervention is essential. Prior to the advent of programs of expanded neonatal screening, many infants probably died without the benefit even of a diagnosis.

A.2 Acute Encephalopathy/Coma

The most important metabolic investigations in comatose patients of all ages are blood glucose, electrolytes, and ammonia. Especially the latter is often omitted in the first line of investigations.

In a comatose neonate without hyperammonemia or acidosis and normal blood glucose, a DNPH test should be performed or alternatively the branched-chain amino acids measured to identify or rule out maple syrup urine disease. If negative, the child may have nonketotic hyperglycinemia. The identical presentation can be seen in babies suffering from sulfite oxidase deficiency, adenylosuccinate lyase deficiency, methylenetetrahydrofolate reductase deficiency, or leukotriene C_4-synthesis deficiency. A urinary sulfite test must be done at the bedside in a fresh urine sample from every child presenting with catastrophic or progressive encephalopathy, and specific tests for homocysteine in blood as well as urinary purine analysis should be ordered. Leukotrienes are best ana-

lyzed in CSF, which must be stored at −70 °C or, as an intermediate measure, on dry ice or liquid nitrogen.

If intractable seizures dominate the clinical picture, folinic acid, pyridoxine-(B_6)-responsive, and pyridoxine phosphate-responsive seizures should be considered. In the case of a positive response, the therapeutic trials give the diagnosis. Pyridoxine (100 mg) is administered i.v.. Higher doses may be necessary to control seizures, at least initially. Having started with a single dose of 100 mg and if the patient is nonresponsive within 10 min, the dose should be increased and repeated up to 500 mg total before being sure about pyridoxine nonresponsiveness. If there is uncertainty about at least a partial response, pyridoxine should be continued with 30 mg/kg per day for 7 days before final conclusions are drawn. If the response to pyridoxine is negative, folinic acid should be administered with 5 mg/kg per day in three doses intravenously or orally for 3 days. If negative, it may be followed by the administration of pyridoxal phosphate with 30 mg/kg per day in three doses orally for 3 days. Pyridoxal phosphate is not available in a pharmacological preparation in Europe or the United States.

Severe infantile epileptic encephalopathy is one indication for specialized CSF analyses testing metabolic pathways of brain metabolism, especially of neurotransmission. Defects in the metabolism of biogenic monoamines are diagnosed this way and so is GABA transaminase deficiency (Hoffmann et al. 1998).

Metabolic stroke has been reported in homocystinurias, mitochondrial disorders, the thiamine-responsive megaloblastic anemia syndrome and Fabry disease, a number of organic acid disorders, and the carbohydrate-deficient glycoprotein (CDG) syndromes. It can be the first manifestation of these disorders, and in these rational approaches to treatment follow the details specified in the respective chapters.

A.3 Anesthesia

A few aspects in the managements of metabolic patients are specific to anesthesia and surgery (Table A.4). Pharmacogenetic defects, of which the most relevant are defects in butyrylcholinesterase, leading to prolongation of the action of succinylcholine, the agent used in surgery for relaxation of muscle, are beyond the scope of this book.

Table A.4. Anesthetics and inherited metabolic diseases

Anesthetic agent	Potential problems
Barbiturates	Generally safe; however, they inhibit complex I of the mitochondrial respiratory chain at high concentrations
Benzodiazepines	Generally safe; however, they inhibit the transport of adenine nucleotides into mitochondria
Propofol	Inhibits fatty acid transport and oxidation. Should not be used in patients with fatty acid oxidations defects, and should be used with caution in patients with mitochondrial respiratory chain defects
Halothane	May precipitate cardiac arrhythmias in patients with mitochondrial respiratory chain defects or fatty acid oxidation defects
Nitrous oxide	Causes impairment of mitochondrial respiratory chain energy generation. It is specifically contraindicated in patients with Vitamin B_{12} deficiency (partially treated PKU) and defects of 1C metabolism including cobalamin defects and methylenetetrahydrofolate reductase deficiency
Nondepolarizing muscle relaxants	Increase risk of prolonged apnea in patients with metabolic myopathies
Bupivacaine	Inhibits ATP production in cardiac muscle; increased risk of cardiac arrhythmias in patients with mitochondrial respiratory chain defects

General anesthesia and the stress of surgery can be responsible for acute breakdown of tissue and consequently metabolic decompensation. This has been observed in all groups of disorders which lead to endogenous intoxication. These are the protein-dependent metabolic disorders, aminoacidopathies, organic acidurias, urea cycle disorders, as well as defects of fatty acid oxidation. The main objective in the management of anesthesia and surgery in such patients is to minimize catabolism. This objective is met best by avoiding anesthesia and surgery, if at all possible, until the patient is in an optimal metabolic state and well over any infection. Elective surgery should then be scheduled in a center with a team experienced in the acute management of this particular metabolic disorder, including in-house facilities of a metabolic laboratory. As a general principle, fasting must be avoided by a continuous supply of intravenous caloric infusions, and stopping and restarting enteral feeds as late as possible and as soon as possible, respectively.

Surgery and anesthesia may also induce a metabolic crisis in Refsum disease via mobilization of phytanic acid in fat stores. The same preventive approaches apply. Disorders with a reduced fasting tolerance or with a disturbed energy metabolism will also need very close monitoring and carefully monitored and adjusted intravenous therapy.

Specific risks of general anesthesia are well recognized in patients with mucopolysaccharidosis type IV (Morquio disease), but also types II and VI. General anesthesia should be undertaken in these patients only in centers in which anesthesiologists have had experience with patients with these diseases. Wherever possible, local anesthesia is preferable, but, in young or uncooperative patients such as those with Hunter or Sanfilippo syndromes, this may not be

possible. General anesthesia is preferable to sedation, because of the need to control the airway.

In preparation for surgery, the patient or parents should be asked about previous problems with anesthesia, obstructive sleep apnea, or transient paralysis, which might be an index of cervical instability. The patient should be examined for evidence of cord compression kyphoscoliosis and excessive upper respiratory secretions. Blood pressure should be determined and an ECG and echocardiogram. Recent X-rays of the chest and of the cervical spine should be reviewed. Those with kyphoscoliosis should have pulmonary function studies. Sleep studies may be useful. Those with evidence or history of cord compression should have an MRI of the spine. Intubation may be difficult and smaller tubes than usual may be required. Careful positioning is required and hyperextension of the neck must be avoided. It may be necessary to immobilize the neck with a halo brace or plaster to avoid damage to the cervical cord. Thick secretions may lead to postoperative pulmonary problems. Recovery from anesthesia may be slow, and postoperative obstruction of the airway has been observed.

A.4 Postmortem Diagnosis

In the event of death when metabolic disease is suspected, it is important to store adequate amounts of biological fluids and available tissues for further diagnostic procedures (Table A.5). The use of these samples should be carefully planned in accordance with advice from specialists in inborn errors of metabolism (Hoffmann et al. 2002; Zschocke and Hoffmann 2004).

In the case of sudden infant death syndrome (SIDS), it is important to recognize that defects of fatty acid oxidation may be responsible, particularly long-chain defects, which can lead to respiratory arrest and heart block or arrhythmias. In most cases, autopsy reveals an excess of fat droplets in liver or heart but, even in the absence of steatosis, blood spots should always be collected on filter paper for analysis of acylcarnitines by electrospray tandem-mass spectrometry.

Table A.5. Specimens to be considered for postmortem investigations in suspected metabolic disease

Material	Amount	Storage	Investigation
Dried blood spots (filter paper)	3 drops	Room temperature	See Table A.1
Plasma, serum	> 2 ml	Frozen, −20 °C	
Urine	5–20 ml		
CSF	1–2 ml	Frozen, −70 °C	Neurometabolic investigations
EDTA Blood	3–10 ml	Frozen, −20 °C	DNA
Heparin-blood	3–10 ml	Room temperature	Enzyme studies
Fibroblasts (4-ml punch placed in sterile saline)		Room temperature	Enzyme studies
Biopsies depending on history and clinical course: muscle (skeletal, cardiac); liver; kidney; skin		Frozen, −70 °C	Enzyme studies; histochemistry (glutaraldehyde for ultrastructural analysis and light microscopy)

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B The Role of Communication in the Treatment of Inborn Metabolic Diseases

Peter Burgard, Udo Wendel

B.1 Introduction

There are at least five reasons to deal with communication in the domain of inborn metabolic diseases (IMD):

1. IMDs are rare diseases, and it is very unlikely that families and patients have some a priori knowledge about these diseases. In a situation perceived as important, lack of resources in terms of knowledge and skills will result in a feeling of helplessness and anxiety. Information can reduce the knowledge gap and communication can establish trust and reduce anxiety, thereby stimulating active coping strategies.
2. Patients and families have to be taught knowledge and skills, since most of the treatment is done in a self-administered way on a daily and, in some diseases, on a 24-h schedule.
3. Evidence-based patient information requires the translation of complicated facts and logic into every day language.
4. Treatment of IMD is an interdisciplinary clinical enterprise requiring rapid transfer of information between the different disciplines as well as with the patient.
5. Information transfer and communication is explicitly required for fulfilling ethical as well as legal rules for the achievement of informed consent.

Communication skills must be learned by exercise, but theoretical knowledge can guide practice and improve performance. This chapter introduces the basic concepts of communication and information transfer in the domain of IMD. The basic reason for this article is not to be seen primarily in content but in structure. Most of the ideas presented here are well known and would intuitively be judged as right. However, the main barrier to successful communication is seen in lack of structure. Therefore, we recommend explicitly planning, monitoring, and evaluating the act of communication instead of relying on intuitive strategies or on the expectation that success in communication is unpredictable or will emerge just in the process of dialogue. Nevertheless, we encourage the reader to modify the techniques whenever it seems appropriate. Like diagnostics and treatment of IMD, successful communication is not art but the result of controlled strategies and techniques. Although not exactly

the same, for reasons of simplicity we use the terms "communication" and "information transfer" synonymously.

B.2 Dimensions of Communication

Communication is the process of information transfer from a sender to a receiver. This process can be *unidirectional* (in mass media communication, e. g., when a booklet is handed to a patient) or *bidirectional* (e. g., personal meeting of a patient in an outpatient clinic). *Verbal* communication primarily relies on spoken or written words (vocabulary and syntax), but in some cases also on motor behaviour (e. g., sign languages). *Nonverbal* aspects of communication include mimic expression of emotions, body posture, prosody – i. e., the melody of speaking, and speed of sending information. Different media can express the content of a message: executing actions, showing pictures, and the presentation of spoken or written words.

In the domain of IMD the metabolic team should be trained in verbal and nonverbal communication and in the use of different media. Iconic media (e. g., graphs, figures, simplified metabolic pathways) can be very helpful for increasing the amount of transmitted information. With regard to verbal communication, empirical research has demonstrated that speakers have a tendency to overestimate the amount of transmitted information. Therefore speakers should be trained to follow the RUMBA rule. Messages should be:

- *R*elevant: avoid irrelevant details
- *U*nderstandable: adapt to the receiver's language and language skills
- *M*easurable: only say what can be proven
- *B*ehavioural: refer to behaviour and its effects and be parsimonious with regard to attitudes
- *A*chievable: adapt to the receiver's (intellectual and behavioural) limitations when making recommendations

B.3 The Ideal Situation

Communication is very sensitive to loss, addition, and deterioration of content if information is transmitted over several steps. In addition receivers of information are very sensitive to even marginal and meaningless differences in messages.

Therefore, it is highly recommended that the therapeutic team is coordinated with respect to the treatment of a particular patient. In the initial phase – usually when the diagnosis and treatment is explained for the first time – the whole team should meet the patient and the family. Participants of such a meeting should be:

A. Both parents or all persons involved in everyday treatment and care
B. The patient
C. The paediatric metabolic specialist
D. The dietician
E. The psychologist
F. The interpreter where necessary

It is often argued that too many people would demand too much from the family and make successful communication impossible. According to our experience, families appreciate very much if they are introduced to the whole team. It is also argued that it is too time-consuming and therefore not efficient to include the whole team, but it will be more time consuming to correct families' perceptions of apparent divergent information given by different members of a team.

To assure successful communication and information transfer with regard to IMD, we recommend being aware of the following conditions:

A. The sender should have a programme, i. e., a specified set of messages arranged in a logical sequence.
B. Who should participate in the communication and receive the messages? At least in the first meeting of a family with the metabolic team all members of the team should be present. The family will learn how the different professions interact and why the multiprofessional team is necessary for diagnosis and treatment.
   In general, treatment of IMD is a family enterprise. Both parents should be present at least during the first meetings, and where necessary other caregivers (e. g., grandparents) should be included. When patients reach school age, communication should be explicitly cut in three phases: speaking with the whole family, speaking with the patient, and speaking with the parents. At the latest, during adolescence it is necessary to speak with the patient as well as with the parents alone.
C. What kind of material (media) should be used to intensify information transfer? In order to avoid unnecessary repetition, it is helpful to use a semi-standardized set of material, allowing later on to bring the family's attention to already transmitted information. It is also necessary that the different professions involved know each other's core messages.
D. How much time will be needed to realise successful communication and information transfer? Allocate sufficient time according to the content of your message. It is better to postpone a subject to another meeting than to say too much at the same time.
E. What are the setting parameters to support communication and information transfer? Setting and sitting extremely influence communication and information transfer. Sitting side by side (instead of face to face) with a family creates an atmosphere of cooperation and is helpful for explaining iconic material. Avoid interruptions by telephone calls and computer or paperwork.

These interruptions are like noise and decrease the quality of communication.

F. Dealing with information from other sources. Be aware that patients and families will also use other medical as well as nonmedical sources of information (other family members, general practioners, encyclopaedias, web sites from the internet). Allow the family to refer to this information and offer room for discussion.

B.4 Prototypes of Communication in the Domain of IMD

There are six prototypes of communicative situations in the domain of IMD (see Table B.1). Each of these prototypes has several exemplars repeatedly emerging in the longitudinal course of counselling and treatment. Explaining the diagnosis is a central issue in the first contact after a positive result in neonatal screening. However, it will reappear in later contexts. First, the diagnosis has to be explained to the parents; second, it has to be explained to the patient; third, parents and patients need support how to explain the diagnosis to relatives, friends, nursery school teachers, and future spouses. Genetic counselling also is a key issue in decision-making concerning further reproduction in families with an index child but also for patients reaching the age of reproduction.

Table B.1. Prototypes of communication in the domain of inborn metabolic diseases

1.	Explaining the diagnosis and disorder: introduction of the vocabulary necessary to explain the name of the disease, its aetiology, physiology, medical and laboratory investigations
2.	Explaining standard treatment and care
3.	Explaining the course of the disease and outcome (chances and risks)
4.	Explaining emergency situations and emergency treatment
5.	Monitoring of the treatment: regular investigations, contacts in outpatient clinics
6.	Genetic counselling

B.5 Critical Issues in the Prototypes of Communication: For Example, Phenylketonuria

■ Explaining the Diagnosis and Disorder

Introduction of the vocabulary is necessary to explain the name of the disease, its aetiology, physiology, and medical and laboratory investigations. The literal meaning of phenylketonuria is “phenylketones in the urine”. This terminology has lost its meaning for historical reasons since this diagnosis, and treatments are no longer are based on parameters in the urine. Instead, the disease is diagnosed and treatment is monitored by parameters in the blood, i. e., hyper-

phenylalaninemia, meaning "increased levels of phenylalanine in the blood". Aetiology refers to a genetic defect and physiology is based on enzyme deficiency. None of these concepts is part of common sense. Genes can be explained as analogues of recipes, enzymes as transforming machines, phenylalanine as a basic nutritional component. All of them are hidden components of life and can only be demonstrated by laboratory techniques.

Explaining the Standard Treatment and Care

The core concept of treatment is secondary prevention, i. e., in the case of successful treatment, the family and the patient will never experience what will be prevented. As a result the reasons for treatment can only be understood on an intellectual basis, whereas the treatment itself has practical implications for each day in the patient's life. Prevention is realised by withdrawal of convenient dietary components and supplementation of special products, often perceived as prohibition of normal living. In the extreme this results in the overgeneralisation of an abnormal life. Parents should be directed to the fact that individual family life-styles or parenting strategies often deviate from mainstream behaviour (e. g., Muslim families have no problems keeping their children away from pork).

Explaining the Course of the Disease and Outcome (Chances and Risks)

Preventive medicine makes the disease a hypothesis instead of a fact. Explaining the course of the "disease" bears the risk of euphemistic explanations such as "development will not be normal". Given the long-term cumulative effect of increased phenylalanine blood levels, the euphemism might loose its explanatory power. Instead phenylalanine in high levels could be introduced as a poison destroying the brain in the same way as continuous drops of water hollow a stone. Prevention can be explained as analogous to seat belts.

Explaining Emergency Situations and Emergency Treatment

In many IMD, emergency situations result from fasting and/or catabolism, particularly during the night or during febrile illness, i. e., hidden concepts. Explanation of metabolism as a continuous and reversible process can support the understanding of recommendations and their benefits and risks.

Monitoring the Treatment

Regular laboratory investigations and contacts in outpatient clinics are necessary for successful treatment of IMD. These are instruments to make hidden variables visible in the same way as rear-view mirrors help people to drive safely.

■ Genetic Counselling

Autosomal recessive inheritance is responsible for the silent transmission of mutant alleles in heterozygotes. The explanation of a diploid set of genes (recipes) can be helpful to explain that both parents' and their ancestors' genes contributed to the disorder of their child. For most people probability calculations of risks are too complicated and abstract for understanding aetiology and the chances of repetition in further reproduction. Exercising a two coin-flip experiment with some trials (in general 20 will be sufficient) will bring evidence to the abstract concept of probability (see also the "measurable" term of the RUMBA rule).

B.6 Teaching Skills

Technical skills such as calculating the diet, tube feeding, taking blood samples, and when and how to contact the metabolic laboratory should be taught and trained in special lessons assisted by dieticians, nurses, and psychologists. Teaching small groups of families and patients can profit from positive modelling and learning from peers. Patient organisations exist for most IMDs. They are helpful for several reasons:

1. Patients in age groups other than the index child can be models for the outcome of treatment.
2. Patients and families can be models for coping with the different aspects of the disease.
3. Patient support groups offer addresses for getting special dietary products.

B.7 Prototypes of Communicative Relations

There are two prototypical relations between sender and receiver in communication. A receiver with *heteronomous orientations* seeks for *directives*, i. e., concrete and executable plans and recommendations of what to do; monitoring functions as external control. These directives can also help parents to comply with recommendations in the interaction with their child by transferring the burden of explaining the necessity of the daily treatment activities to the metabolic team.

A receiver with *autonomous orientations* seeks for *information*, i. e., ideas what could be done. Monitoring has the function of external feedback for internal control. This feedback helps parents and patients to find their own way to be in concordance with treatment recommendations, to make their own (evidence-based) choices, and to design their daily treatment activities. Treating heteronomous receivers as autonomous ones can make them helpless. In addition they might perceive the metabolic team as weak or over-demanding.

Treating autonomous receivers as heteronomous ones can make them rebel, since they might result in the perception of the metabolic team as rigid or authoritarian. Orientations can be variable over time and situations: sometimes patients just want a *trustworthy expert* to tell them what to do. Sometimes they want *to make their own choices* but need details (such as facts and probabilities) in order to do so. Sometimes they want help in *organizing their thinking*.

B.8 Summary

Communication and information transfer in IMD aim at successful coping with the diagnosis and treatment recommendations, as well as with the results of treatment. Successful coping involves cognitive, emotional, and behavioural aspects. Each aspect has its own vocabulary and syntax, its own setting and timing, to be realized by the grammar of the metabolic team (Table B.2).

Table B.2. The grammar of communication in inborn metabolic diseases

Dimensions of disease	Cognitive coping	Emotional coping	Behavioural coping
Structure: etiology and nosology	Knowledge; understanding	Attitude	Learning
Process: treatment and monitoring	Planning: starting/ executing action	Motivation; will	Skills; cooperation
Result: outcome	Analysis of experience; regulation	Tolerance for frustration	Adaptation

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Part Two
Approach to Treatment

1 Disorders of Phenylalanine and Tetrahydrobiopterin Metabolism

Nenad Blau, Peter Burgard

1.1 Introduction

Patients with disorders described in this chapter present either with or without hyperphenylalaninemia (HPA). In those presenting with HPA (1.1–1.5 in the table below), the main goal of treatment is to reduce or normalize blood phenylalanine levels. This can be done either by introduction of the low-phenylalanine or low-protein diet or by administration of the synthetic cofactor tetrahydrobiopterin (BH_4). The mode of treatment depends on the type of disease and may differ with the patient's age, and the policies are different in different countries. In addition, patients with HPA due to a cofactor defect need more strict plasma phenylalanine control and additional supplementations with neurotransmitter precursors L-dopa and 5-hydroxytryptophan in a combination with the peripheral decarboxylase inhibitor carbidopa. Patients with dihydropteridine reductase (DHPR) deficiency (disorder 1.4) need additional folinic acid substitution. In patients revealing levodopa-induced peak-dose dyskinesia, slow-release forms of drugs can be used, and reaching the upper therapeutic limits of L-dopa may be an indication for the use of monoamine oxidase (MAO) and/or catecholamine-*O*-methyl transferase (COMT) inhibitors.

Patients with dopa-responsive dystonia (DRD, dominant GTP cyclohydrolase I (GTPCH I) deficiency; disorder 1.6) and sepiapterin reductase (SR) deficiency (disorder 1.7) respond to low-dosage L-dopa/carbidopa therapy, and patients with SR deficiency need additional supplementation with 5-hydroxytryptophan and probably also BH_4.

Prognosis and outcome strongly depend on the age when the diagnosis is made and treatment introduced, but also on the type of mutation.

Recommendations for treatment and monitoring are not completely uniform worldwide. Therefore, where possible and necessary, recommendations have been combined and ranges of values indicating lower and upper limits are reported (Fig. 1.1).

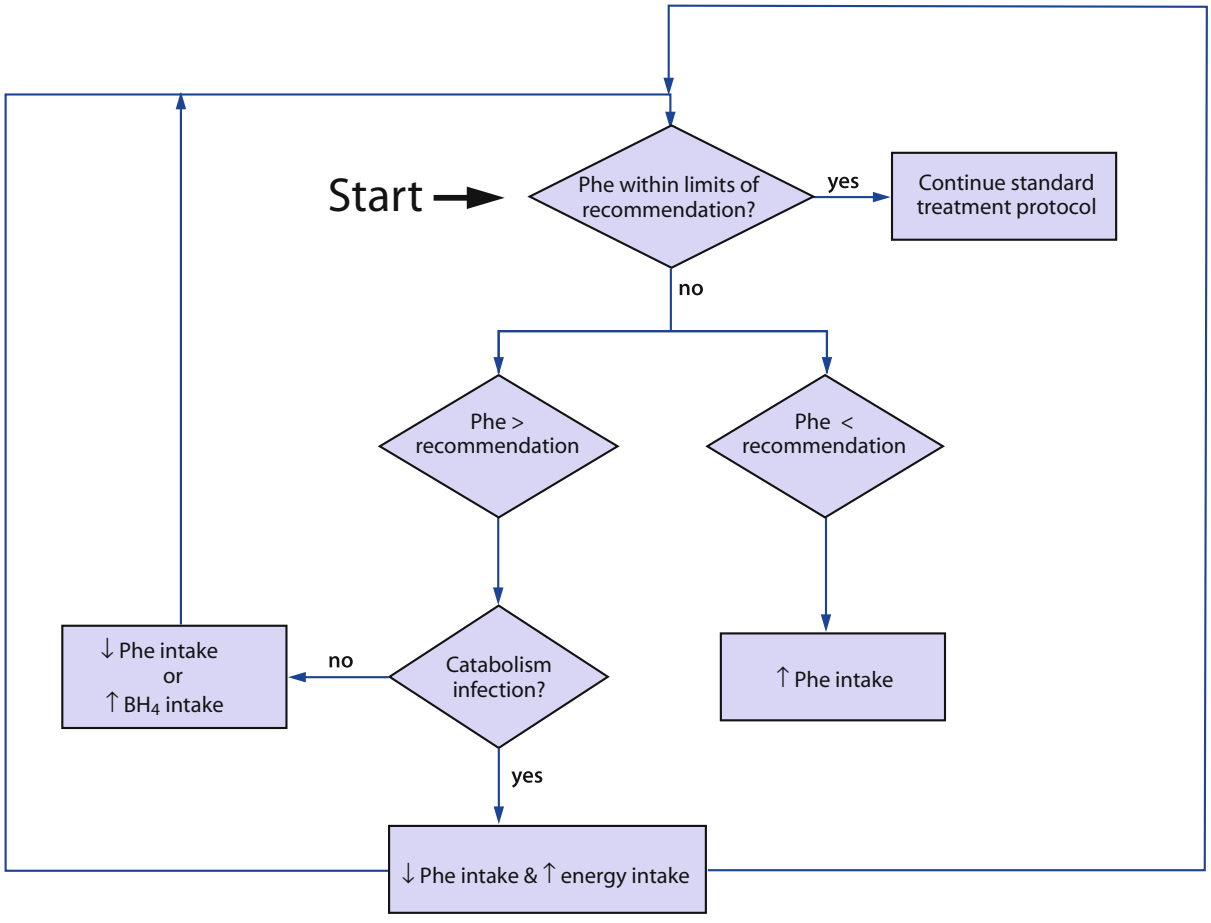

Fig. 1.1. Management of plasma phenylalanine concentrations

1.2 Nomenclature

No.	Disorder	Symbol	Definition/comment	Gene Symbol	OMIM No.
1.1	Phenylalanine hydroxylase deficiency	PAH	Autosomal recessive	*PAH*	261600
1.1.1	Classic phenylketonuria	PKU	Phe > 1200 µmol/l Autosomal recessive	*PAH*	261600
1.1.2	Mild PKU		360–600 µmol/l ≤ Phe ≤ 1200 µmol/l Autosomal recessive	*HPA*	261600
1.1.3	Non-PKU hyperphenylalaninemia	MHPA	80 µmol/l ≤ Phe < 360–600 µmol/l Autosomal recessive	*HPA*	261600
1.1.4	Tetrahydrobiopterin (BH_4)-responsive PKU/HPA	BH_4-PKU	Phe > 360 µmol/l Autosomal recessive	*HPA*	261600
1.1.5	Maternal PKU/HPA	MPKU	Phe > 250–360 µmol/l Autosomal recessive	*HPA*	261600
1.2	GTP cyclohydrolase I deficiency	GTPCH	Autosomal recessive	*GCH1*	233910
1.3	6-Pyruvoyl-tetrahydropterin synthase deficiency	PTPS	Autosomal recessive	*PTS*	261640
1.3.1	Severe PTPS deficiency	PTPS	Autosomal recessive	*PTS*	261640
1.3.2	Mild/peripheral PTPS deficiency	PTPS	Normal CSF neurotransmitters Autosomal recessive	*PTS*	261640
1.4	Dihydropteridine reductase deficiency	DHPR	Autosomal recessive	*QDPR*	261630
1.5	Pterin-4α-carbinolamine dehydratase deficiency	PCD	Transient hyperphenylalaninemia Autosomal recessive	*PCD*	264070
1.6	Dopa-responsive dystonia/autosomal dominant GTPCH deficiency	DRD	Without hyperphenylalaninemia	*GCH1*	600225
1.7	Sepiapterin reductase deficiency	SR	Without hyperphenylalaninemia Autosomal recessive	*SPR*	182185

CSF cerebrospinal fluid

1.3 Treatment

■ 1.1 PAH deficiency

● *1.1.1 Classic phenylketonuria (PKU)*

● *1.1.2 Mild PKU*

Age	Protein requirement (g/kg BW/day)[a]	Phe tolerance (mg/day)	Target blood Phe (µmol/l)			Phe-free AAM	
			Germany	UK	USA	Type	g/day[b]
0–3 months	2.3–2.1	~130–400	40–240	120–360	120–360	1	3–10
4–12 months	2.1–2.0	~130–400	40–240	120–360	120–360	1	3–10
1–2 years	1.7	~130–400	40–240	120–360	120–360	2	20–50
2–3 years	1.7	~200–400	40–240	120–360	120–360	2	20–50
4–6 years	1.6	~200–400	40–240	120–360	120–360	2	20–50
7–9 years	1.4	~200–400	40–240	120–480	120–360	2	20–50
10–12 years	1.1	~350–800	40–900	120–480	120–360	2	50–90
13–15 years	1.0	~350–800	40–900	120–700	120–600	2	50–90
Adolescents/adults	0.9	~450–1000	40–1200	120–700	120–900	3	60–150

AAM amino acid mixture
[a] DGE 1985; RDA; WHO protein requirement for PKU diet is assigned higher than recommendations for healthy people, because bioavailability of amino acids mixtures is equivalent to natural protein
[b] Spread as evenly as possible through the 24 h

● *1.1.3 Non-PKU hyperphenylalaninemia (MHPA)*

Treatment is only necessary for pregnant women with blood Phe levels > 250−360 mol/l (see disorder 1.1.4). Clinical monitoring of all patients with Phe > 360 mol/l is desirable.

● *1.1.4 Tetrahydrobiopterin BH_4-responsive PKU/HPA*

There are no recommendations for the treatment of this group of HPA patients. The following table summarizes the current knowledge based on several experimental trials.

Age	Protein requirement (g/kg BW/day)	Phe tolerance (mg/day)	Target blood Phe (µmol/l)	mg BH_4/kg BW[a]
All ages	See disorder 1.1.1	Near normal	See disorder 1.1.1	5–20

AAM amino acid mixture
[a] To be distributed over at least two doses; no long-term clinical experience; BH_4 tablets contain 100 mg ascorbic acid/100 mg BH_4

1.1.5 Maternal PKU/HPA

Trimenon	Protein requirement (µmol/l)	Phe tolerance (mg/kg BW/day)	Target blood Phe (mg/day)	Phe-free AAM	
				Type	g/day[a]
1	1.1	~180–1600	120–360	3	60–150
2–3	1.3–1.5	~180–1600	120–360	3	60–150

[a] Spread as evenly as possible over the 24 h

1.2 GTP cyclohydrolase I deficiency

1.3.1 6-Pyruvoyl-tetrahydropterin synthase deficiency (severe form)

No.	Symbol	Age	Medication/diet	Dosage (mg/kg per day)	Dose/day (*n*)
1.2	GTPCH	Newborn	L-Dopa	1–3	3–6
1.3.1	PTPS (severe)		Carbidopa	10–20%[a]	3–6
			5-Hydroxytryptophan	1–2	3–6
			Tetrahydrobiopterin (BH4)[b]	5–10	2
		< 1–2 years	L-Dopa	4–7	3–6
			Carbidopa	10–20%[a]	3–6
			5-Hydroxytryptophan	3–5	3–6
			Tetrahydrobiopterin (BH4)[b]	5–10	2
		> 1–2 years	L-Dopa	8–15	3–6
			Carbidopa	10–20%[a]	3–6
			5-Hydroxytryptophan	6–9	3–6
			Tetrahydrobiopterin (BH_4)[b]	5–10	2

[a] Percentage of L-dopa
[b] BH_4 tablets contain 100 mg ascorbic acid/100 mg BH_4

Dangers/Pitfalls

1. Patients are on a unrestricted (i. e. protein-rich) diet.
2. BH_4 may significantly reduce plasma and CSF tyrosine levels. Consider nutrition and tyrosine supplementation.
3. L-Dopa/carbidopa/5-hydroxytryptophan therapy should be introduced slowly and increased in steps of not more than 1 mg/kg over days or weeks. 5-hydroxytryptophan may not be tolerated due to gastrointestinal side-effects; in these cases monotherapy with L-dopa/carbidopa may be sufficient.
4. L-Dopa/carbidopa/5-hydroxytryptophan therapy may reduce CSF folates (CH_3-group trapping by L-dopa to 3-*O*-methyl-dopa). Determine 5-methyltetrahydrofolate in CSF. Consider folinic acid (5-formyltetrahydrofolate, Leucovorine) substitution (10–20 mg/day).
5. Drugs such as trimethoprim sulfamethoxazoles or methotrexate may induce hyperphenylalaninemia by inhibiting DHPR.

● *1.3.2 6-Pyruvoyl-tetrahydropterin synthase deficiency (mild form)*

No.	Symbol	Age	Medication/diet	Dosage (mg/kg per day)	Dose/day (*n*)
1.3.2	PTPS (mild)	All ages	Tetrahydrobiopterin (BH_4)[a]	5–10	2

[a] BH_4 tablets contain 100 mg ascorbic acid/100 mg BH_4

Dangers/Pitfalls

1. Patients are on an unrestricted (i. e. protein-rich) diet.
2. BH_4 may significantly reduce plasma and CSF tyrosine levels. Monitor and consider tyrosine supplementation.
3. Drugs such as trimethoprim sulfamethoxazoles or methotrexate may induce hyperphenylalaninemia by inhibiting DHPR.

■ 1.4 Dihydropteridine reductase deficiency

No.	Symbol	Age	Medication/diet	Dosage (mg/kg per day)	Dose/day (*n*)
1.4	DHPR	Newborn	L-Dopa	1–3	3–6
			Carbidopa	10–20%[a]	3–6
			5-Hydroxytryptophan	1–2	3–6
			Folinic acid	15–20 mg/day	1–2
			Diet (see disorder 1.1, PKU)		
		< 1–2 years	L-Dopa	4–7	3–6
			Carbidopa	10–20%[a]	3–6
			5-Hydroxytryptophan	3–5	3–6
			Folinic acid	15–20 mg/day	1–2
			Diet (see disorder 1.1 PKU)		
		> 1–2 years	L-Dopa	8–15	3–6
			Carbidopa	10–20%[a]	3–6
			5-Hydroxytryptophan	6–9	3–6
			Folinic acid	15–20 mg/day	1–2
			Diet (see disorder 1.1 PKU)		

[a] Percentage of L-dopa

Dangers/Pitfalls

1. Patients are on a low-Phe diet (see disorder 1.1); however, blood Phe levels should be close to normal. These patients are more sensitive to high Phe levels than PKU.
2. L-Dopa/carbidopa/5-hydroxytryptophan therapy should be introduced slowly and increased in steps of not more than 1 mg/kg over days or weeks.
3. Drugs such as trimethoprim sulfamethoxazoles or methotrexate may induce hyperphenylalaninemia by inhibiting DHPR.

1.5 Pterin-4α-carbinolamine dehydratase deficiency

No.	Symbol	Age	Medication/diet	Dosage (mg/kg per day)	Dose/day (*n*)
1.5	PCD	Newborn > 1 year	Tetrahydrobiopterin (BH_4)[a] No treatment	5–10	2

[a] BH_4 tablets contain 100 mg ascorbic acid/100 mg BH_4

Dangers/Pitfalls

1. Patients are on an unrestricted (i. e., protein-rich) diet.
2. BH_4 may significantly reduce plasma and CSF tyrosine levels. Consider tyrosine supplementation.
3. Drugs such as trimethoprim sulfamethoxazoles or methotrexate may induce hyperphenylalaninemia by inhibiting DHPR.

1.6 Dopa-responsive dystonia/autosomal dominant GTPCH deficiency

No.	Symbol	Age	Medication	Dosage (mg/kg per day)	Dose/day (*n*)
1.6	DRD	Newborn	L-Dopa	1–3	3–4
			Carbidopa	10–20%[a]	3–4
		> 1 year	L-Dopa	4–12	3–4
			Carbidopa	10–20%[a]	3–4

[a] Percentage of L-dopa

Dangers/Pitfalls

1. L-Dopa/carbidopa therapy should be introduced slowly and increased in steps of not more than 1 mg/kg over days or weeks.

1.7 Sepiapterin reductase deficiency

No.	Symbol	Age	Medication	Dosage (mg/kg per day)	Dose/day (*n*)
1.7	SR	Newborn	L-Dopa	1–3	3–4
			Carbidopa	10–20%[a]	3–4
			5-Hydroxytryptophan	1–2	3–4
		> 1 year	L-Dopa	4–10	3–4
			Carbidopa	10–20%[a]	3–4
			5-Hydroxytryptophan	3–9	3–4

[a] Percentage of L-dopa

Dangers/Pitfalls

1. L-Dopa/carbidopa/5-hydroxytryptophan therapy should be introduced slowly and increased in steps of not more than 1 mg/kg over days or weeks.
2. BH_4 supplementation may be considered.

1.4 Alternative Therapies/Experimental Trials

No.	Deficiency symbol	Age	Medication	Dosage (mg/kg/day)	Dose/day (*n*)
1.1.4	BH_4-PKU	All ages	BH_4[a]	5–20	2
1.2	GTPCH	All ages			
1.3.1	PTPS		Deprenyl[b]	0.1–0.3	3–4
1.4	DHPR		Entacapone[c]	~ 30	1–2
1.7	SR				

[a] Tetrahydrobiopterin (BH_4) treatment has been recently introduced for children with phenylalanine hydroxylase deficiency who show a decrease in Phe levels after BH_4 loading (see disorder 1.1.4 in the Treatment section)
[b] MAO-B inhibitor (Selegiline)
[c] COMT inhibitor

Dangers/Pitfalls

1. Administration of MAO-B or COMT inhibitors allows a 30% reduction of the daily dosage of neurotransmitter precursors.

1.5 Follow-up/Monitoring

1.1 PAH deficiency

Age	Biochemical monitoring (Phe and Tyr)	Clinical monitoring[a]	Intellectual and personality development
0–3 months	Weekly – Fortnightly	1–3 monthly	
4–12 months	Weekly – Fortnightly	1–3 monthly	Check
1–2 years	Weekly – Fortnightly	2–6 monthly	
2–3 years	Weekly – Fortnightly	2–6 monthly	Check
4–6 years	Fortnightly	3–6 monthly	Check
7–9 years	Fortnightly	6 monthly	
10–12 years	Monthly	6 monthly	Check
13–15 years	Monthly	6 monthly	Check
Adolescents/adults	Monthly – Bimonthly	6–12 monthly	Check
Maternal PKU	Weekly[b]	Bimonthly[c]	

[a] Nutrient intake, body growth, and general health. In general special Laboratory tests are not necessary. In patients with poor dietary and aminoacid mixture compliance B12 monitoring is necessary. After long term poor compliance or failure to thrive further tests may be necessary.
[b] Plasma amino acids (AA), albumin, cholesterol, ferritin, folate, vitamin B12
[c] Nutrient intake, including micronutrients, body growth, general health

1.2–1.7 BH_4 deficiencies

Plasma Phe and Tyr are monitored in all forms of HPA; CSF investigations are only carried out in disorders affecting BH_4 metabolism with and without HPA (see disorders 1.2–1.7).

Test	Age	Frequency	Target values/levels
Phe and Tyr (blood)	1–3 years	Weekly to fortnightly	Phe levels: 40–360 µmol/l[a]
	4–10 years	Fortnightly to monthly	(target value 360 µmol/l)
	11–16 years	Monthly	Phe levels: 40–900 µmol/l[a]
	> 16 years	Every 2–3 months	Phe levels: 40–1200 µmol/l[a]
Neopterin			
Biopterin	< 1 month	Fortnightly	Close to normal range
5-HIAA	1 month to 1 year	Every 4–8 weeks	Close to normal range
HVA	> 1 year	Monthly to yearly	Close to normal range
Folates (CSF)[b]			

5-HIAA 5-hydroxyindoleacetic acid, *HVA* homovanillic acid
[a] In BH_4-deficient patients, Phe levels should be close to 240–360 µmol/l at all ages
[b] Lumbar puncture in the morning before medication. Discard the first 0.5 ml and collect the next 1–2 ml (Storage: −80 °C)

1.6 Standard Protocol for Intercurrent Illness

- The best possible intake of fluid, carbohydrates, and Phe-free AAM.
- High-energy intake, low-phenylalanine regimen.

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2 Disorders of Neurotransmission

Georg F. Hoffmann, Robert Surtees

2.1 Introduction

Monogenic defects of neurotransmission have become recognized as a cause of early onset, severe, progressive encephalopathies. The diagnosis is mostly based on the quantitative determination of the neurotransmitters or their metabolites in cerebrospinal fluid (CSF), i. e., the amino acids glutamate, glycine, and γ-aminobutyric acid (GABA), the acidic metabolites of the biogenic monoamines, and individual pterin species (Hoffmann et al. 1998). In contrast to inborn errors in catabolic pathways, neurotransmitter defects are reflected by the interplay of biosynthesis, degradation, and receptor status. Even borderline abnormalities can be diagnostic, but their recognition requires a strictly standardized sampling protocol and adequate age-related reference values. All laboratories have their own reference values that differ because of local variations in the technique of CSF sampling and the precise aliquot used for analysis. Because of these special logistics of sampling and transport, as well as demanding laboratory techniques due to very low metabolite concentrations, "neurotransmitter defects" are investigated in few specialized laboratories worldwide, and consequently only a small number of patients has been diagnosed. Therefore we suspect a substantial underdiagnosis.

This is in contrast to patients suffering from pterin defects that cause hyperphenylalaninemia, which are diagnosable by neonatal screening programs (see Chap. 1), or to patients with succinic semialdehyde dehydrogenase deficiency resulting in 4-hydroxybutyric aciduria, which is diagnosable by urinary organic acid analysis (see Chap. 3). For the diagnosis of the other defects, plasma or urine investigations are inadequate or even misleading and they require specific CSF analyses. Only elevated concentrations of prolactin in serum (the release of which is normally inhibited by dopamine via dopamine D_2 receptors), and of serotonin in whole blood point to genetic defects of dopamine biosynthesis or monoamine oxidase deficiency, respectively. In our experience neither is sensitive nor specific.

The clinical presentation of neurotransmitter diseases can be quite distinctive and these investigations should not routinely be performed in every child with an unexplained encephalopathy. Patients with *GABA-transaminase* deficiency or *nonketotic hyperglycinemia* usually present with early onset, severe

encephalopathy, dominated by seizures refractory to treatment. For neither is there a satisfactory specific therapy; they are discussed in Chap. 3. *Folinic acid-responsive seizures* (Hyland et al. 1995) or *defects in pyridoxine metabolism* (Baxter 2001; Clayton et al. 2003) can present similarly. For these diseases rational therapies have been developed with satisfactory or even excellent success.

Defects in the biosynthesis of dopamine result in progressive extrapyramidal movement disorders, especially parkinsonism, dystonia, and chorea. Nevertheless, the spectrum of individual symptoms and courses of disease is wide, ranging from intermittent focal dystonia to severe, lethal infantile encephalopathies. In very young infants, the symptoms can be less specific. They present with truncal hypotonia, restlessness, feeding difficulties, motor delay, or even hypoglycemia or signs of autonomic dysfunction, the latter two due to inadequate peripheral catecholamine production. Suggestive are ophthalmologic symptoms such as ptosis, miosis, and oculogyric crises.

Tyrosine hydroxylase and *aromatic L-amino acid decarboxylase* are the two biosynthetic enzymes converting tyrosine to the catecholamine dopamine, which in turn is the precursor for epinephrine and norepinephrine. Several patients with recessively inherited defects of these enzymes have been diagnosed. Most of them suffer from an early onset, severe progressive encephalopathy with hypotonia, hypokinesia, an extrapyramidal movement disorder, mostly dystonia, ptosis, miosis, and oculogyric crises, while some show the features of dopa-responsive dystonia (Surtees and Clayton 1998, Hoffmann et al. 2003, Swoboda et al. 2003).

Deficiency of *dopamine-β-hydroxylase* results in a distinct autonomic disorder due to the deficiency of epinephrine and norepinephrine. The disorder should be suspected in infants presenting with delayed eye-opening, hypoglycemia, hypothermia, or hypotension. Severe orthostatic hypotension becomes the hallmark of this disease in late childhood. Careful examination may further reveal ptosis, nasal stuffiness, and retrograde ejaculation in adult males (Biaggioni and Robertson 1987; Biaggioni et al. 1990).

Only one defect in the catabolism of the biogenic monoamines has been identified so far. Complete deficiency of *monoamine oxidase A* has been demonstrated by biochemical and molecular analyses in several males of a large kindred presenting with borderline mental retardation and abnormal behavior, including aggression, arson, exhibitionism, and rape (Brunner et al. 1993). The enzyme is required for the degradation of serotonin and the catecholamines in the brain, and the gene is located on the X-chromosome. Additional, independent descriptions of the same condition delineated other major characteristics of chronic episodic flushing, diarrhea, headaches, psychiatric problems, increased blood serotonin, and altered urinary concentrations of the catecholamines, serotonin, and their metabolites (Cheung and Earl 2002).

Genetic defects of *neurotransmitter receptor subtypes* are rapidly emerging as a new group of disorders that cause a wide range of neurological and psychiatric symptoms. The first such defects include a defect in the α_1-subunit of the

glycine receptor causing hyperekplexia (Becker 1995), defects in the $GABA_{A1}$, the $GABA_{B1}$, and the $GABA_{G2}$ receptors, and defects in the α_4-subunit and the β_2-subunit of the nicotinic acetylcholine receptor, all of the latter causing familial seizure disorders. Diagnosis of these disorders by mutation analysis may be aided by specific abnormalities of neurotransmitter metabolites in CSF, e. g., reduced CSF levels of GABA in children suffering from hyperekplexia.

2.2 Nomenclature

No.	Disorder	Definition/comment	Gene symbol	OMIM No.
2.1	Pyridoxine-dependant epilepsy	Seizures that respond to pyridoxine and recur on withdrawal pyridoxine	–	266100
2.2	Pyridox(am)ine 5'-phosphate oxidase deficiency	Seizures do not respond to pyridoxine but to pyridoxal phosphate	*PNPO*	603287
2.3	Folinic acid-responsive seizures	Seizures that respond to folinic acid and recur on withdrawal		
2.4	Hyperekplexia	Clinical diagnosis. "Stiff baby" syndrome; nose tap causes an abrupt, exaggerated startle followed by a tonic spasm. Familial forms have mutations in α_1-subunit gene of the glycine receptor	*GLRA1* *GLRB*	138491 138492
2.5	Tyrosine hydroxylase deficiency	Inborn error of dopamine biosynthesis. Variable clinical severity (from severe progressive infantile parkinsonism-dystonia to Segawa disease) and variable response to treatment	*TH*	191290
2.6	Aromatic L-amino acid decarboxylase deficiency	As above	*DDC*	107930
2.7	Dopamine β-hydroxylase deficiency	Syndrome of autonomic failure characterized by severe orthostatic hypotension, ptosis, but normal sympathetic cholinergic and parasympathetic function	*DBH*	223360
2.8	Monoamine oxidase-A deficiency	Episodic facial flushing, headache, diarrhea, borderline mental retardation and psychiatric symptoms, including impulsive aggression and inappropriate sexual behavior	*MAOA*	309850

2.3 Treatment

No.	Gene symbol	Medication	Dosage (mg/kg per day)	Dose/day (*n*)
2.1	*EPD, PDE*	Pyridoxine	5–30	1
2.2	*PNPO*	Pyridoxal phosphate	10–50	3
2.3		Folinic acid	3–5	3
2.4	*GLRA1 GLRB*	Clonazepam	0.1[a]	3

[a] Start dose in infants is 0.25 mg; gradually increase to maintenance of 0.1 mg/kg per day

Dangers/Pitfalls

1. Both pyridoxine and pyridoxal phosphate may cause apnoea and prolonged cerebral depression after the initial dose (Baxter 2001; Clayton et al. 2003). Resuscitation equipment and intensive care facilities should be available.
2. Pyridoxine-responsive seizures may be heterogeneous in their presentation, and sometimes idiopathic epilepsies respond to treatment with pyridoxine. Typical patients present with an intractable seizure disorder within the first 2 days of life, the latest within 28 days. There are, however, three atypical presentations: (1) late onset, i. e., later than 28 days; (2) neonatal onset, but with an initial response to conventional anticonvulsant therapy; (3) neonatal onset with initially negative, but a later sustained positive response to pyridoxine. Because of these, one recommendation is that all patients with "difficult-to-treat" seizures starting before 2 years should have a trial of pyridoxine (usually given orally).
3. There is no universal protocol for a pyridoxine trial. The dose of pyridoxine required is variable and higher doses may be necessary to control seizures, at least initially. In classic cases we suggest a starting dose of 100 mg intravenously. If there is no response within 24 h, the dose should be repeated (and possibly increased up to 500 mg in total) before being sure about pyridoxine nonresponsiveness. If there is uncertainty about at least a partial response, pyridoxine should be continued at 30 mg/kg per day for 7 days before final conclusions are drawn.
4. Doses of folinic acid (Hyland et al. 1995), pyridoxine, and pyridoxal phosphate (Baxter 2001; Clayton et al. 2003) all need to be increased and adjusted to body weight during growth. Patients with these defects require lifelong supplementation. Obvious criteria to increase the doses are breakthrough seizures.
5. Neither pyridoxine nor pyridoxal phosphate will reverse preexisting brain damage caused by late diagnosis or treatment. Neurological disability (including seizures) requires treatment in its own right.
6. In hyperekplexia, duration of treatment is unclear and should be individually determined. One approach is to treat until stable walking is achieved and then slowly withdraw. Risks and benefits of treatment should be carefully reviewed as long as the patient continues treatment. Startle is reduced, but not stiffness usually.
7. Neurological disability needs treatment in its own right.

Sodium valproate may also be helpful in hyperekplexia. Vigabatrin has also been suggested but has been found not to be of benefit to adults with dominantly inherited hyperekplexia (Tijssen et al. 1997).

No.	Gene symbol	Medication	Dosage (mg/kg per day)	Dose/day (*n*)
2.5	*TH*	Levodopa (L-dopa) plus	1–10	2–6
		carbidopa	10% or 25%[a]	2–6
2.6	*AADC*	Bromocriptine or	0.25–0.5	1–2
		pergolide	4 mg/day[b]	2
		Trihexyphenidyl	Up to 10	3
		Tranylcypromine	8 mg/day[b]	2
	DβH	DL-Dihydroxyphenylserine	250–500 mg/day[b]	2–3
	MAO	See Alternative Therapies/Experimental Trials		

[a] Percentage of levodopa dose; use 25% with total daily dose levodopa less than 400 mg, otherwise 10%

[b] Reported doses used

Dangers/Pitfalls

1. L-Dopa/carbidopa/5-hydroxytryptophan therapy should be introduced slowly and increased in steps of not more than 1 mg/kg over days or weeks.
2. Changes in dopamine receptor density can cause difficulties with treatment. Receptor hypersensitivity in early diagnosed, severe cases means that treatment with cocareldopa should start at very low doses (0.25–0.5 mg levodopa/kg per day) given frequently up to 6 times a day. Receptor downregulation in late-diagnosed severe forms means that treatment with cocareldopa in the maximally tolerated dose up to 10 mg levodopa/kg per day should be maintained for as much as 6 months before deciding it is unhelpful.
3. L-Dopa/carbidopa/5-hydroxytryptophan therapy may reduce CSF folate (5′-methyltetrohydrofolate in CSF is the major transport species for the brain folate pool and is utilized by the single carbon transfer pathway to methylate L-dopa to 3-*O*-methyl-dopa). Determine 5-methyltetrahydrofolate in CSF. Consider folinic acid (5-formyltetrahydrofolate) substitution (10–20 mg/day). This may occur "naturally" in AADC deficiency, again requiring folate supplementation (Surtees and Hyland 1990).
4. In AADC deficiency dopamine agonists can produce dyskinesia and increased irritability, and the dose needs to be carefully titrated.
5. The dose of trihexyphenidyl should start at 1 or 2 mg three times a day. The dose is then increased by 1 or 2 mg/day each week until one of three possibilities occur: (1) the child's condition improves; (2) troublesome side-effects occur (dry eyes or mouth, or gastrointestinal disturbance most commonly); or (3) a limit of 10 mg/kg per day is reached.

2.4 Alternative Therapies/Experimental Trials

No.	Gene symbol	Medication	Dosage (mg/kg per day)	Dose/day (*n*)
2.5	*TH*	Selegiline	0.1–0.3	2–3
		Entacapone	30	2
		Bromocriptine	0.25–0.5	1
2.6	*AADC*	Pyridoxine	$\leq$ 200	3
		L-Dopa	$\leq$ 60	3
2.8	*MAO*	Cyproheptadine hydrochloride	Unreported	
		Sertraline hydrochloride	Unreported	

Dangers/Pitfalls

1. Adjunctive treatment with a MAO-B inhibitor such as selegeline, COMT inhibitor such as entacapone, and dopamine agonists such as bromocriptine may be necessary in TH. When introducing a MAO-B inhibitor or a COMT inhibitor, L-dopa should be reduced by approximately 50–30%.
2. Pyridoxine is a natural cofactor of AADC. In most patients, no sustained clinical or biochemical effect is achieved. In one family, in whom kinetic studies showed the mutation to decrease the binding affinity for the substrate, an improvement was achieved by combined therapy of L-dopa, without carbidopa, and pyridoxine.
3. Sertraline hydrochloride should be introduced slowly because of the risk of causing the serotonin syndrome.

2.5 Follow-up/Monitoring

■ Defects in Pyridoxine Metabolism

There is some evidence that lower doses of pyridoxine, whilst controlling seizures, may allow the development of cognitive impairment. Serial cognitive assessment is recommended. High doses of pyridoxine carry the risk of developing skin photosensitivity and a peripheral sensory neuropathy, which must be weighted against the anticipated neurodevelopmental benefit. Doses up to 1 g/day can be regarded as safe in older children.

2.4 Hyperekplexia

The condition is not entirely benign, because of episodes of apnea with the possibility of death as well as repeated falls. The attacks can be prevented by sudden flexion of the head and limbs. During infancy there is the necessity of constant supervision, including apnea monitoring.

2.5 Tyrosine hydroxylase and aromatic – L-amino acid decarboxylase deficiency

Because of intolerable side-effects, mainly chorea, only very small doses of L-dopa may initially be tolerated. In such patients L-dopa can only be increased very slowly, sometimes over several years. During the 1st years of life, paroxysmal episodes with the possibility of death can occur.

The central pathophysiological mechanism is dopamine deficiency in the brain, which can be best assessed by following metabolite concentrations by consecutive lumbar punctures. In individual patients, serum prolactin concentrations may be used as an appropriate functional parameter of dopamine deficiency and to tailor therapy, allowing a reduction in lumbar punctures (Birnbacher et al. 1998). Determination of catecholamines and their products in urine are useless.

CSF investigations[a]	Age	Frequency	Comments
5-HIAA	< 1 year	Every 4–8 weeks	Close to normal ranges
HVA Folates	> 1 year	Monthly to yearly	Close to normal ranges

[a] Lumbar puncture in the morning before medication is given

2.7 Dopamine β-hydroxylase deficiency

Treatment is adjusted clinically to disappearance of orthostatic hypotension. In MAO, treatment is monitored clinically by improvement of symptoms as well as fall of serotonin levels in whole blood.

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3 Disorders of GABA, Glycine, Serine, and Proline

Jaak Jaeken, Tom J. de Koning

3.1 Introduction

Only for three of the known defects in the metabolism of the amino acids GABA, glycine, serine, and proline has a more-or-less efficient treatment been reported: the GABA catabolic defect, succinic semialdehyde dehydrogenase deficiency (vigabatrin, causing substrate depletion by inhibition of GABA transaminase); the glycine catabolic defect, nonketotic hyperglycinemia (diet combined with benzoate and an *N*-methyl-D-aspartate, NMDA, receptor blocker); and 3-phosphoglycerate dehydrogenase deficiency (serine supplementation, in some patients to be associated with glycine supplementation).

No treatment has as yet been attempted in Δ^1-pyrroline-5-carboxylate (P5CS) synthase deficiency; and the remaining six known defects probably have no clinical significance except for prolidase deficiency.

3.2 Nomenclature

No.	Disorder	Definitions/comment	Gene symbol	OMIM No.
3.1	GABA transaminase (GT) deficiency	Increased GABA and β-alanine in body fluids particularly in CSF	*ABAT*	137150
3.2	Succinic semialdehyde dehydrogenase (SSD) deficiency	Increased γ-hydroxybutyric acid in body fluids	*ALDH 5A1*	271980
3.3	Glycine cleavage system (GCS) deficiency (nonketotic hyperglycinemia)	Increased glycine in body fluids particularly in CSF		
	P(pyridoxal phospate-containing) protein		*GCSP*	238300
	H (lipoid acid-containing) protein		*GCSH*	238330
	T (tetrahydrofolate-requiring) protein		*GCST*	238310
3.4	3-Phosphoglycerate dehydrogenase (PGDH) deficiency	Decreased serine (and to a variable extent glycine) in fasting plasma and in CSF	*PHGDH*	601815

No.	Disorder	Definitions/comment	Gene symbol	OMIM No.
3.5	Δ^1-Pyrroline-5-carboxylate synthase (P5CS) deficiency	Decreased proline, ornithine, citrulline, and arginine in plasma	*PYCS*	138250
3.6	Proline oxidase deficiency (hyperprolinemia type 1)	Increased proline in body fluids	*PRODH*	239500
3.7	Δ^1-Pyrroline-5-carboxylate dehydrogenase (P5CDH) deficiency (hyperprolinemia type 2)	Increased proline and Δ^1-pyrroline-5-carboxylate in body fluids	*P5CDH*	239510
3.8	Prolidase deficiency	Increase of iminopeptides in urine	*PEPD*	170100
3.9	Hydroxyproline oxidase deficiency	Increase of hydroxyproline in body fluids		237000
3.10	Sarcosine dehydrogenase deficiency	Increase of sarcosine in body fluids	*SARDH*	268900
3.11	Iminoglycinuria	Increase of glycine, proline and hydroxyproline in urine		242600

3.3 Treatment

3.2 Succinic semialdehyde dehydrogenase deficiency

Vigabatrin, 50–100 mg/kg per day (divided into two daily doses) (Jaeken et al. 1989). This therapy has shown inconsistent results and may have serious side-effects (see below). The associated epilepsy may be controlled by this drug; however, in this condition worsening of epilepsy has also been reported.

3.3 Glycine cleavage system deficiency (nonketotic hyperglycinemia)

Two clinical presentations are observed, the severe neonatal form and a late-onset form (Hamosh and Johnston 2001). In the severe neonatal form, symptoms occur in the 1st days of life, with hypotonia, seizures, coma, and apnea requiring artificial ventilation. Some patients have structural abnormalities of the brain.

Whether treatment of the biochemical abnormalities should be initiated needs to be discussed in detail with the parents, because this condition has a very poor prognosis, with 30% of patients dying early despite intensive care treatment. Those who survive the neonatal period show no psychomotor development and usually live not longer than a few years (Hamosh and Johnston 2001). Treatment is aimed at reducing seizure frequency with moderate protein restriction (1.5–2 g/kg BW per day), in combination with sodium benzoate (250–750 mg/kg BW per day), aiming to normalize plasma glycine levels (100–250 µM) with plasma benzoate levels below 2000 µM. Folinic acid should be administered (15 mg/day).

If control of seizures is insufficient, an NMDA receptor antagonist should be added (such as dextromethorphan, 3.5–22.5 mg/kg BW per day).Great individual differences occur in dextromethorphan metabolism, and this should be taken into account when using dextromethorphan. Biochemical correction and reduction in seizure frequency does not prevent severe psychomotor retardation and spastic tetraplegia. Spontaneous respiration and reduction of apneas usually occurs after 2–3 weeks and should not be interpreted as success of the treatment or a good prognostic sign.

For patients with late-onset forms and psychomotor retardation, abnormal behavior, seizures, or a movement disorder, the same treatment regimen as in the neonatal form can be applied. In these forms, other NMDA receptor antagonists than dextromethorphan have been used with success (Wiltshire et al. 2000)

3.4 Phosphoglycerate dehydrogenase deficiency

3-Phosphoglycerate dehydrogenase deficiency is a severe disorder affecting the central nervous system. Patients present with congenital microcephaly, severe psychomotor retardation, and seizures. The seizures show a poor response to antiepileptic drugs. Treatment with amino acids is primarily aimed at control of seizures and improvement of general well-being and growth. Even for patients diagnosed after the 1st year of life, seizure control can be very satisfactory with amino acid therapy, but has not resulted in significant improvement of psychomotor development (de Koning et al. 2002). For patients diagnosed in the 1st year of life, some amelioration of psychomotor development has been reported, and this underlines the need for early diagnosis and treatment. Fetal amino acid therapy for 3-phosphoglycerate dehydrogenase deficiency is discussed in the section Alternative Therapies/Experimental Trials.

Treatment consists of oral L-serine supplementation (400–650 mg/kg BW per day in 3 doses/day) aiming at normalization of CSF L-serine levels. If seizures persist glycine should be added (up to 200 mg/kg BW per day in 3 doses). Alterations of CSF amino acid composition have been reported at L-serine dosages above 650 mg/kg BW per day combined with glycine. For this reason 650 mg/kg BW per day seems a safe upper limit until additional data becomes available.

Dangers/Pitfalls

1. The most frequent side-effect of vigabatrin is visual field defects, which occur in about 30% of patients after several months to years and seem to be irreversible.
2. Accidental overdosing of sodium benzoate has been reported and causes vomiting, acidosis, and decreased consciousness (up to coma). Thus whenever doses of sodium benzoate > 350 mg/kg BW per day are employed or there is an unexpected decrease in consciousness, serum benzoate levels should be checked (should be below 2000 μM).
3. CSF amino acid analysis is the preferred diagnostic method and plasma can only be used for diagnosis after an overnight fast. The diagnosis of 3-phosphoglycerate dehydrogenase deficiency can be missed on non-fasting plasma samples. Amino acids are well tolerated and in only one patient, aged 2 months, was serine therapy (500 mg/kg BW per day) associated with acoustic startles and myoclonias. Lowering the dose (400 mg/kg BW per day) resulted in cessation of myoclonias, but did not prevent the patient from developing seizures on this lower dose of L-serine. Lowering L-serine has been associated with the onset of seizures in one patient (Hausler et al. 2001), and cessation of L-serine during an episode of gastroenteritis also resulted in the reappearance of seizures (Pineda et al. 2000). In two patients, including the patient who received fetal treatment, severe dental caries occurred, which, according to the parents, was related to the use of amino acids.

3.4 Alternative Therapies/Experimental Trials

■ *3.2 Succinic semialdehyde dehydrogenase deficiency*

Gamma-hydroxybutyric acid receptor antagonists have been shown to lead to significant lifespan extension in SSD-deficient mice (Gupta et al. 2002).

● *3.4 3-Phosphoglycerate dehydrogenase deficiency*

Fetal treatment of this disorder has been attempted in one case. The mother of an affected fetus was treated with L-serine during pregnancy from 27 weeks onwards. The child, aged 3 years, shows a normal psychomotor development and head growth. Giving L-serine before 20 weeks of pregnancy is not recommended, because of lack of data on possible adverse affects of L-serine on the fetus (de Koning et al. 2004).

3.5 Follow-up/Monitoring

3.2 Succinic semialdehyde dehydrogenase deficiency

- Clinical monitoring: 3–6 monthly

3.3 Glycine cleavage system deficiency

- Clinical monitoring: 1–3 monthly
- Biochemical monitoring: plasma glycine (aim at control range) and benzoate (aim at levels below 2,000 μM): 1–3 monthly

3.4 3-Phosphoglycerate dehydrogenase deficiency

- Clinical monitoring: 3–6 monthly
- Biochemical monitoring: CSF amino acids, according to clinical condition, but should be more frequent in infants than in older children. Monitoring L-serine therapy on fasted plasma samples is difficult in newborns and infants given the frequency of meals and the possible interference with dietary serine. One needs to realise that in the 1st year of life serine concentrations in CSF are higher than in later years (Gerrits et al. 1989) and treatment should aim at these higher concentrations. No adverse effects of amino acid therapy on internal organs were documented up to now, but some caution is warranted regarding kidney function because of the large amounts of amino acid ingested (de Koning et al. 2000).

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4 Disorders of Tyrosine Degradation

Elisabeth Holme

4.1 Introduction

The aim of this chapter is to summarize treatment of disorders of tyrosine degradation. The tyrosine degradation pathway includes five enzymatic reactions, and inherited disorders have been identified in four of these enzymes.

The character of the different disorders is quite different with respect to the pathogenic mechanisms and the organs affected. The pathogenesis of the disorders is either related to the high tyrosine level as such or to accumulation of toxic metabolites of tyrosine degradation.

In *tyrosinemia type I*, the hypertyrosinemia is a secondary phenomenon due to the liver damage caused by accumulation of fumarylacetoacetate and its derivatives. Dietary restriction of tyrosine and phenylalanine alone does not reduce production of toxic tyrosine metabolites to a low enough level to prevent progressive liver and kidney disease, although it may alleviate acute symptoms. For a decade the primary treatment has been based on inhibition of tyrosine degradation at the level of 4-hydroxyphenylpyruvate dioxygenase by nitisinone (NTBC). The aim of the treatment is to block the production of fumarylacetoacetate and its derivatives succinylacetone and succinylacetoacetate. The block of tyrosine degradation leads to an increase in the tyrosine level, which has to be controlled by a strict diet to prevent adverse effects of the high tyrosine level. The treatment of tyrosinemia type I includes treatment of acute liver failure of infancy often in combination with sepsis, acute porphyria-like neurological crisis, hypophosphatemic rickets, and liver transplantation due to liver failure or to hepatocellular carcinoma. Management of these conditions is beyond the scope of this chapter, in which only the specific treatment of the metabolic disorder is covered.

Treatment of *tyrosinemia type II and III* is confined to reduction of tyrosine levels by dietary restriction. In tyrosinemia type II, the disorder with the highest tyrosine level, reduction of the tyrosine level is essential to heal and to avoid recurrent corneal and skin lesions, which are directly caused by the high tyrosine level. This requires a moderate reduction of tyrosine intake and might be achieved by protein restriction alone. In addition to these symptoms, tyrosinemia type II is often associated with neurological symptoms and various degrees of mental retardation and intellectual deficiency, as is tyrosinemia

type III, in which there are no other symptoms. There is no evidence that these symptoms can be improved or prevented by a further reduction of the tyrosine level, but, when these cases are picked up by neonatal screening or diagnosed in infancy, it seems appropriate to use a more strict control of the tyrosine level during early childhood. Strict dietary control may also be indicated in pregnancy of women with these disorders, since the impact of high tyrosine levels on the developing brain is not known.

Hawkinsinuria is believed to be caused by an incomplete conversion of 4-hydroxyphenylpyruvate to homogentisate by 4-hydroxyphenylpyruvate dioxygenase. The accumulated intermediary is detoxified by glutathione, which may be depleted resulting in 5-oxoprolinuria. The enzyme defect has not been proven and the cause of this disorder is unknown. There is a reduced tolerance to protein during infancy, but the condition requires no treatment after that age.

Alkaptonuria is caused by accumulation of homogentisate, resulting in ochronosis and destruction of connective tissue with progressive spinal, joint, and heart disease starting in adult life. Traditional treatment of alkaptonuria is based on protein restriction, to reduce homogentisate production, and ascorbate treatment, to prevent oxidation and pigment formation from homogentisate. During childhood such treatment might be successful, but there are obvious long-term difficulties with compliance. There is no evidence of long-term beneficial effects. In a couple of adult cases, it has been shown in a short-term trial that a low dose of nitisinone is effective in reducing homogentisate production. Nitisinone treatment results in an increase in tyrosine concentration, some restriction of dietary protein would probably be required. The clinical effect of reducing homogentisate production has so far not been studied and a pertinent question is whether the start of treatment can be postponed until symptoms occur.

4.2 Nomenclature

No.	Disorder	Definitions/ comment	Gene symbol	OMIM No.
4.1	Tyrosinemia type I (fumarylacetoacetase, FAH)	HTI	*FAH*	276700
4.2	Tyrosinemia type II (tyrosine aminotransferase, TAT)	HTII	*TAT*	276600
4.3	Tyrosinemia type III (4-hydroxyphenylpyruvate dioxygenase, HPD)	TIII	*HPD*	276710
4.4	Hawkinsinuria (unknown)			140350
4.5	Alkaptonuria (homogentisate dioxygenase, HGD)		*HGD*	203500

4.3 Treatment

4.1 Tyrosinemia type I

	Protein requirement	Phe + Tyr tolerance	Natural protein	Tyr + Phe-free AAM	Target	Aim
Diet[a]	See disorder 1.1.1 PAH-deficiency	30–100 mg/kg per day	≈ 0.4–1 g/kg per day	Equivalent to 0.5–2 g protein/kg per day	Plasma tyrosine 250–500 µmol/l in an otherwise normal amino acid profile	To reduce the load on the tyrosine degradation pathway To minimize the risk for possible adverse effects of high tyrosine concentration[b]
Nitisinone[e]	1–1.5 mg/kg per day divided into two doses				30–60[c] µmol/day	To block tyrosine degradation at the level of 4-hydroxyphenylpyruvate dioxygenase to get no production of fumarylacetoacetate and its metabolites to get a normal liver function and to minimize the risk for HCC development. To heal the renal tubular defect and rickets. To cure and prevent neurological crisis

[a] After initiation of therapy in acute cases there is generally a period of rapid catch-up growth. During this period there is an increased tolerance/requirement for protein including tyrosine and phenylalanine
[b] It might be acceptable with higher tyrosine levels in older children and adults
[c] In a few cases an even higher nitisinone concentration is required to normalize succinylacetone and 5-aminolevulinic acid excretion
[d] Signs of treatment failure in acute cases, which may require a liver transplantation, are no signs of improvement with respect to the coagulopathy within a week and increasing jaundice
[e] NTBC (2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione)

4.2 Tyrosinemia type II

	Protein requirement	Phe + Tyr tolerance	Natural protein	Tyr + Phe free AAM	Target[a]	Aim
Diet	See 1.1.1 PAH deficiency	30–150 mg/kg per day	≈ 0.4–1.5 g/kg per day	Equivalent to 0.5–2 g protein/kg per day	Plasma tyrosine 250–800 µmol/l in an otherwise normal amino acid profile	To resolve and prevent occurrence of corneal and skin lesions.

[a] Eye symptoms rarely occur at tyrosine concentration below 800 µmol/l, but because of the uncertainty of possible adverse effects on the developing brain it seems reasonable to aim at a concentration at least below 500 µmol/l during infancy and early childhood

4.3 Tyrosinemia type III

	Protein requirement	Phe + Tyr tolerance	Natural protein	Tyr + Phe-free AAM	Target[a]	Aim[a]
Diet	See 1.1.1 PAH deficiency	30–100 mg/kg per day	≈ 0.4–1.5 g/kg per day	Equivalent to 0.5–2 g protein/kg per day	Plasma tyrosine 250–800 µmol/l in an otherwise normal amino acid profile	To avoid possible adverse effects of tyrosine

[a] Eye and skin lesions have not been described in patients with HTIII, although tyrosine up to 1300 µmol/l has been observed. The only reason for dietary treatment is because of the uncertainty of possible adverse effects on the developing brain, and it seems reasonable to aim at a concentration below at least 500 µmol/l during infancy and early childhood

4.4 Hawkinsinuria

Symptoms have occurred after weaning and return to breastfeeding, or a diet restricted in phenylalanine and tyrosine may be required during infancy. No treatment is required after infancy.

4.5 Alkaptonuria

There is no evidence for long-term effects of ascorbate and/or protein restriction treatment, but improvement of symptoms has been reported with treatment with ascorbate 0.5–1 g/day and protein restricted to the minimum requirement for age (see disorder 1.1.1, PAH deficiency). Experimental treatment with nitisinone 0.05–0.1 mg/kg BW per day has been tried.

4.4 Follow-up/Monitoring

4.1 Tyrosinemia type I

Specific biochemical markers	Amino acid profile	Urine and plasma succinylacetone	RBC porphobilinogen synthase 5-aminolevulinate (urine)	α-Fetoprotein	Urinary amino acids/renal succtubular markers	Nitisinone
	1–2 times weekly until stabilization, then gradual increasing intervals to match the other metabolic controls	+1 week +1 month +2 months +4 months +6 months +9 months +12 months	+1 week +1 month +2 months +4 months +6 months +9 months +12 months	+1 week +1 month +2 months +4 months +6 months +9 months +12 months	+1 week +1 month +2 months +4 months +6 months +9 months +12 months	
Target	Tyrosine concentration of 250–500 µmol/l in an otherwise normal profile	Precipitous disappearance of urinary succinylacetone (< 0.3–0.1 mmol/mol creatinine). Continuous decline of plasma succinylacetone until normalization at 2–4 months depending on the initial concentration	Normalization within 1–2 months	There might be an initial increase due to rapid regeneration of liver tissue. After that there should be a steady decline resulting in normalization during the 2nd year of treatment	Signs of tubular disease disappear within the 1st month in short-standing disease, but may not heal completely in long-standing cases	Minimum concentration of 30 µmol/l. Higher concentration as indicated by incomplete biochemical response

In stable older patients, it may be adequate with biochemical monitoring twice a year. However, I consider it important with continuous, frequent monitoring of serum α-fetoprotein for early detection of HCC in addition to regular monitoring by ultrascan and other imaging techniques as required.

Gradual normalization of liver function is expected to occur during the first 6 months of treatment.

Growth and development should be followed and are expected to be normal.

Eye symptoms should be checked with a slit-lamp investigation by an ophthalmologist to reveal tyrosine-induced corneal lesions.

4.2 Tyrosinemia type II

Amino acid profile as for tyrosinemia type I. The corneal lesions are expected to be alleviated within a week after initiation of therapy. Skin lesion are expected heal within a few months.

Regular follow-up of growth and development.

4.3 Tyrosinemia type III

Amino acid profile as for tyrosinemia type I.

Regular follow-up of growth and development.

4.4 Hawkinsinuria

If a tyrosine and phenylalanine restricted diet is introduced should the amino acid profile be checked monthly. The 5-oxoprolinuria should normalize rapidly and remain normal after protein restriction.

There should be a normal growth and development.

4.5 Alkaptonuria

If protein restriction is introduced there should be regular follow-up of the amino acid profile and growth.

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5 Disorders of Histidine Metabolism

Nenad Blau

5.1 Introduction

Histidinemia, urocanase deficiency, and formiminotransferase deficiency are harmless disorders, although treatment might be considered in a histidinemic infant who is symptomatic (< 1%; Levy et al. 2001). A few patients with speech impairment were found to be mentally retarded. It appears that clinical abnormalities in these patients are coincidental.

5.2 Nomenclature

No.	Disorder	Definitions/comment	Gene Symbol	OMIM No.
5.1	Histidinemia	Histidine ammonia-lyase deficiency	*HAL*	235800
5.2	Urocanase deficiency			276880
5.3	Formiminotransferase deficiency		*FTCD*	229100

5.3 Treatment and Follow-up

Generally no treatment required.

■ Symptomatic Patients

5.1	Histidinemia	Low-His diet
5.3	Formiminotransferase deficiency	Folinic acid, 15 mg/day

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6 Disorders of Leucine Metabolism

Rebecca S. Wappner, K. Michael Gibson

6.1 Introduction

Of the disorders of leucine metabolism, only maple syrup urine disease (MSUD) is associated with elevated body fluid levels of the branched-chain amino acids (BCAA), namely leucine, isoleucine, and valine. Due to irreversible steps early in the metabolism of the BCAA, elevated levels of these amino acids do not occur in those disorders that result from blocks in the pathways distal to the site of MSUD. Rather, the disorders are associated with organic acidemias/acidurias.

Severe forms of the disorders of leucine metabolism present as acute, overwhelming metabolic illness in the neonatal period, often during the 1st week of life. Other milder or variant forms may be episodic and might not become symptomatic until late childhood or even adult life. Also, some patients are asymptomatic and identified only through family studies or by newborn screening.

Maple syrup urine disease results from deficient activity of the branched-chain α-ketoacid dehydrogenase complex (BCKDC). During episodes of metabolic decompensation, the BCAA and their corresponding branched-chain α-ketoacids (BCKA) accumulate. At such times, affected patients have the odor of maple syrup in body fluids and cerumen from 2-oxo-3-methylvalerate, after which the disorder is named. The BCKDC consists of three catalytic components (E1, E2, and E3) encoded by four different genetic loci. The E1 component is a thiamine pyrophosphate-dependent decarboxylase comprised of two subunits, α and β, which are encoded by two separate loci. The E2 component is a dihydrolipoyl acyltransferase and the E3 component a lipoamide dehydrogenase. A regulatory BCKDC-specific kinase and phosphatase are also involved but not yet fully characterized. Mutations in all four of the catalytic loci have been associated with clinical disease.

Five *clinical forms* of MSUD exist, which are differentiated by the amount of residual enzymatic activity, age and severity of onset, and responsiveness to thiamine, a cofactor for the BCKDC. *Classic MSUD* patients present with poor feeding, lethargy, abnormal movements, and a progressive encephalopathy during the 1st week of life. Most patients have less than 2% of normal BCKDC specific activity; they are not responsive to thiamine administration.

Intermediate MSUD has similar symptoms, but with a later, variable age of onset. Patients have between 3 and 30% of normal residual specific activity of the BCKDC and they are not responsive to thiamine. *Intermittent MSUD* is characterized by episodes of ataxia and ketoacidosis that are associated with intercurrent illnesses or increased protein intake. Affected patients have between 5 and 20% of normal residual specific activity of the BCKDC and are not responsive to thiamine. Patients with *thiamine-responsive MSUD* have between 2 and 40% of normal residual specific activity of the BCKDC and show varying degrees of correction of their metabolic abnormalities in response to pharmacologic doses of thiamine. *Deficiency of the E3 component* results in decreased activity of the BCKDC (0–25% of normal) along with reduced activity of the pyruvate dehydrogenase complex and the 2-oxoglutarate dehydrogenase complex, because the E3 component is common to all three mitochondrial complexes. These patients have a combination of symptoms and biochemical findings for all three of the individual deficiencies and present during infancy with acidosis and a progressive encephalopathy. Although all three BCAA are elevated in body fluids, the pathophysiology of all forms of MSUD is thought to be related to the elevated levels of leucine.

With advances in the molecular pathology of MSUD, a certain degree of molecular genotype-clinical phenotype correlation has emerged. Patients with E1α and E2 mutations have varying clinical presentations (classic, intermittent, intermediate), depending upon the specific mutation involved. To date, all reported patients with E1β mutations have had the severe, classic clinical form of the disorder. All reported thiamine-responsive patients have had E2 mutations. The most frequent mutation, the E1α mutation Y393N, is associated with a severe classic presentation and found not only in the Mennonites, among whom it is common, but also in the general population in North America. Another common E1α mutation, G241R, is associated with intermediate clinical disease in the Hispanic-Mexican population. In that specific mutations have been shown to be associated with a certain type of clinical disease, determining the exact mutation involved through mutational analysis will help guide clinical management for the individual patient, especially in regard to the need for thiamine supplementation and the degree of restriction of dietary natural protein necessary to control the disorder (Chuang and Shih 2001; Morton et al. 2002).

Classic isovaleric acidemia (IVA) results from deficient activity of isovaleryl-CoA dehydrogenase and patients present with acute, neonatal metabolic disease or with chronic, intermittent episodes during the 1st years of life. Affected patients have the odor of "sweaty feet." In addition to marked ketoacidosis, they may have bone marrow suppression and significant secondary hyperammonemia. Reduced activity of isovaleryl-CoA dehydrogenase also occurs as part of multiple acyl-CoA dehydrogenase deficiency, which is discussed with the disorders of mitochondrial fatty acid oxidation (Sweetman and Williams 2001; Ogier de Baulny and Saudubray 2002).

Patients with *isolated 3-methylcrotonyl-CoA carboxylase* (3MCCC) *deficiency* often have acute episodes of vomiting, hypotonia, seizures, and coma, accompanied by an "acid" odor. Mutations in either of the loci that encode for the two subunits of the enzyme are clinically indistinguishable. Both mild and severe clinical forms of the disorder have been reported. Still others, detected through newborn screening or family studies, are asymptomatic. Many of the patients detected through newborn screening have had transient elevations of abnormal metabolites suggestive of 3MCCC deficiency. Others do not have the disorder, but have abnormal metabolites from affected mothers with mild forms of the disorder. It is important that the appropriate testing (urine organic acid analysis, enzymatic assay) be done on such infants, and their mothers if indicated, to confirm whether they have the disease prior to placing the infant on a protein-restricted diet (Gibson et al. 1998). 3MCCC deficiency also occurs as part of multiple CoA carboxylase deficiency, which is discussed with the disorders of biotin metabolism in Chap. 7, Disorders of Valine-Isoleucine Metabolism.

Patients with the four types of *3-methylglutaconic aciduria* have varying symptoms. Patients with type I, associated with reduced activity of 3-methylglutaconyl-CoA hydratase, present with a wide spectrum of clinical symptoms, from none to severe neurological impairment or acute acidosis (Sweetman and Williams 2001). The basic enzymatic defect and etiology for the presumed secondary 3-methylglutaconic aciduria in types II, III, and IV is unknown. Type II, also known as Barth syndrome, is an X-linked disorder characterized by skeletal myopathy, dilated cardiomyopathy, short stature, recurrent neutropenia, and mild hypocholesterolemia. Barth syndrome has been associated with the *TAZ* genetic locus at chromosome Xq28, which encodes a protein of unknown function, tafazzin, that is highly expressed in cardiac and skeletal muscle (Barth et al. 1999; Ostman-Smith et al. 1994). Type III, known as Costeff optic atrophy syndrome, presents with a movement disorder in addition to optic degeneration. The syndrome has been linked to the genetic loci OPA3 at chromosome 19q13.2-q13.3 (Costeff et al. 1989; Elpeleg et al. 1994). Type IV, or the unclassified form, is often seen with neurological, peripheral organ, and other metabolic disturbances. Because types II, III, and IV do not involve defects in the leucine pathway, treatment for patients with these forms of the disorder will not be discussed in this chapter.

Patients with *3-hydroxy-3-methylglutaric acidemia* (HMG-CoA lyase deficiency) most often present with neonatal hypoketotic hypoglycemia and acidosis. Milder forms of the disorder also have been reported (Dasouki et al. 1987; Gibson et al. 1988).

The mainstay of treatment with all the disorders is to limit leucine intake while preventing catabolism. With severe forms of the disorders, special medical foods, devoid of leucine or the BCAA, are needed to allow for adequate caloric, protein, and other nutrient intake. Milder forms may only require a reduced natural protein intake. The amount of leucine or BCAA needed for growth and tissue repair is supplied from measured amounts of standard infant formula

in young children and whole cow's milk and table foods in older patients. The amount of natural whole protein tolerated is determined by monitoring parameters such as growth, control of acidosis, blood quantitative amino acid levels, and testing for body protein stores. Protein intake should be adequate to promote normal growth without contributing to uncontrolled disease. The least restrictive dietary approach should be taken in order to avoid overtreatment and BCAA deficiency.

Patients with the severe forms of MSUD (classic, intermediate forms) have a very low tolerance of natural dietary leucine. To control the disorder yet have adequate nutrition, special medical foods devoid of the BCAA are needed, usually for the life of the affected individual (Acosta and Yannicelli 2001; Chuang and Shih 2001; Morton et al. 2002; Strauss and Morton 2003) (Table 6.1).

Table 6.1. Nutritional treatment for severe forms of maple syrup urine disease[a]

Age	Protein requirement[b] (g/kg per day)	Leucine tolerance[c] (mg/kg per day)	Isoleucine intake (mg/kg per day)	Valine intake (mg/kg per day)	Energy requirement[c] (kcal/kg per day)
Neonates	2.5–3.0	50–90	20–50	30–60	120–145
Infants	2.0–3.0	40–80	20–50	30–60	115–145
Young children	1.5–2.0	20–40	5–15	10–30	60–80
Older children and adults	1.0–1.2	5–15	5–15	10–30	40–60

[a] Modified from Strauss and Morton 2003 and Acosta and Yannicelli 2001. These recommendations are only a guide and should be individualized for each patient, based on the severity of their disorder and blood quantitative amino acid levels
[b] Includes protein intake from special medical foods devoid of BCAA plus that from natural whole protein sources
[c] Leucine (milligrams) to kilocalorie ratio of 0.5–0.8 for neonates and infants; ratio of 0.25–0.30 in children and older. Lipids should comprise 40–50% of total calories. Formula concentrations over 0.8 kcal/ml may result in loose stools, diarrhea, and dehydration

Milder forms of MSUD (intermittent, thiamine-responsive) often respond to a lowered natural protein intake of 1.5–2.0 g/kg per day in young infants or 0.6–1.5 g/kg per day in older children and adults. Additional nonprotein calories may be supplied with otherwise complete, protein-free, special medical foods to meet energy requirements. Special low-protein food products, i. e., bread, pasta, cereals, are also available.

Leucine competes with other large, neutral amino acids, including valine and isoleucine, for an L-amino acid transporter-1 (LAT1) that is responsible for carrying the amino acids across cell membranes. By supplying the other amino acids involved in increased concentration, this not only corrects any intracellular deficit of the other amino acids that may have occurred from the elevated leucine levels, but also decreases leucine uptake. Supplements of isoleucine and valine are routinely given with MSUD for this reason, as well as to maintain target blood levels. Additional supplements of glutamine, alanine,

and occasionally of tyrosine, are used. This approach is especially useful in controlling leucine levels in severe forms of MSUD (Strauss and Morton 2003).

In the disorders of leucine metabolism other than MSUD, the toxic metabolites are organic acids and not the precursor amino acid leucine. Treatment is aimed at reducing leucine intake and thereby reducing the organic acid formation, while preventing catabolism. Although control of leucine intake is needed, strict control of blood leucine levels is not as critical as in MSUD. Rather, it is important that overtreatment does not occur and leucine deficiency not develop. For this reason, treatment should employ the least restrictive dietary approach needed for metabolic control (Ogier de Baulny and Saudebray 2002; Sweetman and Williams 2001; Thompson et al. 1990).

With the severe, early onset forms of IVA, 3MCCC deficiency, 3MG1, and HMGCL deficiency, special medical foods devoid of leucine may be needed in order to control the disorder and prevent toxic organic acid accumulation, especially during the neonatal period and early infancy. Many patients with these disorders, however, even some with early onset forms, do not require this restrictive a diet and will respond to a reduction in the intake of natural protein without the need for the special medical food. Two approaches to the initial nutritional management may be taken. Firstly, a lowered natural protein diet may be started, along with supplements of otherwise complete, protein-free, special medical food to meet energy requirements. If the protein requirement for growth cannot be tolerated without organic acid accumulation, then special medical food devoid of leucine is added until growth is established and the disorder controlled. Alternatively, a diet employing special medical foods devoid of leucine may be given initially. As natural protein intake is added and advanced, the growth pattern and degree of control of the disorder are monitored. Assessment of the clinical course and the amount and source of protein intake (natural vs special medical food) are helpful in determining whether the special medical food devoid of leucine needs to be continued or not. As occurs with chronic diseases, including other inborn errors (i. e., PKU, homocystinuria), many of the patients self-discontinue treatment, including the use of special medical foods, during late childhood or early adolescence for various reasons, e. g., odor, taste. Protein-free, otherwise complete special medical foods and special low-protein food products are often needed to supply the caloric requirement of such individuals (Table 6.2).

Table 6.2. Nutritional treatment for severe forms of isovaleric acidemia[a]

Age	Protein requirement[b]	Leucine intake[c] (whole natural protein)	Energy requirement[d]
Neonates	2.5–3.0 g/kg per day	80–150 mg/kg per day	120 (100–145) kcal/kg per day
Infants	2.0–3.0 g/kg per day	50–140 mg/kg per day	115 (95–145) kcal/kg per day
Young children	1.5–2.0 g/kg per day	500–900 mg per day	900–1800 kcal per day
Older children and adults	1.0–1.2 g/kg per day	650–1500 mg per day	1200–3900 kcal per day

[a] Modified from Acosta and Yannicelli 2001. These recommendations are only a guide and should be individualized for each patient, based on the severity of their disorder. Patients with milder forms of the disorder will tolerate a higher leucine intake and may only require a reduced natural protein diet

[b] Includes protein intake from special medical food devoid of leucine plus that from natural whole protein sources

[c] These figures reflect leucine intake if special medical foods devoid of leucine are used and may be too low for some actively growing infants and children

[d] Formula concentrations over 0.8 kcal/ml may result in loose stools, diarrhea, and dehydration

Close, frequent monitoring is needed for those patients on BCAA-, leucine-, or protein-restricted diets. Blood quantitative amino acid measurements should be done 2–4 h after a meal. The results should be available within a few days if not 48 h. Families and local health care personnel can be instructed in obtaining fingerstick dried blood filter paper or whole blood samples for quantitative amino acid measurements, which can be sent from their home or local community to testing laboratories between clinic visits. Changes in dietary recommendations need to be made and communicated to the family promptly after the levels are available. Frequent monitoring is needed in actively growing infants and young children, especially those on restricted diets, in whom increases in nutrient intake may need to be as high as 10% weekly. Using the rate of weight gain (grams per day), an estimate of the weight gain expected over the next week or prior to the next clinical monitoring may be made. The expected increase in weight should be taken into account when determining the amount of increase in nutrient intake needed in young infants so as not to fall behind growth requirements. Persistently low leucine levels can result in decreased appetite, poor feeding, lethargy, poor growth, weight loss, skin rashes, hair loss, and desquamation. With MSUD, deficiency of isoleucine and valine also may occur and result in symptoms similar to those of leucine deficiency. Older patients who discontinue the use of special medical foods yet continue to take a lowered protein intake without supplemental vitamins and minerals are at risk for multiple nutrient deficiencies.

Supplements of L-carnitine are used with the organic acidemias, but not with MSUD, to serve as a means for excretion of abnormal metabolites through the formation of acyl-carnitines and to prevent secondary L-carnitine deficiency. With IVA, glycine may be similarly given to promote the formation and excretion of isovalerylglycine (Fries et al. 1996, Naglak et al. 1988; Sousa et al. 1986). Cofactor therapy is employed with thiamine-responsive MSUD. In general, the remainder of the disorders are not vitamin- or cofactor-responsive. Intake of polyunsaturated omega-3 fatty acids and trace minerals may not be adequate with artificial diets and require supplementation. Those patients on reduced natural protein diets may also need supplements of multivitamin-mineral formulations and calcium.

Plans for sick-day management should be formulated for each patient and the family instructed to make these changes when the first signs of intercurrent illness or loss of metabolic control are noted. Often, the patient will respond to such measures and not progress to overt metabolic decompensation. Home monitoring of urine dinitrophenylhydrazine (DNPH) in MSUD and ketones in IVA may help guide clinical management. Families should be cautioned, however, that dilute urine samples may produce false-negative results. Evaluation of clinical symptoms remains of paramount importance.

Asymptomatic confirmed affected neonates, detected by newborn screening or due to a positive family history prior to clinical symptoms, should be treated as potentially developing an acute episode of metabolic decompensation and started on sick-day management. Intake of natural protein should be added slowly, with close monitoring.

Aggressive treatment is needed for those patients with overwhelming metabolic disease at their initial presentation, which most often occurs in the neonatal period. The patients are also at risk for similar episodes with intercurrent illnesses or increased protein intake for the remainder of their lives. Prevention of cerebral edema and correction of dehydration, hypoglycemia, and acidosis are critical to outcome (Berry et al. 1991; Strauss and Morton 2003; Thompson et al. 1990). Removal of toxic metabolites and reduction of high ammonia levels may require hemodialysis or hemofiltration (Jouvet et al. 2001). Treatment of an episode of acute, severe, metabolic decompensation is at times very difficult to manage, even for those experienced in treating such patients. Consultation with, if not referral to, an experienced center is recommended. Not all infants or children presenting with severe metabolic disease are rescued and survive. Those that do are often mentally and physically handicapped (Kaplan et al. 1991).

In addition to counseling concerning treatment and prognosis, families of affected individuals should receive genetic counseling concerning recurrence risks for subsequent children. Prenatal testing is available for most of the severe forms of the disorders. Carrier testing is variable and often depends upon the availability of DNA mutation analysis.

Other than MSUD and IVA, the remainder of the disorders of leucine metabolism are exceedingly rare and were only recognized and defined after

clinical organic acid determinations became available in the 1970s. The clinical experience in managing these cases is relatively limited and fragmented among the metabolic centers around the world. Thus, the recommendations for treatment, monitoring, and optimum outcome are still being defined. What is presented in this chapter should be considered only a basic guide for where to begin. With the advent of expanded newborn screening, additional cases will be identified, treated early, and hopefully add to our understanding of the pathophysiology of the disorders, and improve treatment and outcomes (Fig. 6.1).

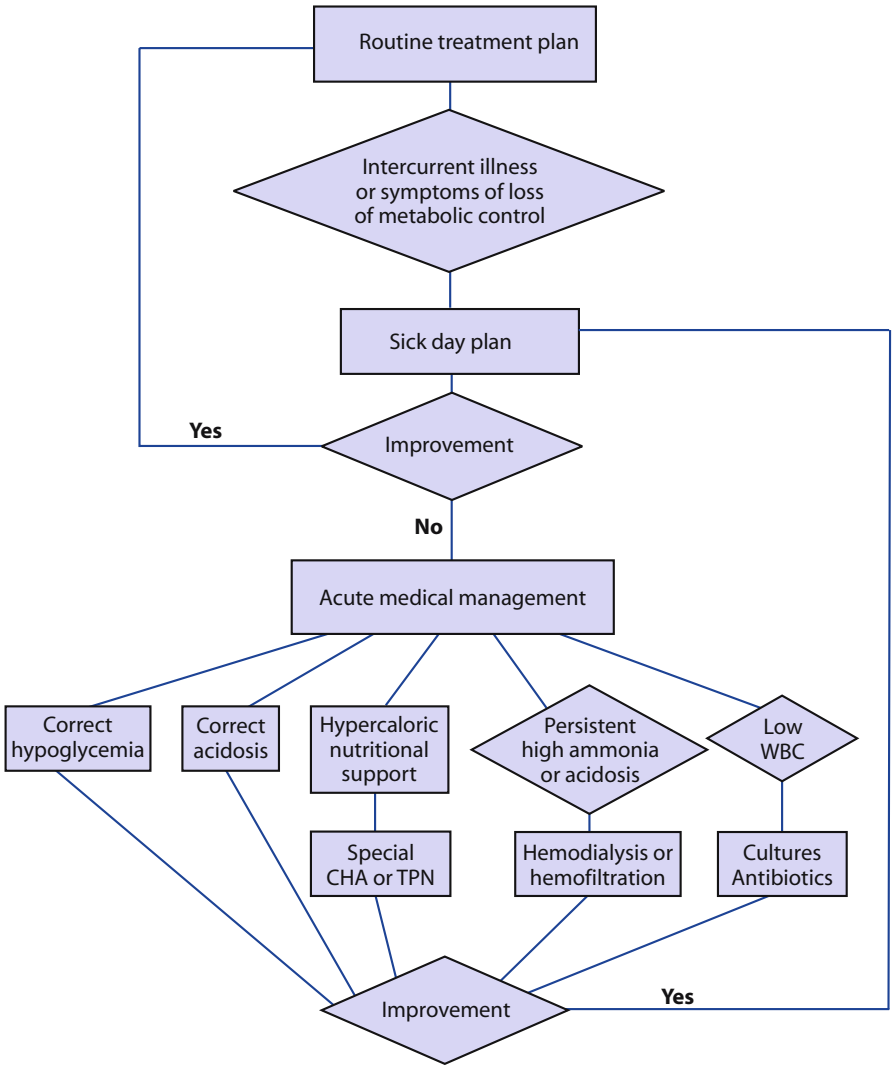

Fig. 6.1. Management of disorders of leucine metabolism

6.2 Nomenclature

No.	Disorder	Definition/comment	Gene symbol	OMIM No.
6.1	Maple syrup urine disease (MSUD; branched-chain α-ketoacid dehydrogenase complex, BCKDC, deficiency)			
6.1.1	Decarboxylase, E1 component α-subunit deficiency (MSUD 1A)	Elevation of all three branched-chain amino acids (BCAA): leucine, isoleucine, and valine Alloisoleucine present Leucine to alanine ratio > 0. 4 Elevated urine branched-chain α-ketoacids (BCKA): 2-oxoisocaproate, 2-oxo-3-methylvalerate, 2-oxoisovalerate, 2-hydroxyisovalerate, 2-hydroxyisocaproate, 2-hydroxy-3-methylvalerate	*BCKDHA*	248600
6.1.2	Decarboxylase, E1 component β-subunit deficiency (MSUD 1B)	See disorder 6.1.1.	*BCKDHB*	248611
6.1.3	Dihydrolipoyl acyl-transferase, E2 component deficiency (MSUD 2)	See disorder 6.1.1	*DBT*	248610
6.1.4	Lipoamide dehydrogenase, E3 component deficiency (combined deficiency of branched-chain α-ketoacid, pyruvate, and α-ketoglutarate dehydrogenase complexes; MSUD 3)	Elevated blood lactate, pyruvate, and alanine along with BCAA. Alloisoleucine present. Elevated urine lactate, pyruvate, 2-oxoglutarate, 2-hydroxyisovalerate, 2-hydroxyglutarate, and BCKA. See also Chap. 27	*DLD*	246900
6.2	Isovaleric acidemia (isovaleryl-CoA dehydrogenase deficiency)			
6.2.1	Classic isovaleric acidemia; isolated isovaleryl-CoA dehydrogenase deficiency (IVA)	Elevated plasma or serum isovaleric acid and urine isovalerylglycine	*IVA*	243500
6.2.2	Part of multiple acyl-CoA dehydrogenase deficiency	See Chap. 14		
6.3	3-Methylcrotonyl-CoA carboxylase (3MCCC) deficiency			
6.3.1	Isolated, biotin-unresponsive 3MCCC deficiency; subunit-1 deficiency (3MCCC1)	Elevated urine 3-methylcrotonylglycine and 3-hydroxyisovaleric acid.	*MCCC1*	210200
6.3.2	Isolated, biotin-unresponsive 3MCCC deficiency; subunit-2 deficiency. (3MCCC2)	See disorder 6.3.1	*MCCC2*	210210
6.3.3	Part of multiple CoA carboxylase deficiency, secondary to biotinidase or holocarboxylase deficiencies	See Chap. 7		

No.	Disorder	Definition/comment	Gene symbol	OMIM No.
6.4	3-Methylglutaconic aciduria, type 1. (3-methylglutaconyl-CoA hydratase deficiency; 3MGI)	Elevated urine 3-methylglutaconic, 3-methylglutaric, and 3-hydroxyisovaleric acids	*AUH*	2650950
6.5	3-Hydroxy-3-methylglutaric aciduria (3-hydroxy-3-methyl-glutaryl, HMG, -CoA lyase deficiency; HMGCL)	Elevated urine 3-hydroxy-3-methyl-glutaric, 3-methylglutaconic, 3-methylglutaric, and 3-hydroxy-isovaleric acids, and occasionally 3-methylcrotonylglycine	*HMGCL*	246450

No.	Symbol	Age	Medication/diet	Dosage	Target plasma amino acid levels
6.1.1–6.1.3	MSUD 1A MSUD 1B MSUD 2 (severe forms)	All ages	Lowered BCAA diet[a] Isoleucine and valine supplements[b] Glutamine/alanine NaCl Thiamine[c]	 Adjusted to blood levels 100–250 mg/kg per day each 3–5 mEq/kg per day 10 mg/kg per day (50–300 mg/day)	Leucine 150–300 μM Isoleucine 150–300 μM Valine 200–400 μM[f]
6.1.1, 6.1.3	MSUD 1A MSUD 2 (milder forms)	All ages	Reduced natural protein diet[d] Multivitamin with minerals daily Thiamine[c]	 10 mg/kg per day (50–300 mg/day)	Within normal limits for age for the laboratory
6.1.3	MSUD 2 (thiamine-responsive form)	All ages	Reduced natural protein diet[d] Multivitamin with minerals daily Thiamine	 10 mg/kg per day (50–1000 mg/day)	Within normal limits for age for the laboratory
6.1.4	MSUD 3 (combined dehydrogenases deficiency)	All ages	See disorders 6.1.1–6.1.3 (severe forms)[e]		See disorders 6.1.1–6.1.3

[a] Special medical food devoid of the branched-chain amino acids

[b] As 10 mg/ml solutions. Leucine supplements also may be needed during the 1st year of life

[c] Thiamine given until molecular genotype known; not given if the patient is Mennonite

[d] Protein intake of approximately 1.5–2.0 g/kg body weight/day in young infants and 0.6–1.5 g/kg body weight/day in older children and adults

[e] Attempts at treatment with diet and cofactors have been unsuccessful in preventing CNS deterioration; thiamine not given

[f] Target ratios of approximately 1:1:2 for leucine, isoleucine, and valine, respectively

6.3 Treatment

■ *6.1 Branched-chain α-ketoacid dehydrogenase complex deficiency*

6.1.1 MSUD 1A
6.1.2 MSUD 1B
6.1.3 MSUD 2
6.1.4 MSUD 3

● *6.1.1–6.1.4 Treatment – Comments/Additions*

1. Intake of whole protein and supplements of individual amino acids are adjusted based on plasma quantitative amino acids levels to meet the target levels.
2. All patients with MSUD 1A, MSUD 1B, and MSUD 2 should be given a trial of thiamine therapy for at least 3 weeks, or until the molecular genotype is known. Patients homozygous for the Y393N Mennonite mutation are not thiamine-responsive.

6.2.1 Classic isovaleric acidemia

No.	Symbol	Age	Medication/diet	Dosage	Target plasma levels
6.2.1	IVA (severe forms)	All ages	Lowered leucine diet[a]		Leucine 50–150 µM, or normal range for laboratory
			L-Carnitine	100 mg/kg per day in 3–4 doses[c]	Normal range for laboratory
			Glycine	250 (150–300) mg/kg per day[c,d]	Glycine 200–400 µM
6.2.1	IVA (mild forms)	All ages	Reduced natural protein diet[b]		
			Multivitamin with minerals	Daily	
			L-Carnitine	100 mg/kg per day in 3–4 doses[c]	Normal range for laboratory
			Glycine	250 (150–300) mg/kg per day[d]	Glycine 200–400 µM

[a] Special medical food devoid of leucine may be needed for severe forms of the disorder. Patients with milder forms of the disorder will only require a reduced natural protein intake. The least restrictive diet should be used

[b] Protein intake of approximately 1.5–2.0 g/kg body weight per day in young infants and 0.6–1.5 g/kg body weight per day in older children and adults

[c] Calculate the amount present in the special medical food or protein-free product and add supplements to this to meet the recommended intake

[d] Glycine is added to the daily special formula as weighed dry powder or 100 mg/ml solution

6.2.1 Treatment – Comments/Additions

1. Although leucine is the precursor amino acid for the disorder, it is the organic acids that are toxic to the patients and not the leucine per se as with MSUD. Monitoring leucine levels gives an indication as to whether there is sufficient intake of natural protein to support growth and tissue repair. The plasma leucine range of 50–150 µM, however, may be too low for some growing infants and children. Many affected patients are able to tolerate a near-normal leucine intake and may be treated with a lowered natural protein diet, without selective leucine restriction. The least restrictive dietary approach should be used order to avoid overtreatment and leucine deficiency.

6.3.1–6.3.2 Isolated 3-methylcrotonyl-CoA carboxylase deficiency

No.	Symbol	Age	Medication/diet	Dosage	Target plasma levels
6.3.1	3MCCC1	All ages	Lowered leucine diet[a]		Leucine 50–150 µM, or normal range for laboratory
	3MCCC2		L-Carnitine	100 mg/kg per day in 3 or 4 doses[b]	Normal range for laboratory

[a] Special medical food devoid of leucine may be needed for severe forms of the disorder. Patients with milder forms of the disorder will only require a reduced natural protein intake. The least restrictive diet should be used. Glycine is not given
[b] Calculate the amount present in the special medical food if used and add supplements to this to meet the recommended intake

6.3.1 Treatment – Comments/Additions

1. See comment 1 for disorder 6.2.1.
2. Patients are not responsive to biotin therapy.
3. Recently, asymptomatic children and adults have been found to have 3MCCC deficiency when family studies are done. These patients may not need dietary restrictions or L-carnitine, but may occasionally need blood and urine monitoring.

6.4 3-Methylglutaconic aciduria, type I

No.	Symbol	Age	Medication/diet	Dosage	Target plasma levels
6.4	3MGI	All ages	Lowered leucine diet[a]		Leucine 50–150 µM, or normal range for laboratory
			L-Carnitine	100 mg/kg per day in 3 or 4 doses[b]	Normal range for laboratory

[a] Special medical food devoid of leucine may be needed for severe forms of the disorder. Patients with milder forms of the disorder will only require a reduced natural protein intake. The least restrictive diet should be used. Glycine is not given
[b] Calculate the amount present in the special medical food if used and add supplements to this to meet the recommended intake

6.4 Treatment-Comments/Additions

1. See comment 1 for disorder 6.2.1.

■ *6.5 3-Hydroxy-3-methylglutaric aciduria*

No.	Symbol	Age	Medication/diet	Dosage	Target plasma amino acid levels
6.5	HMGCL	All ages	Lowered leucine and fat diet[a]	Fat is limited to 20–25% of total daily caloric intake	Leucine 50–150 µM, or normal range for the laboratory
			L-Carnitine	100 mg/kg per day in 3 or 4 doses[b]	Normal range for laboratory

[a] Special medical food devoid of leucine may be needed for severe forms of the disorder. Patients with milder forms of the disorder will only require a reduced natural protein intake and low fat diet. The least restrictive diet should be used. Glycine is not given

[b] Calculate the amount present in the special medical food if used and add supplements to this to meet the recommended intake

● *6.5 Comments/Additions*

1. See also comment 1 for disorder 6.2.1.
2. In addition to leucine restriction, daily caloric intake of fat is limited to 20–25% of total caloric intake per day. Use a protein-free product that contains carbohydrates and other nutrients, but no or very low fat.
3. Avoid fasting. Overnight drip nasogastric or gastrostomy feedings may be needed.
4. Uncooked cornstarch slurries or uncooked cornstarch added to the special metabolic formula may be used to prevent hypoglycemia.

6.4 Alternative Therapies/Experimental Trials

None known at present time.

6.5 Follow-up/Monitoring

6.1.1 MSUD 1A (severe forms)
6.1.2 MSUD 1B
6.1.3 MSUD 2 (severe forms)
6.1.4 MSUD 3

Age	Clinical monitoring: growth (weight, height, head circumference)[a]	Biochemical monitoring: blood quantitative amino acid levels[b]	Other[c]
Neonates	Weekly	Twice weekly to weekly	Every 1–3 months
Young infants	Weekly	Weekly to every 2 weeks	Every 1–3 months
Older infants and children	Every 1–3 months	Every 2 weeks to monthly	Every 3 months
Older children and adults	Every 1–3 months	Every 1–3 months	Every 6–12 months

This schedule is only a guide for those patients using special medical food devoid of leucine. Monitoring should be individualized for each patient, based on the severity of their disorder. Less frequent monitoring is needed for patients on a reduced natural protein diet

[a] Growth parameters may be obtained in the local physician's office and sent to the metabolic center after early infancy

[b] Blood amino acid levels should be determined by a quantitative method and the results include a total panel. Nutrient intake should be evaluated with each determination and appropriate and prompt changes made to the dietary prescription. Fingerstick dried blood filter paper or whole-blood samples may be obtained by the family or local health care providers and sent to testing laboratories between clinic visits

[c] The frequency and type of testing done for follow-up monitoring varies between metabolic clinics. As appropriate, the following testing may be considered. Complete blood count with differential, total protein, albumin, and protein stores (prealbumin, retinol-binding protein, transferrin, and/or transthyretin). Urine DNPH spot tests should be monitored daily at home in young infants as treatment is initiated, then weekly in young infants, and as indicated in older children and adults. Urine DNPH should be measured more frequently after diet changes or with signs of intercurrent illness. Monitor erythrocyte lipid composition, zinc, and serum iron/TIBC every 3 months when younger, every 6–12 months when older

■ Standard Protocol for Intercurrent Illness

● *Initial Measures*

Step	Branched-chain amino acid-free special medical food	Natural high-quality protein addition to special formula mix	Natural food leucine intake
1	1.2–1.5 times usual daily amount with extra added isoleucine and valine[a]	None	None
2	1.2–1.5 times daily amount with added isoleucine and valine[a]	One-half usual dietary intake	None to half usual dietary intake
3	Usual daily amount with well-day additions of isoleucine and valine	Full dietary intake	Gradual increase to usual full dietary intake

This plan should be individualized for each patient, based on the degree of severity of their disorder and blood quantitative amino acid levels. The exact products and measures (g) should be recorded, shared with the family, and periodically updated as the patient grows

[a] Additions of isoleucine and valine should be increased during sick days and be approximately equivalent to the patient's usual daily intake of these two amino acids from table foods and high-quality protein (milk, formula). Solutions are 10 mg/ml. The goal is to keep levels of isoleucine and valine above 400–600 μM

● *6.1.1–6.1.4 Intercurrent Illness – Comments/Additions*

A. Families/individuals should start sick-day formula (to decrease leucine intake, increase isoleucine and valine intake, and suppress catabolism) with the onset of intercurrent illness or symptoms related to loss of metabolic control. Fluids without calories or electrolytes should be avoided, or intake minimized.
B. Monitor urine DNPH, which will become positive with loss of metabolic control or inadequate caloric intake.
C. Ondansetron may be given for nausea/emesis (0.15 mg/kg per dose q 4–8 h).
D. If the patient is unable to take in oral fluids, has persistent vomiting, or the clinical condition deteriorates, they should proceed urgently to an experienced emergency care facility.

■ Acute Emergency Management: (Includes Management of Ill Neonates)

Clinical finding	Treatment
1. Dehydration	IV D10/W with 155 mEq/l NaCl and 20 mEq/l KCl (if adequate renal output) at maintenance until CNS status established. Normal saline bolus may be given, if indicated, as 10 ml/kg over 1 h in addition to the glucose-containing fluids
2. Hypoglycemia	10% dextrose, 1–2 ml/kg per dose (max 5–10 ml/kg) slow IV push
3. Acidosis	Sodium bicarbonate, 1–2 mEq/kg drip over 20–30 min, diluted with IV fluids. May repeat. Part or all of sodium in IV fluids may be replaced with sodium bicarbonate in severely acidotic patients (maximum total sodium concentration 155 mEq/l)
4. Maintain normal serum sodium and osmolality levels	(a) Monitor intake and output, body weight, urine specific gravity (b) 3% NaCl, dosage carefully calculated to replace deficit if hyponatremic. May also need furosemide 0.25–0.50 mg/kg per dose every 6–8 h if receives too much free water or serum osmolality falls (c) Mannitol 0.5 g/kg per dose, as indicated
5. Blood glucose > 200 mg/dl	Regular insulin drip, 0.05–0.10 units/kg per h
6. Increase calories to suppress catabolism	(a) Give step 1 sick-day diet by PO or NG/G-tube[b] (b) 20% fat emulsion, rate 1 ml per each 4 ml D10/W IV (c) If NPO use lowered BCAA mixture for CHA/TPN
7. Persistent elevated leucine levels or hyperammonemia	(a) Hemodialysis or continuous venovenous hemofiltration (CVVH) usually not needed, but if done should be *in addition* to measures in 6 (b) IV propranolol, to suppress catecholamines

This plan should be individualized for each patient, based on the severity and type of their disorder

[a] Supplements of isoleucine and valine are not given initially if blood levels are markedly elevated for all three BCAA, i. e., presenting episode. They usually need to added at 2–3 days into therapy

● *6.1.1–6.1.4 (severe forms) Acute Emergency Management – Comments/Additions*

A. Obtain a clinical history and perform an examination promptly on arrival of the patient, to assess the etiology of the intercurrent illness and determine the clinical status. Specific attention should be made to the degree of hydration and presence of signs of encephalopathy or cerebral edema (odor of maple syrup, altered respiratory rate and type, perfusion, lethargy, stupor, coma). Stop all protein sources.
B. Obtain baseline laboratory studies to include Dextrostix, blood glucose, electrolytes, CO_2, ammonia, and any other laboratory tests indicated by the clinical history and examination.
C. Monitor blood quantitative amino acid levels at least daily. Expect rate of decrease in leucine levels to approach 750 M/day. Isoleucine and valine levels should be high, at more than 400–600 M to suppress entry of leucine into the brain. Monitor urine DNPH at least daily; persistent positive testing may occur with elevated isoleucine levels however.
D. Carefully observe patients for pancreatitis, which may occur on the 2nd or 3rd day of hospitalization as leucine levels are returning to normal.
E. Patients with the E3 subunit deficiency may experience severe lactic acidosis and hypoglycemia.

6.1.1 MSUD 1A (mild forms)
6.1.2 MSUD 2 (mild forms)

● *6.1.1–6.1.2 (mild forms) Follow-up/Monitoring – Comment/Additions*

1. Monitoring may be less frequent than for severe forms of MSUD.

■ Standard Protocol for Intercurrent Illness

1. Most patients do not become as seriously ill as in classic MSUD, but the same general approach to care applies while they are ill.

6.2.1 Classic isovaleric acidemia
6.3.1–6.3.2 Isolated 3-methylcrotonyl-CoA carboxylase deficiency
6.4 3-Methylglutaconic aciduria, type I
6.5 3-Hydroxy-3-methylglutaric aciduria

Age	Clinical monitoring	Biochemical monitoring		Other[d]
	Growth (weight, height, head circumference)[a]	Blood quantitative amino acid levels[b]	Urine organic acids[c]	
Neonates	Weekly	Weekly	Every 1–3 months	Every 1–3 months
Young infants	Weekly to every 2 weeks	Every 2 weeks	Every 1–3 months	Every 1–3 months
Older infants and young children	Monthly	Every 1–3 months	Every 3 months	Every 3 months
Older children and adults	Every 6–12 months.	Every 6–12 months	Every 6–12 months	Every 6–12 months

This schedule is only a guide for patients with severe forms of the disorders. It should be individualized for each patient, based on the severity of their disorder. Less frequent monitoring is needed for patients on reduced natural protein diets, not taking special medical foods devoid of leucine

[a] Growth parameters may be obtained in the local physician's office and sent to the metabolic center after early infancy

[b] Blood quantitative amino acid levels should be determined by a quantitative method and the results include a total panel. Nutrient intake should be monitored with each determination and appropriate and prompt changes made to the dietary prescription. Levels may need to be done more frequently when initiating therapy. Fingerstick dried blood filter paper or whole-blood samples may be obtained by the family or local health care providers and sent to testing laboratories between clinic visits.

[c] Monitor pattern and amount of abnormal organic acids present and compare with clinical status for the individual patient, i. e., elevated levels of 3-hydroxyisovalerate may indicate lack of complete metabolic control

[d] The frequency and type of testing done for follow-up monitoring varies between metabolic clinics. As appropriate, the following testing may be considered. Complete blood count with differential and platelet count, electrolytes with CO_2, glucose, total protein, albumin, calcium, phosphorus, zinc, and protein stores (prealbumin, retinol-binding protein, transferrin, and/or transthyretin). Free carnitine and total carnitine levels, iron/TIBC or ferritin, zinc, and erythrocyte lipid composition every 3 months under 1 year of age, then twice yearly. Urine ketones should be monitored at home daily when initiating therapy in infants, then weekly for young infants, and then intermittently, i. e., after diet changes or with signs of intercurrent illness or loss of metabolic control for older infants and children. Note that patients with HMGCL cannot make ketones.

Standard Protocol for Intercurrent Illness

Initial Measures

Step	Leucine-free special medical food[a]	Protein free special medical food	Natural food leucine intake	L-Carnitine
1	None	Supply at least usual dietary caloric intake	None	Double usual daily dose
2	One-half to full usual dietary intake	Add as needed to supply at least usual dietary caloric intake	None	Double usual daily dose
3	Usual dietary intake	Add as needed to supply usual dietary caloric intake	Gradual increase to usual dietary intake	Routine dose

This plan should be individualized for each patient, based on the degree of severity of their disorder. Mildly affected patients may go directly to step 2 and skip step 1. Step 1 should not be used for more than a few days or protein mobilization may occur. For sensitive, severely affected patients, multiple substeps will be needed in steps 2 and 3. The exact products and measures (g) should be recorded, shared with the family, and updated as the patient grows

[a] Leucine-free and low fat for HMGCL

- *6.2–6.5 Intercurrent Illness – Comments/Additions*

A. Families/individuals should start sick-day formula (to decrease leucine intake and suppress catabolism) and increase the L-carnitine dose with the onset of intercurrent illness or symptoms related to loss of metabolic control. Fluids without calories or electrolytes should be avoided, or intake minimized.
B. Monitor urine ketones, which will become positive with loss of metabolic control or inadequate caloric intake. The exception is in patients with HMGCL deficiency, who are unable to make ketones. Monitoring urine ketones in this disorder is uninformative.
C. Ondansetron may be given for nausea/emesis (0.15 mg/kg/dose q 4–8 h).
D. If the patient is unable to take in oral fluids, has persistent vomiting, or the clinical condition deteriorates, they should proceed urgently to an experienced emergency care facility.

- *Acute Emergency Management: (Includes Management of Ill Neonates)*

Clinical finding	Treatment
1. Dehydration	IV D10/W with 75 mEq/l NaCl and 20 mEq/l KCl (if adequate renal output) at 1.2–1.5 times maintenance. Normal saline bolus may be given, if indicated, as 10 ml/kg over 1 h in addition to the glucose-containing fluids
2. Hypoglycemia	10% dextrose, 1–2 ml/kg/dose (max 5–10 ml/kg) slow IV push
3. Acidosis	Sodium bicarbonate, 1–2 mEq/kg drip over 20–30 min, diluted with IV fluids. May repeat. Part or all of sodium in IV fluids may be replaced with sodium bicarbonate in severely acidotic patients (maximum total sodium concentration 155 mEq/l)
4. Maintain normal serum sodium and osmolality levels	(a) Monitor intake and output, body weight, urine specific gravity (b) 3% NaCl, dosage carefully calculated to replace deficit if hyponatremic. May also need furosemide 0.25–0.50 mg/kg per dose every 6–8 h, if receives too much free water or serum osmolality falls (c) Mannitol 0.5 g/kg per dose, if indicated
5. IV L-carnitine	100 mg/kg per day in 4–6 divided doses, slow IV bolus over 20–30 min
6. Blood glucose > 200 mg/dl	Regular insulin drip, 0.05–0.10 units/kg per h
7. Increase calories to suppress catabolism	(a) Give step 1 sick-day diet by PO or NG/G-tube (b) 20% fat emulsion, rate 1 ml per each 4 ml D10/W IV (*Do Not give with HMGCL*) (c) If NPO use lowered leucine amino acid mixture for CHA/TPN
8. Glycine (IVA only)	Usual daily dose in sick-day enteral formula or in special amino acid mixture for CHA/TPN
9. Neutropenia, thrombocytopenia	Body fluid cultures, antibiotics
10. Persistent acidosis or hyperammonemia	Hemodialysis or continuous venovenous hemofiltration (CVVH) *in addition* to 7

This plan should be individualized for each patient, based on the clinical findings at the time of the episode

- *6.2–6.5 Acute Emergency Management – Comments/Additions*

A. Obtain a clinical history and perform an examination promptly on arrival of the patient, to assess the etiology of the intercurrent illness and determine the clinical status. Specific attention should be made to the degree of hydration and presence of signs of acidosis, hypoglycemia, or hyperammonemia (odor of sweaty feet, altered respiratory rate and type, perfusion, lethargy, stupor, coma). Stop all protein sources.
B. Obtain baseline laboratory studies to include Dextrostix, blood glucose, electrolytes, CO_2, ammonia, and any other laboratory tests indicated by the clinical history and examination.
C. Monitor serial blood levels of electrolytes with CO_2, osmolality, and ammonia; urine specific gravity and ketones; fluid intake and output, body weight.

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7 Disorders of Valine-Isoleucine Metabolism

Bruce A. Barshop

7.1 Introduction

The principles of therapy in disorders of valine and isoleucine metabolism are similar to those used in other organic acidemias and disorders of amino acid metabolism. Both valine and isoleucine are nondispensible (essential) amino acids which are highly metabolically active (have high flux rates). Disorders of valine and isoleucine metabolism have the potential to cause recurrent, life-threatening ketoacidotic crises, and the cornerstone of management involves careful application of diets with low protein (isoleucine and/or valine) content. In some cases, specific vitamin treatment may be of great value. It is strongly recommended that the treatment of these disorders involve a clinical biochemical genetics specialist team (see Table 7.1).

Table 7.1. Nomenclature

No.	Category	Disorder (symbol)	Gene symbol	OMIM No.
	Multiple carboxylase deficiency (MCD)			
7.1		Biotinidase (BTD)	*BTD*	253260
7.2		Holocarboxylase synthetase (HCS)	*HLCS*	253270
	Propionic acidemia (PA)			606054
7.3		Propionyl-CoA carboxylase (PCC)	*PCCA PCCB*	232000, 232050
	Beta-ketothiolase (3-oxothiolase) deficiency (BKT)			203750
7.4		2-Methylacetoacetyl-CoA thiolase (MAT, T2)	*ACAT1*	607809
	3-Hydroxyisobutyric aciduria (HIBA)			236795
7.5		Methylmalonic semialdehyde dehydrogenase (MMSDH)	*ALDH6A1*	603178

Table 7.1. (continued)

No.	Category	Disorder (symbol)	Gene symbol	OMIM No.
7.6		3-Hydroxyisobutyrate dehydrogenase (HIBDH)		608475
		3-Hydroxyisobutyric aciduria, unspecified		
	3-Hydroxy-2-methylbutyric aciduria (HMBA)			
7.7		3-Hydroxy-2-methylbutyry-CoA dehydrogenase (HMBDH)	*HADH2*	300256
	Methylmalonic acidemia (MMA)			
7.8		Methylmalonyl-CoA mutase (mut^0, mut^-)	*MUT*	251000
		Cobalamin-A (CblA)	*MMAA*	251100, 607481
		Cobalamin-B (CblB)	*MMAB*	251110, 607568
7.9		Cobalamin-C (CblC)		277400
7.10		Cobalamin-D (CblD)		277410
		Cobalamin-F (CblF)		277380
	Methacrylic aciduria (MAcrA)			250620
7.11		3-Hydroxyisobutyryl-CoA deacylase (hydrolase) (HIBDA)		–
	2-Methylbutyric aciduria (MBA)			
7.12		2-Methylbutyryl-CoA dehydrogenase (MBDH)	*ACADSB*	600301
	Isobutyryl-CoA dehydrogenase deficiency (IBDD)			
7.13		Isobutyryl-CoA dehydrogenase (IBDH)	*ACAD8*	604773

7.2 Disorders Affecting Both Valine and Isoleucine Metabolism

Valine and isoleucine share the propionate pathway for their terminal steps of catabolism, and propionic acidemia (PA, propionyl-CoA carboxylase deficiency) and methylmalonic acidemia (MMA, methylmalonyl-CoA mutase deficiency) affect the metabolism of both of these amino acids and other precursors of propionate (threonine and methionine, as well as odd-chain fatty acids and cholesterol). Bacterial activity in the gut may also account for a significant fraction of the substrate production.

There have been four decades of experience in treating PA and MMA, yet the management of the acute acidotic episodes is difficult (see Table 7.2), and

Table 7.2. Management of acute crisis

No.	Disorder	Treatment
7.1	BTD	Initiate biotin, 10–20 mg/day Generally institution of biotin is sufficient. In extreme cases, where the specific diagnosis has not been defined, acute management principles are as in 7.3; transient limitation of protein may be required
7.2	HCS	Initiate biotin, 10–20 mg/day As in 7.1, above. Principles of acute management are as in 7.3
7.3	PA	Hydrate (~ 120% maintenance, 150% if dehydrated, less if concern about cerebral edema), replace fluid and electrolyte deficits. Bicarbonate replacement (Table 7.3). Manage hyperammonemia if necessary In event of treatment failure (uncontrollable acidosis and/or hyperammonemia) Haemofiltration or haemodialysis Carnitine 100–300 mg/kg per day IV Anticipate and treat potential infection Immediately initiate high calorie feeding Target energy input: Infant 120–150 kcal/kg per day; Child 80–120 kcal/kg per day; Adult 40–50 kcal/kg per day Able to feed enterally Val/Met/Ile/Thr-free formula: continuous drip: QS for above Unable to feed enterally Central line: Hypertonic glucose +/− insulin drip; Parenteral lipid suspension Peripheral line: Isotonic glucose solution; Parenteral lipid suspension When acidosis, ketonuria resolve and/or plasma Val limiting (< 50 µM), add protein. Note: Generally add protein/valine over ≥ 2 days; use half target amount on day 1 Whole protein (formula): calculated to provide protein (see Table 7.4) Or: Whole protein (formula): calculated to provide valine (see Table 7.4) Then: If limiting plasma concentrations of other propiogenic amino acids (e. g., Ile < 15 µM, Met < 10 µM, Thr < 35 µM), may supplement individually (Table 7.4). Note: More practical to utilize natural protein If unable to tolerate enteral feeding for prolonged period Hyperalimentation. Careful use of standard solution (Kahler et al. 1989) and/or special formulation (limited Val/Ile/Thr/Met)

Table 7.2. (continued)

No.	Disorder	Treatment		
7.4	BKT	Hydrate (~ 150% maintenance), replace fluid and electrolyte deficits. Bicarbonate replacement (see Table 7.3)		
		Carnitine 100–200 mg/kg IV TID		
		Anticipate and treat potential infection		
		Immediately institute high-calorie feeding		
		Target energy input	Infant	120–150 kcal/kg per day
			Child	80–120 kcal/kg per day
			Adult	40–50 kcal/kg per day
		Able to feed enterally		
		Protein-free formula (or, in principle, Ile/Leu/Val-free formula with supplemented Leu and Val)	Continuous drip: QS for above	
		Unable to feed enterally		
		Central line	Hypertonic glucose +/− insulin drip	
			Parenteral lipid suspension	
		Peripheral line	Isotonic glucose solution	
			Parenteral lipid suspension	
		After ketosis resolves and/or plasma isoleucine limiting (< 20 µM) add protein. Note: Add protein/Ile over ≥ 2 days; use half target amount on day 1		
		Protein/isoleucine (see Table 7.5)		
7.5	MMSDH	Little information published. Suggested guidelines would be as with HIBA (7.6)		
7.6	HIBA	Hydrate (~ 150% maintenance), replace fluid and electrolyte deficits. Bicarbonate replacement (see Table 7.3)		
		Carnitine 100–200 mg/kg IV TID		
		Anticipate and treat potential infection		
		Immediately institute high calorie feeding		
		Target energy input	As above (7.3)	
		Able to feed enterally		
		Protein-free formula (or, in principle, Ile/Leu/Val-free formula with supplemented Leu and Ile)	Continuous drip: QS for above	
		Unable to feed enterally		
		Central line	Hypertonic glucose +/− insulin drip	
			Parenteral lipid suspension	
		Peripheral line	Isotonic glucose solution	
			Parenteral lipid suspension	
		After ketosis resolves and/or plasma valine limiting (< 95 µM) add protein. Note: Add protein/Ile over ≥ 2 days; use half target amount on day 1		
		Protein/Valine (see Table 7.5)		
7.7	MHBA	Little information published. Suggested guidelines would be as with BKT (7.4)		
7.8	MMA	Manage as in 7.3		
	CblA	Manage as in 7.3, plus vitamin B_{12} (Cbl)	CN-Cbl or OH-Cbl	1000 µg IM/day
	CblB	Manage as in 7.3, plus vitamin B_{12} (Cbl)	CN-Cbl or OH-Cbl	1000 µg IM/day
7.9	CblC	Manage as in 7.3, plus vitamin B_{12} (Cbl)	HO-Cbl	1000 µg IM/day
7.10	CblD	Manage as in 7.3, plus vitamin B_{12} (Cbl)	HO-Cbl	1000 µg IM/day
	CblF	Manage as in 7.3, plus vitamin B_{12} (Cbl)	CN-Cbl or OH-Cbl	1000 µg IM/day
7.11	MAcrA	No information published. Suggested guidelines would be as with HIBA (7.6)		
7.12	MBA	Little information published. Suggested guidelines would be as with BKT (7.4)		
7.13	IBDD	Little information published. Suggested guidelines would be as with HIBA (7.6)		

it must be said that in some cases, despite optimal treatment with the current state of the art, multisystem failure and death may still ensue. The principles of treatment include curtailment of intake of propiogenic amino acids and provision of high-calorie nonprotein nutrients to promote anabolism (Acosta and Yannicelli 1997). Correction of the acidosis often requires aggressive use of bicarbonate therapy (see Table 7.3), and it is sometimes important for the practitioner to advocate this modality despite intensivists' concerns regarding bicarbonate in the settings of diabetes or cardiac arrest (Vukmir et al. 1996). Carnitine is used to support excretion of organic acids as carnitine adducts (primarily propionyl-carnitine), thus sparing coenzyme A and preserving the function of the Krebs cycle. Hyperammonemia may occur, particularly in propionic acidemia, and particularly in the neonatal presentation. When hyperammonemia is extreme, in order to avoid neurological damage it may be necessary to use the same measures to control hyperammonemia as used in disorders of the urea cycle, including hemodialysis and scavenger therapy (with benzoate expected to be more effective than phenylacetate, owing to the high levels of glycine and low levels of glutamine associated with hyperammonemia in this disease; Tuchman and Yudkoff 1999). Mild or moderate hyperammonemia with recurrent episodes may be followed and expected to resolve with correction of the acidosis.

Table 7.3. Bicarbonate therapy during acute acidosis in disorders of valine-isoleucine metabolism

Therapy			
Option A:	Administer isotonic solution with bicarbonate as needed. Same principle can be used to formulate solutions of various normalities. Example is for approx. 1 × physiological saline solution		
	Serum HCO_3 (mEq/l)	IV $NaHCO_3$ (mEq/l)	IV NaCl (mEq/l)
	< 19, ≥ 16	25	125
	< 16, ≥ 13	50	100
	< 13, ≥ 10	100	50
	< 10	150	0
	Advantages	Allows better regulation of sodium and fluid load. Avoids wide swings in pH, tonicity	
	Disadvantages	Must reduce added $NaHCO_3$ promptly as serum HCO_3 normalizes	
Option B:	In addition to maintenance and replacement fluids, administer intermittent boluses of hypertonic $NaHCO_3$ (as 8.4%, 1 mmol/ml, solution)		
	Advantages	Allows rapid adjustment	
	Disadvantages	Rapid administration may cause paradoxical acidosis (especially, cerebral). Requires frequent serum measurements; serious tendency to undertreat; tendency for sodium overload. Must monitor accrued sodium load, with ongoing adjustment of IV fluids	

Table 7.4. Approximate daily protein and amino acid targets in propionic and methylmalonic acidemia

Age	Whole protein (g/kg per day)	Valine	Isoleucine	Threonine	Methionine
0–3 months	1.2–1.8	65–105 mg/kg	70–120 mg/kg	50–135 mg/kg	20–50 mg/kg
3–6 months	1.0–1.5	60–90	60–100	50–100	15–45
6–9 months	0.8–1.3	35–75	50–90	40–75	10–40
9–12 months	0.6–1.2	30–60	40–80	20–40	10–30
1–4 years	0.6–1.2	500–800 mg/day	480–730 mg/day	400–600 mg/day	180–390 mg/day
4–7 years	0.6–1.2	700–1100	600–1000	500–750	250–500
7–11 years	0.5–1.1	800–1250	700–1100	600–900	290–550
11–15 years	0.4–1.0	1000–1600	750–1300	800–1200	300–800
15–19 years	0.4–0.8	1100–2000	800–1500	800–1400	300–900
> 19 years	0.3–0.6	900–2000	900–1500	800–1500	250–1000

In addition to the whole-protein guidelines, specialized formulas are recommended (devoid of, or limited in Val, Ile, Met, Thr), to provide an equivalent total protein intake of approximately 2.5–3.5 g/kg per day for infants, > 30–40 g/day for children, and > 50–65 g/day for adults

Note: These are approximate guidelines, and individual patients' requirements may vary substantially. Also, for a given patient, variations must be anticipated in relationship to growth rate, pubarche, activity, etc.

The chronic treatment of PA and MMA is also challenging (see Tables 7.4–7.8). Since the four propiogenic amino acids are essential, dietary protein must be judiciously prescribed to prevent overwhelming the residual capacity of the deficient enzyme, but at the same time providing enough of these amino acids to prevent catabolism and support growth (Ney et al. 1985), for which the requirements vary from individual to individual and from time to time, particularly as a child grows. Late complications of these diseases must be anticipated, including renal dysfunction and failure in MMA (van Calcar et al. 1998), acute episodes of pancreatitis (Kahler et al. 1994), and acute basal ganglion infarction (Haas et al. 1995), for which supportive and symptomatic measures are adopted. Liver transplantation has been applied in a small number of cases (Kayler et al. 200; Yorifuji et al. 2000), and there is evidence of benefit, but concerns arise because of documented cases of neurological complications after successful transplantation in MMA (Nyhan et al. 2002; Chakrapani et al. 2002).

In addition to the primary deficiencies of propionyl-CoA carboxylase (PCC) and methylmalonyl-CoA mutase (MUT), there are a number of conditions causing secondary defects of these enzymes. PCC, being biotin-dependent, is deficient in the multiple carboxylase deficiencies caused by biotinidase deficiency and holocarboxylase synthetase deficiency. MUT, being B_{12}-dependent, is deficient in a variety of defects involving the metabolism of cobalamin (CblF), adenosylcobalamin (CblA, CblB), and adenosyl- and methylcobalamin (CblC, CblD). The therapeutic approaches which have been used in these disorders are the same as in PA and MMA (Waggoner et al. 1998; Andersson et al. 1983), but in these cases there is an expectation that vitamin treatment (biotin and cobalamin, respectively) will significantly alter the phenotype, reducing the

Table 7.5. Approximate daily protein and amino acid targets in disorders limited to isoleucine or valine

Age	Isoleucine[a] Whole protein (g/kg per day)	Isoleucine	Valine[b] Whole protein (g/kg per day)	Valine
0–3 months	1.5–2.5	90–150 (mg/kg per day)	1.2–1.8	65–105 mg/kg per day
3–6 months	1.2–2.0	75–125	1.0–1.5	60–90
6–9 months	1.0–1.6	65–115	0.8–1.3	35–75
9–12 months	0.8–1.5	50–100	0.6–1.2	30–60
1–4 years	0.8–1.5	600–920 mg/day	0.6–1.2	500–800 mg/day
4–7 years	0.8–1.5	750–1250	0.6–1.2	700–1100
7–11 years	0.6–1.4	850–1400	0.5–1.1	800–1250
11–15 years	0.5–1.3	900–1600	0.4–1.0	1000–1600
15–19 years	0.5–1.0	1000–1900	0.4–0.8	1100–2000
> 19 years	0.3–0.8	1100–1900	0.3–0.6	900–2000

In addition to the whole-protein guidelines, it may be useful to add specialized formulas (limited in ile, val), to provide an equivalent total protein intake of approximately 2.5–3.5 g/kg per day for infants, > 30–40 g/day for children, and > 50–65 g/day for adults

Note: These are approximate guidelines, and individual patients' requirements may vary substantially. Also, for a given patient, variations must be anticipated in relationship to growth rate, pubarche, activity, etc.

[a] The targets relating to isoleucine curtailment would apply to methylbutyryl-CoA dehydrogenase deficiency (MBA), hydroxymethylbutyryl-CoA dehydrogenase deficiency (HMBA), and in principle to beta-ketothiolase deficiency (BKT)

[b] The targets relating to valine curtailment would apply to methylmalonylsemialdehyde dehydrogenase deficiency (MMSDH), hydroxyisobutyryl-CoA dehydrogenase deficiency (HIBA), isobutyryl-CoA dehydrogenase deficiency (IBDH), and in principle to methacrylyl acidemia (MAcrA)

required stringency of treatment and favorably affecting the outcome. Whereas the neurological outcome in early onset CblC and CblD may be disappointing, despite hydroxocobalamin treatment (Andersson et al. 1983), the response in CblF (Waggoner et al. 1998) and CblA (Matsui et al. 1983) is generally very satisfactory, and moderately so in CblB (Matsui et al. 1983). There is controversy regarding whether biotin treatment is necessary in patients with partial deficiency of biotinidase (Moslinger et al. 2001), but it has been argued that any case of significant biotinidase deficiency should be treated (Wolf 2002).

Table 7.6. Chronic management

No.	Symbol	Measure	Age/criteria	Dosage/intervals
All		Written directives	In all cases where emergency intervention anticipated, provide written instructions for emergency care, information to contact specialist. Medical alert bracelets also recommended	
		Vaccination	Routine vaccination: per local recommendations. Annual influenza vaccination (if < 100% vitamin-responsive)	

Table 7.6. (continued)

No.	Symbol	Measure	Age/criteria	Dosage/intervals
7.1	BTD	Biotin	Residual activity < 50% normal	10–20 mg/day
7.2	HCS	Biotin	All	10 to > 40 mg/day
7.3	PA	Carnitine	All	50–150 mg/kg per day BID-TID
		Low-protein diet	See Table 7.4. Individualize depending upon tolerance to protein, growth, nutritional adequacy, guided by parameters in Table 7.7	
		Gut motility agent	Avoid constipation; use of mild laxative may be beneficial	
		Gut flora agent	> 6 months. Use if dietary management insufficient to maintain control or urine MC + 3OHP + TG > 5× baseline	
		Metronidazole	Short or subchronic	5–10 mg/kg BID, max 1 g TID
		or Neomycin	Short course	25–50 mg/kg BID, max 1 g TID
7.4	BKT	Carnitine	All	50–100 mg/kg per day
		Low-protein diet	See Table 7.5. Individualize depending upon tolerance to protein, growth, nutritional adequacy, guided by parameters in Table 7.7	
7.5	MMSDH	Carnitine	All	50–100 mg/kg per day
		Low-protein diet	See Table 7.5. Individualize depending upon tolerance to protein, growth, nutritional adequacy, guided by parameters in Table 7.7	
7.6	HIBA	Carnitine	All	50–100 mg/kg per day
		Low-protein diet	See Table 7.5. Individualize depending upon tolerance to protein, growth, nutritional adequacy, guided by parameters in Table 7.7.	
7.7	HMBA	Little information published. Suggested guidelines would be as with BKT (7.4), above		
7.8	MMA	Low-protein diet	See Table 7.4. Individualize depending upon tolerance to protein, growth, nutritional adequacy, guided by parameters in Table 7.7	
		Carnitine	All	50–150 mg/kg per day BID-TID
		Metronidazole *or* Neomycin	> 6 months	As in 7.3
	CblA, -B	As above *plus* CN-Cbl or HO-Cbl	All	≥ 1000 μg IM weekly
7.9	CblC	As above *plus* HO-Cbl	All	≥ 1000 μg IM weekly
7.10	CblD	As above *plus* HO-Cbl	All	≥ 1000 μg IM weekly
	CblF	CN-Cbl or HO-Cbl	All	≥ 1000 μg IM weekly
7.11	MAcrA	No information published. Suggested guidelines would be as with HIBA (7.6)		
7.12	MBA	Little information published. Suggested guidelines would be as with BKT (7.4)		
7.13	IBDD	Little information published. Suggested guidelines would be as with HIBA (7.6)		

Table 7.7. Monitoring

No.	Disorder	Test	Age	Interval
7.1	BTD	Urine organic acids	0–2 years	Q 6 months
			2–10 years	Q 1 years
			> 10 years	Q 2 years
		Hearing, vision screening	< 16 years	If diagnosed as presymptomatic newborn: Q 5 years. If diagnosed after symptoms: Q 1–2 years
			> 16 years	Q 1–2 years
7.2	HCS	Urine organic acids	0–2 years	Q 6 months
			2–10 years	Q 1 years
			> 10 years	Q 2 years
7.3	PA	Urine ketones (instruct and supply for home testing)	All	PRN; with intercurrent illness
		Charting of anthropometrics	All	With each visit
		Plasma amino acids	0–2 years	Q 1–3 months
			> 2 years	Q 6 months
		Plasma carnitine	0–2 years	Q 3 months or as needed to assure compliance
			> 2 years	Q 6 months
		Urine organic acids	0–2 years	Q 3 months and with acute episodes
			> 2 years	Q 6 months
		Plasma ammonia	0–1 years	With intercurrent illness
			> 1 years	If encephalopathy considered.
		Blood hemogram, chem panel	0–2 years	Q 1–3 months
			> 2 years	Q 3–6 months
		Serum prealbumin, ferritin	0–2 years	Q 6 months or PRN
			> 2 years	Q years or PRN
7.4	BKT	Urine ketones (instruct and supply for home testing)	All	PRN; with intercurrent illness.
		Plasma amino acids	0–5 years	Q 6 months or as needed to assure adequate diet
			> 5 years	Q 1 years
		Urine organic acids	0–5 years	Q 6 months and with intercurrent/acute episodes
			> 5 years	Q 1 years
		Plasma carnitine	0–5 years	Q 6 months or as needed to assure compliance
			> 5 years	Q 1–2 years
7.5	MMSDH	As in 7.3		
7.6	HIBA	As in 7.3		
7.7	MHBA	Little information published. Suggested guidelines as in BKT (7.4)		
7.8	MMA	As in 7.3		
	CblA, B	As in 7.3		Note: If vitamin response is good, diet may be normal or near-normal. Serum B_{12} if compliance uncertain
7.9	CblC	As in 7.3		Serum B_{12} if compliance uncertain
7.10	CblD	As in 7.3		Serum B_{12} if compliance uncertain
	CblF	As in 7.3		Serum B_{12} if compliance uncertain
7.11	MAcrA	No information published. Suggested guidelines as in HIBA (7.6)		
7.12	MBA	Little information published. Suggested guidelines as in BKT (7.4)		
7.13	IBDD	Little information published. Suggested guidelines as in HIBA (7.6)		

Table 7.8. Experimental/additional therapies

No.	Symbol	Measure	Comments
7.3	PA	Biotin	Trial may be reasonable, though no clinically effective cases of response have been reported
		IV benzoate, phenylacetate	May be beneficial in acute hyperammonemia, particularly in neonatal episode. ("Experimental" as IV formulation not approved for this indication in USA)
7.4, 7.5, 7.6, 7.8		Growth hormone	May be useful in promoting anabolism, blunting catabolic response to stress
		Liver transplantation	Experience accruing

7.3 Disorders of Valine Metabolism

Confirmed enzyme defects in the valine pathway above the level of propionyl-CoA are rare, and there have been limited reports regarding treatment outcomes. Patients with 3-hydroxyisobutyric aciduria (HIBA) may be found to have defects of methylmalonic semialdehyde dehydrogenase or hydroxyisobutyrate dehydrogenase. There has been some experience in managing acute ketoacidotic episodes in HIBA (Ko et al. 1991), but no details reported regarding acute episodes in other defects of valine metabolism. There has been only one patient reported with methylacrylic acidura, and the presentation of multiple malformations may relate to the mutagenic potential of methacrylate, which forms sulfur adducts (carboxypropyl-cysteine and carboxylpropyl-cysteamine), but no reported abnormal organic acids (Brown et al. 1982). Isobutyryl-CoA dehydrogenase (IBDH) as an enzyme specific to the valine pathway has only recently been resolved from the short branched-chain acyl-CoA dehydrogenase which acts on 2-methylbutyryl-CoA in the isoleucine pathway (whereas there is a single enzyme in the rat). The only reported clinical details for IBDH deficiency are cardiomyopathy and carnitine depletion, and the only reported intervention is carnitine supplementation (Nguyen et al. 2002). It is reasonable to assume that acute presentations are possible in these disorders, so the guidelines written here are based on first principles and the experience of treating HIBA (Ko et al. 1991; Sasaki et al. 1998, 2001).

7.4 Disorders of Isoleucine Metabolism

Beta-ketothiolase deficiency is relatively well characterized as an intermittent ketoacidotic disease, with generally normal health and development between episodes. A recent survey indicated about a 50% recurrence rate, and about a 12% incidence of impaired cognitive development, and some 75% of patients managed with a dietary protein restriction (Fukao et al. 2001). Methylhydroxyisobutyric aciduria is characterized by mental retardation, with or without progressive degeneration, and demonstrated short-term benefit to protein (isoleucine) restriction (Ensenauer et al. 2002). Methylbutyryl-CoA deydrogenase deficiency has been reported in cases with static mental retardation (Andresen et al. 2000) and with neonatal metabolic decompensation (Gibson et al. 2000). Protein restriction and carnitine supplementation have been used (Gibson et al. 2000), but the long-term outcome is not known.

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8 Various Organic Acidurias

Alberto Burlina, John Walter

8.1 Introduction

This chapter is concerned with the treatment the following disorders: 2-ketoglutarate dehydrogenase complex deficiency (2-ketoglutarate dehydrogenase deficiency and dihydrolipoamide *S*-succinyltransferse deficiency); fumarase deficiency; malonyl CoA decarboxylase deficiency; L-2-hydroxyglutaric aciduria; D-2-hydroxyglutaric aciduria and aspartoacylase deficiency (Canavan disease) (see Nomenclature section).

2-Ketoglutarate dehydrogenase and fumarase deficiency are disorders involving enzymes of the Krebs cycle; malonyl CoA decarboxylase is responsible for the conversion of intramitochondrial malonyl-CoA to acetyl-CoA and plays an important role in fatty acid oxidation; no enzyme deficiencies have yet been found for either L-2-hydroxyglutaric aciduria or D-2-hydroxyglutaric aciduria; aspartoacylase is a key enzyme within the central nervous system.

All these disorders are rare. In the section Clinical Features and Prognosis is a summary of the clinical presentation and prognosis of these disorders. The method of diagnosis and further details of the clinical presentation are described in the corresponding chapter of the *Physicians Guide to the Laboratory Diagnosis of Metabolic Diseases*.

8.2 Nomenclature

No.	Disorder (symbol)	Definitions/comment	Gene symbol	OMIM No.
8.1	2-Ketoglutarate dehydrogenase deficiency, dihydrolipoamide *S*-succinyltransferse deficiency (2-ketoglutarate dehydrogenase complex deficiency, E1 and E2 components)	2-KGA (U) 5–1700 mmol/mol Creat	*OGDH* *DLST*	203740, 126063
8.2	Fumarase deficiency	FA (U) > 20–3829 mmol/mol Creat	*FH*	606812
8.3	Malonyl CoA decarboxylase deficiency	MA (U) 21–5440 mmol/mol Creat	*MLYCD, MCD*	248360
8.4	L-2-Hydroxyglutaric aciduria	L-2-HGA (U) 226–4294 mmol/mol Creat		236792
8.5	D-2-Hydroxyglutaric aciduria	D-2-HGA (U) 676–7076 mmol/mol Creat		600721
8.6	Aspartoacylase deficiency	NAA (U) 61–9647 mmol/mol Creat	*ASPA*	271900

8.3 Clinical Features and Prognosis

	Disorder	Clinical features	Prognosis
8.1	2-Ketoglutarate dehydrogenase complex deficiency (E1 and E2 components)	Variable: hypotonia, developmental-delay, pyramidal and extrapyramidal dysfunction, spasticity, and hepatomegaly. E1 deficiency cause of the AR form of DOOR syndrome (deafness, onycho-osteodystrophy, dystrophic thumbs, sensorineural deafness; Surendran et al. 2002)	Variable
8.2	Fumarase deficiency	Variable encephalopathy	Usually fatal in infancy
8.3	Malonyl CoA decarboxylase deficiency	Developmental delay, seizures, vomiting, hypoglycemia, hypertrophic cardiomyopathy (Santer et al. 2003)	Variable
8.4	L-2-Hydroxyglutaric aciduria	Developmental and motor delay, seizures, cerebellar ataxia, migraine, macrocephaly, leukoencephalopathy, spinal canal stenosis (Kossoff et al. 2001; Warmuth-Metz et al. 2000; Sztriha et al. 2002)	Usually slowly progressive with survival into Adulthood
8.5	D-2-Hydroxyglutaric aciduria	Mild infantile form: epilepsy, hypotonia, and psychomotor retardation, facial dysmorphism. Severe neonatal form: as above plus absence corpus callosum, intracranial haemorrhage, episodic vomiting, cardiomyopathy, intractable seizures, inspiratory stridor, and apneas (Kwong et al. 2002; Wang et al. 2003). Intermediate form also described (Clarke et al. 2003)	severe form: death in infancy, other forms: variable
8.6	Aspartoacylase deficiency	Macrocephaly, psychomotor regression, optic atrophy,seizures (Rapin 2000)	Often death in childhood or teens; severe disability

8.4 Treatment

With the exception of malonyl-CoA decarboxylase deficiency, there are no treatments that have been shown to modify the natural history of these disorders. Clinical variability has been described in all of these disorders except for Canavan disease, which is often fatal within early childhood, although survival in a vegetative state or near-vegetative state may extend to the second decade (Rapin 2000). Each patient must be assessed on an individual basis. Treatment will be primarily supportive and for complications of the conditions that may arise. Knowledge of the natural history is important in order to anticipate such problems. Care for affected families includes genetic advice (see Follow-up/Monitoring section).

For patients with malonyl-CoA decarboxylase deficiency, a low-fat, high-carbohydrate diet has been reported to reduce the excretion of malonic acid and the risk from hypoglycemia and carnitine supplementation to prevent the development of cardiac decompensation (Haan et al. 1986; Matalon et al. 1993; Krawinkel et al.1994; Yano et al.1997; Wightman et al. 2003; Santer et al. 2003). However, less than 20 patients have been reported in the literature and, despite such treatment, the outcome appears variable.

	Disorder	Specific treatment
8.1	2-Ketoglutarate dehydrogenase complex deficiency	Low CHO; bicarbonate
8.2	Fumarase deficiency	None
8.3	Malonyl CoA decarboxylase deficiency	High-carbohydrate, low-fat diet and carnitine, but response very variable. Systemic symptoms and cardiomyopathy often improve but not developmental delay
8.4	L-2-Hydroxyglutaric aciduria	None (spinal decompression for spinal cord stenosis).
8.5	D-2-Hydroxyglutaric aciduria	None
8.6	Aspartoacylase deficiency	None

8.5 Alternative Therapies/Experimental Trials

There is no established therapy for preventing the neurological damage in these disorders. Recently the use of topiramate has been suggested in the treatment of Canavan disease and L-2-OH glutaric aciduria, but the results are still too preliminary to define as a new treatment (Topcu et al. 2003).

Several studies using viral and nonviral gene delivery gene systems have been carried out in an attempt to correct the enzyme deficiency in Canavan

disease. Canavan disease may be a reasonable target for an *ASPA* gene transfer strategy, since it is a single-gene defect and it is possible that the neuropathology could be reversed by reduction of enhanced brain *N*-acetylaspartic acid (NAA) levels (Kirmani et al. 2002). Although different approaches have been reported, including attempts in humans (nonviral gene delivery of human *ASPA* in an AAV plasmid in two children with Canavan disease, one with a homozygous mutation and the other with a heterozygous mutation; Leone et al. 2000; Matalon et al. 2003), an efficacious therapy has yet to be reached.

	Disorder	Alternative therapies/ experimental trials
8.1	2-Ketoglutarate dehydrogenase complex deficiency	None
8.2	Fumarase deficiency	None
8.3	Malonyl CoA decarboxylase deficiency	None
8.4	L-2-Hydroxyglutaric aciduria	None
8.5	D-2-Hydroxyglutaric aciduria	None
8.6	Aspartoacylase deficiency	Topiramate; gene therapy

8.6 Follow-up/Monitoring

	Disorder	Follow-up/monitoring
8.1	2-Ketoglutarate dehydrogenase deficiency	Supportive; acid/base status, blood lactate
8.2	Fumarase deficiency	Supportive; acid/base status, blood lactate
8.3	Malonyl CoA decarboxylase deficiency	Carnitine status, acid base status, urine organic acids
8.4	L-2-Hydroxyglutaric aciduria	Supportive
8.5	D-2-Hydroxyglutaric aciduria	Supportive
8.6	Aspartoacylase deficiency	Supportive

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9 Disorders of the γ-Glutamyl Cycle

Ellinor Ristoff, Agne Larsson

9.1 Introduction

Glutathione (GSH), a tripeptide present in all mammalian cells, takes part in several fundamental biological functions, including handling of reactive oxygen species (ROS), detoxification of xenobiotics and carcinogens, redox reactions, biosynthesis of DNA and leukotrienes, as well as neurotransmission and neuromodulation. Glutathione is metabolised via the γ-glutamyl cycle, which is catalysed by six enzymes. In man, hereditary deficiencies have been found in four of the six enzymes: i. e. γ-glutamylcysteine synthetase, GSH synthetase, γ-glutamyl transpeptidase and 5-oxoprolinase (see Larsson and Anderson 2001). Mutants have not yet been found in γ-glutamyl cyclotransferase and dipeptidase. Most of the mutations are leaky so that many patients have residual enzyme activity. Patients with defects in the biosynthesis of GSH (i. e. γ-glutamyl cysteine synthetase and GSH synthetase) have haemolytic anaemia and may also show CNS involvement and metabolic acidosis. The aim of the treatment for these disorders is to avoid haemolytic crises and to support the endogenous defence against reactive oxygen species.

The clinical findings in patients with defects in the degradation of GSH are heterogeneous, more complex and frequently include damage to the CNS. No treatment has been recommended for these disorders.

γ-Glutamylcysteine synthetase deficiency (OMIM 230450) has been described in 8 patients in six families. All have had well-compensated haemolytic anaemia and three have also had neurological symptoms such as spinocerebellar degeneration, neuropathy, myopathy, psychosis and learning disabilities (Richards et al. 1974; Beutler et al. 1999). The recommended treatment is to avoid drugs and foods known to precipitate haemolytic crises in patients with glucose-6-phosphate dehydrogenase deficiency. Early supplementation with the antioxidant vitamins C and E seems to prevent damage to the CNS in patients with GSH synthetase deficiency (Ristoff et al. 2001). In analogy supplementation with vitamins C and E might be worth testing also in patients with γ-glutamylcysteine synthetase deficiency. However, no studies of this treatment have yet been made.

Glutathione synthetase deficiency (OMIM 266130) has been confirmed in more than 70 patients in about 60 families. Approximately 25% of these patients have died in childhood – usually in the neonatal period – of electrolyte

imbalance and infections. Treatment in the neonatal period involves correction of acidosis and electrolyte imbalance, and early treatment with the antioxidants vitamins E and C to prevent damage to the CNS (Ristoff et al. 2001). GSH synthetase deficiency can be classified according to the severity of clinical signs as mild, moderate or severe (Ristoff et al. 2001). The clinical symptoms range from only haemolytic anaemia to metabolic acidosis, 5-oxoprolinuria, progressive neurological symptoms and sometimes also recurrent bacterial infections, due to defective granulocyte function. In some patients with the severe form, the eyes are affected: e.g. retinal pigmentations, crystalline opacities in the lenses, poor adaptation to darkness and pathological electroretinograms (Larsson et al. 1985). Several patients with a deficiency of GSH synthetase have died, but few have been autopsied. The first patient described with GSH synthetase deficiency died at 28 years of age. The autopsy of the CNS showed selective atrophy of the granular cell layer of the cerebellum, focal lesions in the frontoparietal cortex, the visual cortex and thalamus (Skullerud et al. 1980). The lesions in the brain resemble those seen after intoxication with the toxic compound mercury, i. e. Minamata disease, and it has therefore been suggested that treatment of GSH synthetase deficiency with antioxidants may be beneficial (Skullerud et al. 1980). The goal of treatment in patients with GSH synthetase deficiency is to correct the acidosis and to compensate for the lack of antioxidant capacity in the cells. A long-term follow-up study of 28 patients showed that early supplementation with the antioxidant vitamins C and E is useful for preventing damage to the CNS in patients with GSH synthetase deficiency (Ristoff et al. 2001). Recommended treatment does not normalize the elevated excretion of 5-oxoproline in urine.

A pregnancy in one woman with moderate GSH synthetase deficiency has been described and resulted in a healthy infant (Ristoff et al. 1999).

9.2 Nomenclature

No.	Disorder (symbol)	Definitions/comment	Gene symbol	OMIM No.
9.1	γ-Glutamylcysteine synthetase deficiency	Decreased synthesis of GSH and γ-glutamylcysteine due to low activity of γ-glutamylcysteine synthetase	*GLCLC* (catalytic subunit), *GLCLR* (regulatory subunit)	230450
9.2.1	Mild GSH synthetase deficiency	Decreased synthesis of GSH due to low activity of GSH synthetase May have 5-oxoprolinuria	*GSS*	266130 601002
9.2.2	Moderate GSH synthetase deficiency	5-Oxoprolinuria, decreased synthesis of GSH due to low activity of GSH synthetase	*GSS*	266130 601002
9.2.3	Severe GSH synthetase deficiency	5-Oxoprolinuria, decreased synthesis of GSH due to low activity of GSH synthetase	*GSS*	266130 601002
9.3	γ-Glutamyl transpeptidase (GT) deficiency	Glutathionuria, increased levels of GSH in plasma, low activity of GT	*GGT* (a multigene family on chromosome 22)	231950
9.4	5-Oxoprolinase deficiency	5-Oxoprolinuria, low activity of 5-oxoprolinase		260005

9.3 Treatment

No.	Disorder	Treatment/diet	Dosage (mg/kg per day)
9.1	γ-Glutamylcysteine synthetase deficiency	Avoid the drugs and foods known to precipitate haemolytic crises in patients with glucose-6-phosphate dehydrogenase deficiency	
		Vitamins C (ascorbic acid) can be tried	100
		Vitamin E (α-tocopherol) can be tried	10
9.2	Glutathione (GSH) synthetase deficiency	Correction of acidosis (bicarbonate, citrate or THAM)	
		Vitamin C (ascorbic acid)[a]	100
		Vitamin E (α-tocopherol)[b]	10
		Avoid the drugs and foods known to precipitate haemolytic crises in patients with glucose-6-phosphate dehydrogenase deficiency	
9.3	γ-Glutamyl transpeptidase (GT) deficiency	No treatment has been recommended	
9.4	5-Oxoprolinase deficiency	No treatment has been recommended	

[a] A trial with short-term treatment of GSH synthetase-deficient patients with vitamin C has been reported to increase the levels of lymphocyte GSH (Jain et al. 1994). Vitamin C and GSH can spare each other in a rodent model (Martensson et al. 1991)

[b] Vitamin E has been claimed to correct the defective granulocyte function (Boxer et al. 1979)

9.4 Alternative Therapies/Experimental Trials

No.	Disorder	Treatment/diet	Dosage (mg/kg per day)
9.1	γ-Glutamylcysteine synthetase deficiency	No treatment has been recommended	
9.2	Glutathione synthetase deficiency	*N*-Acetylcysteine[a] Glutathione esters[b]	15
9.3	γ-Glutamyl transpeptidase (GT) deficiency	No treatment has been recommended	
9.4	5-Oxoprolinase deficiency	No treatment has been recommended	

[a] Since *N*-acetylcysteine (NAC) protects cells in vitro from oxidative stress, it has been suggested that NAC supplements (15 mg/kg per day) should be given to GSH-deficient patients. However, today we know that patients with GSH synthetase deficiency accumulate cysteine and, in our opinion, NAC therefore should not be recommended (Ristoff et al. 2002)

[b] Glutathione esters have been tried in animal models of GSH deficiency and in two patients with GSH synthetase deficiency (Anderson et al. 1994; W. Rhead, personal communication). The GSH esters, which are more lipid-soluble, are readily transported into cells and converted intracellularly into GSH. The esters increase GSH levels in several tissues, but their use is limited because of associated toxic effects, i. e. when they are hydrolysed to release GSH, alcohols are produced as a by-product

9.5 Follow-up/Monitoring

No.	Disorder	Clinical investigations	Laboratory investigations
9.1	γ-Glutamylcysteine synthetase deficiency	Neurological investigation	Hb, reticulocytes
9.2	Glutathione synthetase deficiency	Neurological investigation	Acid-base balance
		Eye examination (retinal pigmentations, corneal opacities)	Hb, reticulocytes
9.3	γ-Glutamyl transpeptidase (GT) deficiency	Neurological investigation	
9.4	5-Oxoprolinase deficiency	Neurological investigation	Acid-base balance

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10 Disorders of Sulfur Amino Acid Metabolism

Bridget Wilcken

10.1 Introduction

Disorders of sulfur amino acid metabolism include disorders of transsulfuration and disorders of the remethylation of homocysteine (Hcy) to methionine (Mudd et al. 2001; Rosenblatt and Fenton 2001). Disorders involving cystine – cystinuria and cystinosis – are dealt with elsewhere in the book. This introduction identifies the individual disorders, the treatment aims, and the evidence, where it exists, for the different treatment modalities.

■ Transsulfuration Disorders

Methionine adenosyltransferase I/III deficiency is rare and can be benign, but demyelination has been reported in some patients. Methionine levels are very high, but there is a deficiency of *S*-adenosyl methionine (SAM), and the aim of treatment is to elevate the latter, with anecdotal success (Surtees et al. 1991), and perhaps to reduce methionine levels. One case of *adenosylhomocysteine hydrolase deficiency* has recently been described, in which there was elevated methionine and SAM. (Mudd et al. 2003). The phenotype is still unclear. The need for treatment in this disorder is not yet substantiated, but there is increasing evidence that very high levels of methionine (over at least 1500 µmol/l, which may not occur in these disorders) can possibly cause cerebral edema (Yaghmai et al. 2002). Glycine *N*-methyl transferase deficiency also leads to elevated methionine and SAM levels, but also *N*-methyl glycine (see below; Mudd et al. 2001).

Cystathionine beta synthase (CβS) deficiency, classic homocystinuria, results in elevated levels of circulating Hcy and methionine, *S*-adenosylmethionine and *S*-adenosyl homocysteine, and reduced circulating cystathionine and cysteine (Mudd et al.). CβS deficiency is associated with lens dislocation, skeletal and intellectual problems, and increased risk of thromboembolism. While the pathophysiology of CβS is not fully understood, the main goal of treatment is to lower Hcy levels in plasma while maintaining methionine within or above the normal range, with cysteine within the normal range (Fig. 10.1). There are few data to suggest optimal treatment targets for any of the analytes to obtain good outcomes, and in practice it is very difficult to achieve a normal level of plasma total homocysteine (tHcy) in all but a very few patients.

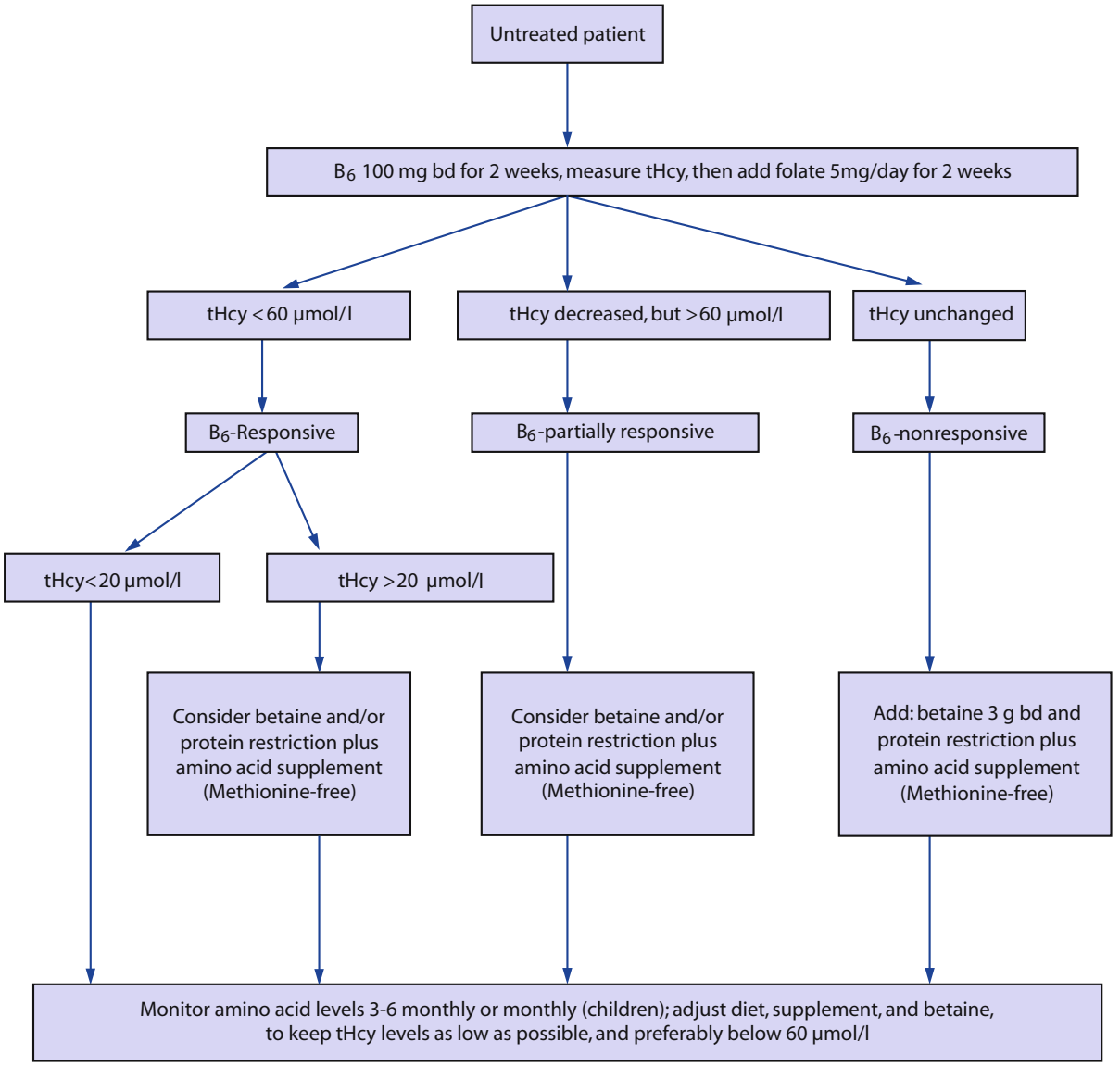

Fig. 10.1. Cystathionine β-synthase deficiency: flow chart for institution of treatment and monitoring of homocysteine levels (*tHcy*, total homocysteine)

The outcome in 158 patients treated for up to 18 years has recently been reported (Yap et al. 2001a). Those patients responsive to pyridoxine (vitamin B_6; see below) maintain tHcy levels of < 60 µmol/l (reference < 15 µmol/l), while B_6-nonresponsive patients have levels usually > 80 µmol/l. Treatment regimens vary somewhat. There is a substantial decrease in thromboembolic episodes from the number expected in untreated patients. In a subset of patients whose

treatment has been standardized and similar to that described below, the same clinical outcome has been seen (Wilcken et al. 1983). In patients with neonatal diagnosis and treatment, there is also evidence of improved outcome, with avoidance of intellectual deficit and dislocation of the lens with free homocysteine (fHcy) levels maintained at usually < 19 µmol/l (Yap et al. 2001b).

Several strategies are used to lower Hcy levels (Mudd et al.):

- The methionine load is reduced by a low-protein diet combined with a methionine-free amino acid mixture, containing supplemented cysteine.
- Transsulfuration can be increased in some patients by using pharmacological doses of the cofactor vitamin B_6.
- Remethylation can be increased both by the folate cycle, using folate and vitamin B_{12} medication, and by betaine methyl transferase, using betaine medication (Wilcken et al. 1983, 1985).

About half of all CβS patients are very responsive to pharmacological doses of vitamin B_6, and this treatment alone will substantially reduce plasma Hcy levels. All of these patients will eventually become folate depleted on treatment, and probably also B_{12} depleted, and they need these vitamins in addition. A few patients are partially responsive to B_6. Most B_6-responsive patients cannot achieve a normal level of Hcy on B_6, folate, and B_{12} treatment alone, although the levels obtained evidently result in a greatly improved outcome. Addition of diet and methionine-free amino acid supplement, if tolerated, will result in near-normal tHcy levels in most patients. B_6-nonresponsive patients need betaine in addition to folate, vitamins B_{12}, and B_6, and a low-protein diet with a methionine-free amino acid supplement (Wilcken et al. 1983). Usually only patients diagnosed as neonates are fully compliant with diet and the amino acid supplement.

γ-Cystathionase deficiency appears to be a benign disorder, needing no treatment (Mudd et al.).

Sulfite oxidase deficiency occurs both as an isolated disorder and, combined with xanthine oxidase deficiency, as a molybdenum cofactor disorder. This severe disorder usually causes intractable seizures and death. No treatment has been successful except in late-onset cases, which may respond to a diet low in protein and an amino acid mixture without methionine or cystine (Touati et al. 2000).

Remethylating Defects

5,10-Methylene tetrahydrofolate reductase (MTHFR) deficiency is associated with elevated circulating Hcy but low or low-to-normal levels of methionine, and there is much clinical heterogeneity, with symptoms including gait disturbance, intellectual deficits, and sometimes isolated thromboembolic episodes. Treatment regimens aim at lowering Hcy while raising methionine and *S*-adenosyl methionine levels, but clinical benefit is not clear, and several aspects of treat-

ment remain experimental. Key aspects of treatment include oral folates, betaine and/or methionine, vitamin B_{12}, and riboflavin (Rosenblatt and Fenton; Fowler 1998). Homozygosity for a common polymorphism in the *MTHFR* gene, 667C>T, confers a slightly increased risk of thromboembolism, especially where dietary folate is low.

● *Disorders of Cobalamin Metabolism*

Disorders of cobalamin metabolism and transport are associated with moderately high levels of circulating Hcy but, as above, low or low-to-normal plasma methionine. Deficiencies may affect hydroxocobalamin, resulting in combined functional deficiencies of methylmalonyl CoA mutase (CblC, CblD, and CblF) or methyl cobalamin alone, (CblE and CblG), resulting in a functional deficiency of methionine synthase. All these disorders can be associated with developmental delay, and to a varying degree, psychiatric disturbance, megaloblastosis, and other problems. Treatment aims are to increase methionine and *S*-adenosyl methionine levels into the normal range and to reduce plasma Hcy (and methylmalonic acid in CblC, -D, and -F). Initial treatment with intramuscular vitamin B_{12} is certainly life-saving in cases presenting in infancy, and early treatment clearly improves the outcome. Other treatment modalities, including folates and betaine, are probably important, but their clinical efficacy has not been studied systematically (Rosenblatt and Fenton).

■ Adverse Effects of Specific Treatments

- Vitamin B_6: doses > 400 mg daily have been associated with peripheral neuropathy (Bendeich and Cohen 1990).
- Betaine: accidental inhalation of the powder has been reported to cause very serious pulmonary problems.
- Methionine levels: very high plasma levels, > 1500 µmol/l may possibly be associated with cerebral edema, although this is uncertain (Mudd et al. 2001).

10.2 Nomenclature

No.	Disorder/deficiency	Definition/comment	Gene symbol	OMIM No.
10.1.1	Methionine adenosyl transferase I/III	Hepatic form	*MAT1A*	250850
10.1.2	*S*-Adenosylhomocysteine hydrolase	One case, with myopathy	*AHCY*	180960
10.1.3	Glycine *N*-methyltransferase	Possibly benign	*GNMT*	606664
10.2	Cystathionine β-synthase		*CBS*	236200
10.2.1	Cystathionine β-synthase	Pyridoxine-responsive form	*CBS*	236200
10.2.2	Cystathionine β-synthase	Pyridoxine intermediate form	*CBS*	236200
10.2.3	Cystathionine β-synthase	Pyridoxine-nonresponsive form	*CBS*	236200
10.3	γ-Cystathionase	Appears benign	*CTH*	219500
10.4.1	Molybdenum cofactor deficiency	Sulfite oxidase plus xanthine and aldehyde oxidase deficiencies	*MOCS1* *MOCS2*	252150
10.4.2	Sulfite oxidase	Isolated	*SUOX*	272300
10.5	5,10-Methylene tetrahydrofolate reductase		*MTHFR*	236250
10.5.1	5,10-Methylene tetrahydrofolate reductase severe		*MTHFR*	236250
10.5.2	5,10-Methylene tetrahydrofolate reductase thermolabile variant	Common in most populations, benign in presence of adequate folate intake	*MTHFR*, $667C > T$	236250
10.6	Methionine synthase	Functional defect		
10.6.1	Cobalamin E defect	Methionine synthase reductase	*CblE*	236270
10.6.2	Cobalamin G defect	Defects within methionine synthase	*CblG*	250940
10.7	Methylmalonyl mutase and methionine synthase	Functional defect		
10.7.1	Cobalamin C defect	Cytosolic reduction of hydroxocobalamin	*CblC*	277400
10.7.2	Cobalamin D defect	Cytosolic reduction of hydroxocobalamin	*CblD*	277410
10.7.3	Cobalamin F defect	Lysosomal transport	*CblF*	277380

10.3 Treatment

● *10.1.1 Methionine adenosyltransferase I/III deficiency*

No.	Symbol	Age	Medication/diet	Dosage
10.1.1	MAT I/III	All ages?	*S*-Adenosyl methionine[a]	

[a] Treatment reported in one patient with MAT I/III, with restoration of normal CSF *S*-adenosylmethionine levels and remyelination seen on magnetic resonance image (MRI) (Surtees et al. 1991)

10.1.2 S-Adenosyl hydrolase deficiency

Only one patient with this disorder has been reported. Treatment with methionine restriction, phosphatidyl choline and creatine appear to have improved myopathy (Mudd et al. 2003).

10.1.3 Glycine N-methyl transferase deficiency

Recently described. May be a benign disorder.

10.2 Cystathionine β-synthase deficiency

10.2.1 CβS deficiency, pyridoxine responsive
10.2.2 CβS deficiency, pyridoxine intermediate

No.	Symbol	Age (years)	Medication/diet	Dosage	Frequency	Target plasma Hcy
10.2.1	CβS-R	> 2	Pyridoxine	50 mg	Daily	tHcy < 20 µmol/l
10.2.2	CβS-I	2–15	Folic acid	1–2 mg	Daily	
			Diet and aminoacid supplement if required[a]			
			Pyridoxine	50–100 mg	Twice daily	tHcy < 60 µmol/l
		Over 15	Folic acid	5 mg	Daily	
			Hydroxocobalamin, oral[b], from c. 5 years	1 mg	Daily	
			Betaine, if indicated[c]	1.5–3 g	Twice daily	
			Diet and aminoacid supplement if required[a]			
			Pyridoxine	50–100 mg	Twice daily	tHcy < 60 µmol/l
			Folic acid	5 mg	Daily	
			Hydroxocobalamin, oral	1 mg	Oral, daily	
			Betaine, if indicated[c]	3 g	Twice daily	
			Aspirin, if indicated[d]	100 mg	Daily	
			Vitamin C[e]		Daily	

[a] Protein-restricted diet and methionine-free supplement can be used in patients who cannot maintain target Hcy levels. See schedule for CβS-NR patients, below. Modest protein restriction is recommended for all patients

[b] Hydroxocobalamin could alternatively be given as an intramuscular injection, 1 mg, monthly. The optimal frequency of IMI hydroxocobalamin in CβS deficiency has not been determined

[c] Betaine is indicated in all CβS-I patients, and in CβS-R patients who cannot maintain target levels of total homocysteine (tHcy) and cannot tolerate a formal low-protein diet with aminoacid supplementation

[d] Aspirin is indicated if there are other thrombophilic factors present, such as factor V Leyden, or if there has been a thromboembolic event

[e] Vitamin C has been shown to improve the impairment of nitric oxide-dependent vasodilatation that occurs in CβS-deficient patients (Pullin et al. 2002)

10.2.3 CβS deficiency, pyridoxine-nonresponsive

No.	Symbol	Age (years)	Medication/diet	Dosage	Frequency	Target plasma Hcy
10.2.3	CβS-NR	> 2	Pyridoxine[a]	50 mg	Daily	tHcy < 20 µmol/l
			Folic acid	2 mg c.	Daily	
			Low-protein diet	c.2 g/kg per day		
			Methionine-free amino acid supplement		With meals	
		2–15	Betaine	1.5–3 g	Twice daily	tHcy < 60 µmol/l
			Pyridoxine[a]	50–100 mg	Daily	
			Folic acid	5 mg	Daily	
			Hydroxocobalamin, oral[b] from c. 5 years	1 mg	Daily	
			Low-protein diet			
			Methionine-free amino acid supplement		With meals	
		Over 15	Betaine[c]	3–4.5 g	Twice daily	tHcy < 60 µmol/l
			Pyridoxine[a]	50–100 mg	Daily	
			Folic acid	5 mg	Daily	
			Low-protein diet			
			Methionine-free amino acid supplement	1 g/kg per day	With meals	
			Hydroxocobalamin, oral	1 mg	Daily	
			Aspirin, if indicated[d]	100 mg	Daily	
			Vitamin C[e]		Daily	

[a] Pyridoxine appears to improve the response to betaine in some pyridoxine-nonresponsive patients, but its use in this situation has not been rigorously investigated

[b] Hydroxocobalamin could alternatively be given as an intramuscular injection, 1 mg, monthly. The optimal frequency of IMI hydroxocobalamin in CβS deficiency has not been determined

[c] Anecdotally, betaine has been given in much higher doses, with no evidence of adverse effect. There is no evidence of advantage in a daily dosage of greater than 150 mg/kg (Matthews et al. 2002)

[d] Aspirin is indicated if there are other thrombophilic factors present, such as factor V Leyden, or if there has been a thromboembolic event

[e] Vitamin C has been shown to improve the impairment of nitric-oxide-dependent vasodilatation that occurs in CβS-deficient patients (Pullin et al. 2002)

10.3 γ-Cystathionase deficency

This defect appears benign, and no treatment is indicated.

10.4.1, 10.4.2 Molybdenum cofactor deficiency, and isolated sulfite oxidase deficiency

No.	Symbol	Age	Medication	Dose/kg	Frequency	Comment
10.4.1	MOCS1	Child	Low-protein diet			Reportedly useful in late-presenting cases. No treatment effective in early presenting cases
10.4.2	SUOX		Methionine + cysteine-free amino acid mixture		With meals	
			Dextromethorphan (NMDA receptor inhibitor)	12.5 mg		

10.5 5,10-Methylenetetrahydrofolate (MTHFR) deficiency

No.	Symbol	Age	Medication	Dosage	Frequency	Target
10.8.1	MTHFR	1–2 years	Folic acid[a]	2 mg	Daily	Maximize MTHFR activity
			Methyl THF[b]			Replacement
			Betaine – oral	150 mg/kg	Twice daily	To increase methionine and SAM
			Hydroxocobalamin – oral[c]	0.5 mg	Daily	Cofactor for methionine synthase
			Riboflavin[d]	5 mg	Daily	MTHFR cofactor
		2 years to adult	Folic acid	5 mg	Daily	As above
			Methyl THF if available			
			Betaine	3–4.5 G	Twice daily	
			Hydroxocobalamin – oral	1 mg	Daily	
			Riboflavin	5–10 mg	Daily	

[a] Folinic acid, 7.5–15 mg daily may be tried instead, but is more expensive

[b] Methyl THF may not be available, and there is little experience with this as a medication

[c] Intramuscular hydroxocobalamin could be used instead, perhaps 1 mg monthly

[d] A trial of riboflavin should be given. Dosages up to 50 mg/day are safe even for babies

10.5.2 MTHFR 667C > T

Homozygosity for this thermolabile variant is common (10–20% or more in many populations). Treatment is not indicated unless there has been a related adverse event, when 2–5 mg folic acid is given daily.

10.6 Functional defects of methionine synthase

10.6.1 Cobalamin E defect
10.6.2 Cobalamin G defect

10.7 Functional defects of methylmalonyl mutase plus methionine synthase

10.7.1 Cobalamin C defect
10.7.2 Cobalamin D defect
10.7.3 Cobalamin F defect

No:	Symbol	Age	Medication[a]	Dosage	Comment
10.6.1 10.6.2 10.7.1 10.7.2 10.7.3	CblE CblG CblC CblD CblF	0–6 months	Hydroxocobalamin, IMI Folic acid, oral Betaine, oral	1 mg/day 1 mg daily 250–500 mg Twice daily	For CblC, D and F, the mutase defect does not produce sufficient methylmalonic acid to require specific treatment other than B_{12}
10.6.1 10.6.2 10.7.1 10.7.2 10.7.3	CblE CblG CblC CblD CblF	6 months–5 years	Hydroxocobalamin, IMI Hydroxocobalamin, oral[b] Folic acid, oral Betaine, oral	1 mg twice weekly 1 mg/day 2 mg/day 75 mg/kg per day Twice daily	See footnote for CblF
10.6.1 10.6.2 10.7.1 10.7.2 10.7.3	CblE CblG CblC CblD CblF	5 years +	Hydroxocobalamin, IMI Hydroxocobalamin, oral[b] Folic acid, oral Betaine, oral	1 mg twice weekly 1 mg/day 5 mg/day 75 mg/kg per day twice daily	

[a] There is evidence to support these medications, but the suggested dosage schedule for hydroxocobalamin does not have published data to support it.
[b] Oral hydroxocobalamin is not indicated for use in CblF, as there is probably a transport defect also affecting ileal transcytosis.

10.4 Follow-up/Monitoring

10.2 Cystathionine β-synthase deficiency

Age	Biochemical	Frequency	Clinical	Frequency
0–5 years	Plasma amino acids Total homocysteine	1–3 monthly	Outpatient visit	1–3 monthly
5–16 years	Total homocysteine Plasma amino acids	3-monthly 3–6 monthly	Outpatient visit Bone mineral density	3–6 monthly Baseline, then every 3–4 years
	Serum B_{12} (unless on B_{12})	Yearly	Opthalmology	Yearly
16 years +	Total homocysteine	6 monthly	Outpatient and other monitoring as indicated	6 monthly
	Plasma amino acids Lipids Thrombophilic factors	6 monthly 2–3 yearly Once		

10.5–10.7 Disorders of folate and B_{12} metabolism and transport

The monitoring of these patients depends heavily on the clinical circumstances, and the schedule given below is only a rough guide.

Age	Biochemical	Frequency	Clinical	Frequency
0–6 months	Plasma total homocysteine Plasma amino acids Plasma methylmalonic acid	c. monthly	Outpatient visit	Monthly
6 months–5 years	As above	3 monthly	Outpatient visit	3-monthly
			Developmental assessment	At c. age 4–5 years
5 years to adult	As above	6–12 months	Outpatient visit	6–12 monthly
	Thrombophilic screen Lipid screen	Once As adult		

Dangers/Pitfalls

Nitrous oxide should not be used as an anesthetic agent (it irreversibly deactivates methionine synthase).

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11 Inherited Hyperammonaemias

James V. Leonard

11.1 Introduction

Several syndromes are associated with symptomatic hyperammonaemia (Table 11.1; Scriver et al. 2000; Fernandes et al. 2000). The patterns of clinical presentation are broadly similar and rather characteristic for all disorders, with certain exceptions (for example arginase deficiency). These are discussed separately.

Patients with hyperammonaemia may present at almost any age, but they are more likely to do so in the neonatal period, during late infancy and around puberty. The early symptoms are often not specific and therefore easily overlooked. Nevertheless it is important to think of hyperammonaemia to establish the diagnosis quickly and reduce complications.

Table 11.1. Nomenclature

No.	Disorder	Definitions/comment	Gene symbol	OMIM No.
11.1	Carbamyl phosphate synthetase deficiency (CPS)	Autosomal recessive	*CPS1*	237300
11.2	Ornithine transcarbamylase deficiency (OTC)	X-linked	*OTC*	311250
11.3	Citrullinaemia (argininosuccinate synthetase deficiency; CIT1or ASS)	Autosomal recessive	*ASS*	215700
11.4	Argininosuccinic aciduria (argininosuccinate lyase deficiency; ASL)	Autosomal recessive	*ASL*	207900
11.5	Arginase deficiency (ARG)	Autosomal recessive	*ARG1*	207800
11.6	*N*-Acetylglutamate synthetase deficiency (NAGS)	Autosomal recessive	*NAGS*	237310
11.7	Lysinuric protein intolerance (LPI)	Autosomal recessive	*SLC7A7*	222700
11.8	Hyperammonaemia-hyperornithinaemia-homocitrullinuria syndrome (HHH)	Autosomal recessive	*SLC25A15*	238970
11.9	Pyrroline-5-carboxylate synthase (PYCS)	Autosomal recessive	*PYCS*	138250
11.10	Hyperinsulinaemia-Hyperammonaemia syndrome (HIHA)	See Chap. 35		
11.11	Citrullinaemia type 2 (CIT 2)	Autosomal recessive	*SLC25A13*	603471, 605814

In the neonatal period, babies with hyperammonaemia, most commonly those with urea cycle disorders, appear normal, but they soon become progressively unwell, with poor feeding, vomiting, lethargy, irritability and tachypnoea. The babies may deteriorate rapidly, with neurological and autonomic problems, including vasomotor instability, fits, apnoea and coma.

In infancy the symptoms are generally less acute and more variable than in the neonatal period. These include anorexia, lethargy, vomiting and failing to thrive with poor developmental progress. Irritability and behavioural problems are also common.

In children and adults, patients commonly present with a more obvious neurological illness. These may be acute and may be precipitated by "metabolic stress" such as infection or anaesthesia. Symptoms may be episodic and often the patient is initially anorexic and lethargic, but sometimes they may be agitated and irritable. Vomiting and headaches may be prominent or the patient may be ataxic. The patient may then recover completely but may progress to develop a fluctuating level of consciousness with focal neurological signs. Alternatively the patients may have chronic neurological illness with learning difficulties and sometimes with neurological signs such as ataxia that are worse with intercurrent infections. The first step is to establish the diagnosis by measuring plasma ammonia, amino acids and urine organic acids and orotate.

Arginase deficiency most commonly presents with a spastic diplegia that is commonly initially diagnosed as cerebral palsy. Some patients may present with fits and a subacute encephalopathy. Those with lysinuric protein intolerance (LPI) usually have typical symptoms of hyperammonaemia, but they may also present with failure to thrive and an aversion to high-protein foods. Later presentation includes growth failure and hepatosplenomegaly.

Hyperornithinaemia-hyperammonaemia-homocitrullinuria (HHH) often presents with typical symptoms of hyperammonaemia, most commonly in infancy.

Pyrroline-5-carboxylate synthetase deficiency is a very rare disorder, the features of which may include joint hypermobility, skin hyperelasticity, cataract and mental retardation. Hyperammonaemia is preprandial.

Citrin deficiency (citrullinaemia type 2) may present as cholestatic jaundice in early infancy or as hyperammonaemic encephalopathy in adults.

11.2 Treatment

Hyperammonaemia has a high morbidity and mortality. Early intervention can prevent many of the complications so that treatment should never be delayed. The treatment of hyperammonaemic syndromes has two phases: that of the acute hyperammonaemia and the long-term management (Brusilow 1991; Urea Cycle Disorders Conference Group 2001).

Acute Hyperammonaemia

Severe hyperammonaemic encephalopathy is a major emergency because of the risk of cerebral oedema (Table 11.2).

Table 11.2. Emergency treatment of severe acute hyperammonaemia

	Treatment
1	General supportive care e. g. ventilation (particularly prior to transfer) treatment of sepsis, seizures etc.
2	Stop protein intake
3	Give a high energy intake, either (a) oral: (i) 10–25% soluble glucose polymer, depending on age, or (ii) protein-free formula (80056, Mead Johnson; Duocal, SHS); or (b) intravenously: (i) 10% glucose by peripheral infusion, or (ii) 10–25% glucose by central venous line. Fluid volumes may be restricted if there is concern about cerebral oedema
4	Alternative pathways for nitrogen excretion (if diagnosis known) Sodium benzoate up to 500 mg/kg per day – oral or intravenously Sodium phenylbutyrate up to 600 mg/kg per day L-Arginine In citrullinaemia and ASA – up to 700 mg/kg per day OTC at CPS deficiencies – up to 50 mg/kg per day For the emergency treatment of hyperammonaemia before the diagnosis is known, some centres consider the following to be a safer alternative: 300 mg L-arginine/kg per day; 200 mg L-carnitine/kg per day. Both can be given orally or intravenously
5	Dialysis (haemodialysis, haemodiafiltration or haemofiltration). Start immediately if plasma ammonia > 500 µmol/l or if ammonia does not fall with the above measures. In very small babies, haemofiltration may not be technically possible and it may be necessary to resort to peritoneal dialysis, but this is less efficient

At conventional doses of 250 mg/kg, sodium benzoate contains 1.74 mmol/kg of sodium and sodium phenylbutyrate 1.35 mmol/kg

These regimens are not nutritionally complete and will cause malnutrition if prolonged. They must not be continued longer than absolutely necessary

Long-Term Treatment

The aim of long-term treatment is to control the metabolic disorder whilst at the same time giving a nutritionally complete diet to achieve as near normal growth and development as possible. The major components of the treatment are diet, replacement of missing metabolites and medication that utilises alternative pathways for nitrogen removal (Table 11.3).

Table 11.3. Summary of treatment of hyperammonaemic syndromes

No.	Disorder	Long-term diet	Emergency regimen	Medication
11.1	Carbamyl phosphate synthetase deficiency	Low protein	Yes	Sodium benzoate Sodium phenylbutyrate Arginine (citrulline)
11.2	Ornithine carbamyl transferase deficiency	Low protein	Yes	Sodium benzoate Sodium phenylbutyrate Arginine (citrulline)
11.3	Citrullinemia	Low protein	Yes	Sodium benzoate Sodium phenyl butyrate Arginine
11.4	Argininosuccinic aciduria	Low protein	Yes	Sodium benzoate Sodium phenylbutyrate Arginine
11.5	Arginase deficiency	Low arginine	Yes	Sodium benzoate Sodium phenylbutyrate
11.6	*N*-Acetylglutamate synthetase deficiency	Normal/reduced protein	Yes	*N*-Carbamylglutamate
11.7	Lysinuric protein intolerance	Low protein		Citrulline
11.8	HHH syndrome	Low protein		
11.9	PYCS			Uncertain
11.10	Hyperinsulinemia-hyperammonaemia syndrome[a]			
11.11	Citrullinaemia type 2 (citrin deficiency)	Galactose-free diet	Yes	Galactose restriction Sodium benzoate Sodium phenylbutyrate Arginine

[a] See Chap. 35

Low-Protein Diet and Essential Amino Acid Supplements

Diet forms an essential part of the management of most patients with hyperammonaemic syndromes. Some patients self-select low-protein diets, while others do not. The aim should be restrict protein to attain good metabolic control while at the same time ensuring that the diet is nutritional complete and requirements for normal growth are met. Protein requirements vary with age, being highest in infancy (FAO/WHO/UNU Expert Committee 1985; Dewey

et al. 1996). There is considerable individual variation in requirements, and the values widely quoted in nutritional texts are usually the "safe" values, being mean + 2 SDs. Some patients may be treated with considerably less that these values (Table 11.4).

Table 11.4. Protein requirements by age (expressed as grams per kilogram per day)

	Age	FAO/WHO/UNU 1985[a] (Mean)	FAO/WHO/UNU 1985[a] (safe: mean +2 SD)	Revised mean[b]	Revised safe values[b]
	0–1 months			1.99	2.69
	1–2 months	2.25		1.54	2.04
	2–3 months	1.82		1.19	1.53
	3–4 months	1.47	1.86	1.06	1.37
	4–5 months	1.34	1.86	0.98	1.25
	5–6 months	1.3	1.86	0.92	1.19
	6–9 months	1.25	1.65	0.85	1.09
	9–12 months	1.15	1.48	0.78	1.02
	1–1.5 years	1.0	1.26	0.79	1.0
	1.5–2 years	0.94	1.17	0.76	0.94
	2–3 years	0.91	1.13	0.74	0.92
	3–4 years	0.88	1.09	0.73	0.9
	4–5 years	0.86	1.06	0.71	0.88
	5–6 years	0.83	1.02	0.69	0.86
	6–7 years	0.82	1.01	0.69	0.86
	7–8 years	0.81	1.01	0.69	0.86
	8–9 years	0.81	1.01	0.69	0.86
	9–10 years	0.80	0.99	0.69	0.86
Girls	10–11 years	0.81	1.00	0.71	0.87
	11–12 years	0.79	0.98	0.69	0.86
	12–13 years	0.77	0.96	0.69	0.85
	13–14 years	0.75	0.94	0.68	0.84
	14–15 years	0.72	0.9	0.66	0.81
	15–16 years	0.7	0.87	0.66	0.81
	16–17 years	0.66	0.83	0.63	0.78
	17–18 years	0.64	0.8	0.63	0.77
Boys	10–11 years	0.79	0.99	0.69	0.86
	11–12 years	0.79	0.98	0.69	0.86
	12–13 years	0.81	1.0	0.71	0.88
	13–14 years	0.78	0.97	0.69	0.86
	14–15 years	0.77	0.96	0.69	0.86
	15–16 years	0.74	0.92	0.68	0.84
	16–17 years	0.72	0.9	0.67	0.83
	17–18 years	0.69	0.86	0.66	0.81

[a] FAO/WHO/UNU 1985

[b] Dewey et al. 1996

Some patients with severe variants or those who are anorexic may need an essential amino acid supplement to meet their nutritional needs. These provide only essential amino acids, and waste nitrogen is utilised to synthesise nonessential amino acids. They are usually given in doses up to 0.7 g/kg per day. The composition of the supplements are given in Table 11.5.

Table 11.5. Composition of essential amino acid supplements

Constituents/100 g	Dialamine	UCD 1	UCD 2	Cyclinex-1	Cyclinex-2
Protein (Eq g)	25	56	67	7. 5	15.0
Energy (kcal)	360	250	290	515	480
Carbohydrate (g)	65	5.8	4.4	52	40
Fat	Nil	Nil	Nil	27	20.7
Cystine (g)	1.2 (0.23)	3.1 (0.24)	Trace (< 0.1)	0.3 (0.14)	0.6 (0.14)
Histidine (g)	1.2 (0.23)	3.1 (0.24)	3.6 (0.24)	0.36 (0.17)	0.72 (0.17)
Isoleucine (g)	3.3 (0.64)	7.6 (0.59)	8.9 (0.59)	1.28 (0.59)	2.56 (0.59)
Leucine (g)	5.13 (1.00)	12.8 (1.00)	15.0 (1.00)	2.17 (1.00)	4.34 (1.00)
Lysine (g)	4.2 (0.82)	9.0 (0.70)	10.7 (0.71)	1.11 (0.51)	2.22 (0.51)
Methionine (g)	1.2 (0.23)	3.1 (0.24)	7.1 (0.47)	0.34 (0.16)	0.68 (0.16)
Phenylalanine (g)	1.8 (0.35)	5.3 (0.41)	14.1 (0.94)	0.75 (0.35)	1.5 (0.35)
Threonine (g)	3.6 (0.70)	6.0 (0.47)	7.1 (0.47)	0.75 (0.35)	1.5 (0.35)
Tryptophan (g)	0.75 (0.15)	2.2 (0.17)	2.8 (0.19)	0.28 (0.13)	0.56 (0.13)
Tyrosine (g)	3 (0.58)	6.5 (0.51)	Trace (< 0.1)	0.88 (0.40)	1.76 (0.40)
Valine (g)	4.62 (0.90)	9.0 (0.70)	10.7 (0.71)	1.43 (0.66)	2.86 (0.66)
Other constituents: all products have added vitamins and minerals				Carnitine Taurine	Carnitine Taurine

Aminoacid ratio to leucine shown in parentheses

Medication

Medication is used for two purposes: firstly to replace compounds that are not transported or synthesised normally; secondly to remove waste nitrogen that is not excreted by the usual pathways, utilising alternative pathways instead. The medicines are listed in Table 11.6.

Table 11.6. Medicines used in the treatment of inherited hyperammonaemias

Medication (route)	Dose	Side-effects
Sodium benzoate (oral or intravenous)	250 mg/kg per day; maximum 500 mg/kg per day. Caution in neonates: high sodium content	Vomiting, anorexia, irritability, lethargy. Accidental overdose: metabolic acidosis, cerebral oedema and hypotension Cautions in neonates: conjugation may be incomplete: theoretical risk or precipitating kernicterus
Sodium phenylbutyrate/ phenylacetate (oral or intravenous)	Maximum 600 mg/kg per day or 20 g/day. Caution in neonates: high sodium content	Vomiting, Mucositis, anorexia, rash, marrow suppression, renal tubular acidosis Accidental overdose: metabolic acidosis, cerebral oedema and hypotension
Arginine (oral or intravenous)	OTC and CPS deficiency 100–150 mg/kg per day ASS and ASL deficiency up to 700 mg/kg per day	Hydrochloride–hyperchloraemic acidosis IV: vomiting, flushing, hypotension, local venous irritation and hyperchloraemic acidosis Theoretical risk of neurological problems if plasma arginine levels chronically > 200 µmol/l
Citrulline (oral: intravenous?)	OTC and CPS deficiency 100–150 mg/kg per day LPI 100–500 mg/kg per day	None ascertained
N-Carbamylglutamate (oral)	100–300 mg/kg per day	Flushing (Chinese restaurant syndrome)

Arginine and Citrulline

Arginine is an amino acid that is normally synthesised in the urea cycle and is therefore not essential. However with any block in the pathway arginine may become essential or semi-essential and must be replaced (Brusilow 1984). Citrulline can be given in severe variants of CPS and OCT instead of arginine to which it is converted, utilising one molecule of nitrogen.

In citrullinaemia and argininosuccinic aciduria, ornithine is not recycled and must be replaced. This requires larger doses (Walser et al. 1977; Brusilow and Batshaw 1979).

In lysinuric protein intolerance, there is a relative deficiency of dibasic amino acids. Arginine and ornithine can be replaced by supplements of citrulline, as

this is transported by a alternative carrier and converted into these amino acids. Lysine remains deficient.

- *Conjugation with Amino Acids*

The principle of this therapy is that compounds are given that are metabolised to substances that are rapidly excreted in the urine or less toxic that the original.

Sodium benzoate is conjugated with glycine to form hippurate, which is rapidly excreted by the kidneys. This creates an alternative route for the excretion of waste nitrogen reducing the load on the urea cycle. One molecule of nitrogen is lost for each molecule of hippurate formed.

Sodium phenylbutyrate is oxidised to phenylacetate and conjugated with glutamine to form phenylacetylglutamine, which is excreted in the urine. Phenylacetate may be given but it is an unpleasant malodorous compound. Two nitrogen molecules are excreted with each molecule of phenylacetylglutamine, but recent studies have shown that conjugation is not complete (Konsumov et al. 2004).

Some studies have suggested that patients with urea cycle disorders may become carnitine deficient, but not all studies have confirmed this. The therapeutic value of supplements is not clear (Mori et al. 1990; Mayatepek et al. 1991).

Citrate reduces postprandial elevation of ammonia and it may replenish aspartate in argininosuccinate synthetase (ASS) deficiency (Iafolla et al. 1990), but its role in the long-term treatment is uncertain (Renner et al. 1995).

- *Dosage*

The doses of these medicines are not fixed but should be adjusted for each individual to achieve god metabolic control. The aim is to keep plasma glutamine less that 1000 µmol/l if possible. Essential amino acids and arginine should be maintained within the normal range except for plasma arginine concentrations in ASS and argininosuccinate lyase (ASL) deficiency, in which concentrations at the upper end or higher are recommended.

- *N-Carbamylglutamate*

N-Carbamylglutamate is an orally active compound that can replace *N*-acetylglutamate, the allosteric activator of carbamyl phosphate synthetase.

11.3 Emergency Regimes

Most patients with hyperammonaemic syndromes are at risk of acute decompensation with hyperammonaemia. (see Table 11.3). This can be precipitated by any metabolic stress, such as fasting, a protein load, infection, anaesthesia or surgery (Morris and Leonard 1997). For this reason all patients should have clear detailed instructions of what to do when they are at risk. A three-stage procedure is recommended. If the patient is off-colour, protein is reduced and carbohydrate increased. If symptoms continue, all protein is stopped and high-energy intake given together with the patient's medication both during the day and night; however, if they cannot tolerate oral drinks and medicines, are vomiting or becoming encephalopathic, then the patient should be assessed in hospital and given intravenous therapy if necessary. For further information see Dixon and Leonard 1992.

Management Out of Hospital

Patients are generally instructed to follow the procedure shown in Fig. 12.1. See also Table 11.7.

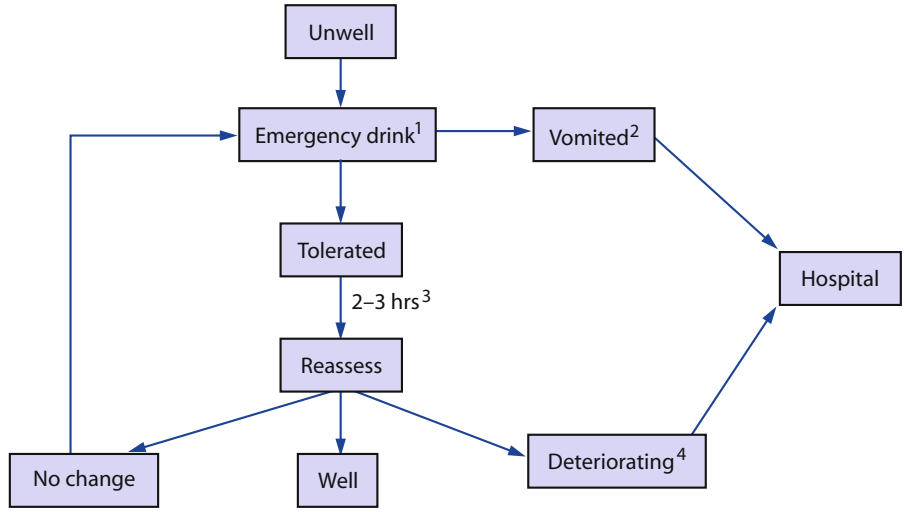

Fig. 11.1. Flow chart for management during illness: 1, volumes and concentrations of carbohydrate-containing drinks vary with age – each child will have their own instructions (Table 11.7). Glucose polymer preparations include Polycose, Maxijul and Polycal; 2, if the parents are experienced and feel confident that their child is stable, they may try repeating the drink after a short interval, but if this is still unsuccessful, admission is needed. The child's regular medicines should be continued. Giving the medicines in small, frequent doses (or as a continuous NG infusion) may reduce the likelihood of vomiting. Vomiting of the drugs is an indication for admission; 3, patients should be reviewed and given carbohydrate-containing drinks every 2 h, day and night. This can sometimes be increased to 3 h in older children; 4, under these circumstances, admission is urgent, particularly if the child is encephalopathic

Table 11.7. Volumes and concentrations of glucose polymer solution to be used during intercurrent illness

Age (years)	Glucose polymer concentration (g/100 ml)	Total daily volume[a]
0–1	10	150–200 ml/kg
1–2	15	95 ml/kg
2–6	20	1200–1500 ml
6–10	20	1500–2000 ml
> 10	25	2000 ml

[a] For each drink the volume will generally be this figure divided by 12

11.4 Alternative and Experimental Therapy

See Table 11.8.

Table 11.8. Radical and experimental therapies

No.	Disorder	Trans-plantation	Other therapy
11.1	Carbamyl phosphate synthetase deficiency	Liver	
11.2	Ornithine carbamyl transferase deficiency	Liver	Hepatocyte infusion Gene transfer (suspended)
11.3	Citrullinemia	Liver	Gene transfer under development
11.4	Argininosuccinic aciduria	Liver	
11.5	Arginase deficiency	Liver	
11.6	*N*-Acetylglutamate synthetase deficiency	None	
11.7	Lysinuric protein intolerance		*N*-Acetyllysine
11.8	HHH syndrome		Ornithine, arginine, citrulline
11.9	PYCS		
11.10	Hyperinsulinemia-hyperammonaemia syndrome		See Chap. 35
11.11	Citrullinaemia type 2 (Citrin deficiency)	Liver	

11.5 Follow-up and Monitoring

The aim of all long-term therapy is to maintain normal plasma ammonia and amino acid concentrations, although this is not always possible. Ideally the plasma ammonia should be less than 60 µmol/l or realistically less that

80 µmol/l; the plasma glutamine less that 1000 µmol/l and essential amino acids within the normal range (Maestri et al 1992; Tuchman and Yudkoff 1999).

All patients on a diet should be monitored carefully to include clinical examination and measurement of growth. Laboratory investigations should include plasma ammonia, amino acids (quantitative), liver functions tests and urine orotate (ornithine transcarbamylase deficiency, OTC, and LPI). Adjustments to the protein and amino acid intake should be made to maintain concentrations within the normal range.

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12 Disorders of Ornithine, Lysine, and Tryptophan

Georg F. Hoffmann, Andreas Schulze

12.1 Introduction

Hyperornithinemia-associated gyrate atrophy of the choroid and retina (HOGA) is caused by deficiency of ornithine-5-aminotransferase. HOGA is an autosomal recessive disorder characterized by progressive chorioretinal degeneration with myopia, night blindness, and loss of peripheral vision, starting late in the first decade, proceeding to tunnel vision and eventual blindness by the third and fourth decade. Plasma ornithine values range from 400 to 1400 µM. Permanent reduction of plasma ornithine to values < 200 µM slows or stops the chorioretinal degeneration. A small proportion of patients respond to pharmacological doses of vitamin B_6 (Weleber et al. 1978). Additional therapeutic approaches to reduce ornithine are substrate deprivation by dietary arginine restriction (Kaiser Kupfer et al. 1991) and augmenting of renal losses by administration of pharmacological doses of L-lysine (Giordano et al. 1978; Peltola et al. 2000; Elpeleg and Korman 2001) or the nonmetabolizable amino acid α-aminoisobutyric acid (Valle et al. 1981). Combined treatment approaches appear to be necessary, since no form of therapy is unequivocally effective. Creatine administration improves the histological abnormalities in muscle (Heinanen et al. 1999), but does not halt the progress of chorioretinal degeneration.

Hyperlysinemia/saccharopinuria appears to be a rare "non-disease." It is caused by deficiency of the bifunctional protein 2-aminoadipic semialdehyde synthase, the first enzyme of the main pathway of lysine degradation. The two functions of the enzyme, lysine:2-oxoglutarate reductase and saccharopine dehydrogenase, may be differently affected by mutations. In most cases, both activities are severely reduced, resulting predominantly in hyperlysinemia and hyperlysinuria, accompanied by relatively mild sacccharopinuria (hyperlysinemia I). About half of the patients described were detected incidentally and are healthy (Dancis et al. 1979, 1983). Symptoms described to be associated with the disorder include psychomotor retardation, epilepsy, spasticity, ataxia, and short stature. Single patients were described with joint laxity and spherophakia, respectively. These observations suggest that it can be accounted for by sampling bias.

2-Aminoadipic and/or 2-oxoadipic aciduria may also have no clinical significance, but some patients are retarded and show variable neurological ab-

normalities. The metabolic profile is heterogeneous, with most patients showing elevations of 2-aminoadipic acid, 2-oxoadipic acid, and 2-hydroxyadipic acid, whereas some excrete 2-aminoadipic acid only. It can be assumed that isolated 2-aminoadipic aciduria without significant 2-oxoadipic aciduria is caused by a deficiency of 2-aminoadipate aminotransferase; whereas combined 2-aminoadipic/2-oxoadipic aciduria would be caused by a deficiency of the 2-oxoadipate dehydrogenase complex. However, the biochemical profile of the reported patients overlap, loading studies were inconclusive, and a deficiency of either enzyme has as yet not been shown directly.

Glutaric aciduria type I (GAI; synonyms: glutaric acidemia type I, glutaryl-CoA dehydrogenase deficiency) is an autosomal recessive inherited neurometabolic disease with an estimated incidence of 1:50,000 Caucasian newborns (Schulze et al. 2003). Early diagnosis and treatment of the asymptomatic child is essential, as current therapy has little effect upon the brain-injured child. In the natural course of the disease, 75% of undiagnosed and untreated children develop acute encephalopathic crises during infancy or early childhood (modal age 6–12 months) precipitated by febrile illnesses or routine vaccinations (Hoffmann et al. 1996; Bjugstad et al. 2000). These crises most often result in irreversible damage of vulnerable brain areas, in particular the striatum, and consequently in the development of a dystonic dyskinetic movement disorder. Restriction of protein and lysine, administration of L-carnitine, timely vigorous treatment during intercurrent illness and neuropharmaceutical agents during the first 6 years of life may completely prevent or at least halt the unfavorable course of the disease. There are, however, some high-risk patients in whom the disease progresses despite therapy (Kölker et al. 2001; Monavari et al. 2000). As GAI has become a treatable neurometabolic disorder, increased inclusion in neonatal screening programs to allow early detection and onset of therapy is the key to further progress. A deeper understanding of the pathological mechanisms will reveal additional therapeutic approaches, which will hopefully also prevent brain damage in those 20–30% of patients that suffer neurodegeneration under current therapeutic strategies (Strauss et al. 2003).

12.2 Nomenclature

No.	Disorder/deficiency	Definition/comment	Gene symbol	OMIM No.
12.1	Hyperornithinemia (ornithine-5-aminotransferase)	Gyrate atrophy of the choroid and retina	*OAT, HOGA*	258870
12.2	2-Aminoadipic semialdehyde synthetase deficiency (hyperlysinemia)	Bifunctional protein of 2-oxoglutarate reductase and saccharopine dehydrogenase	*AASS*	238700, 268700
12.2a	Hyperlysinemia I	Combined decreases in both enzyme activities	*AASS*	238700
12.2b	Hyperlysinemia II or saccharopinuria	Pronounced decrease in saccharopine dehydrogenase activity	*AASS*	268700
12.3	2-Aminoadipic/2-oxoadipic aciduria	Presumed 2-aminoadipate aminotransferase/2-oxoadipate dehydrogenase deficiency		204750
12.4	Tryptophanuria	Presumed tryptophan-2,3-dioxygenase deficiency		276100
12.5	Hydroxykynureninuria	Presumed kynureninase deficiency	*KYNU*	236800
12.6	Hydroxylysinuria	Presumed hydroxylysinekinase deficiency		236900
12.7	Glutaric aciduria I (glutaryl-CoA dehydrogenase deficiency)	Pronounced decrease in glutaryl-CoA dehydrogenase	*GCDH, GAI*	231670

12.3 Treatment

Disorders 12.2, 12.3, 12.6

No treatment.

12.7 Glutaric aciduria I – Emergency treatment

Neurosurgical interventions of subdural hygromas and hematomas in infants and toddlers with GAI should be avoided if at all possible.

- *At Home (for max. 2 h)*

Age (years)	Maltodextrin %	kcal/100 ml	Volume/day
0–1	10	40	min. 150 ml/kg BW
1–2	15	60	120 ml/kg BW
2–6	20	80	1200–1500 ml
> 6	No-disease specific precautions and interventions		

Within 2 h, patients must be stabilized under this treatment. If the patients do not respond, they should be taken to the local metabolic center as soon as possible. If treatment is beneficial, formula diet should by reintroduced stepwise during the next 24 h. In any case, the local metabolic center must be informed in good time by the parents. Emergency treatment must be considered during intercurrent illness and after vaccinations.

- *In Hospital*

- Stop oral intake of natural protein for a maximum of 24 h.
- Intravenous infusion of:
  1. Glucose: 10–15%; 1800 ml/m^2
  2. Electrolyte solution
  3. L-Carnitine: 100 mg/kg BW
- Early implementation of broad-spectrum antibiotics and antipyretics.
- Start stepwise increase in oral intake after 24 h. If oral intake cannot be reestablished after 24 h, start parenteral nutrition including lipids.

Monitor:

- Blood: glucose, pO_2, pCO_2, base excess, electrolytes, transaminases, L-carnitine, ammonia, clotting, blood culture, lactate, amylase
- Urine: ketone bodies, organic acids

12.4 Pharmacological/Dietary Treatment

12.1 Gyrate atrophy

(Fig. 12.1, Flowchart)

12.2 Hyperlysinemia/saccharopinuria

Long-term dietary restriction of lysine has no proven benefit. As patients with hyperlysinemia/saccharopinuria do not suffer from metabolic decompensations, specific interventions during intercurrent illnesses do not appear necessary.

12.3 2-Aminoadipic aciduria/2-oxadipic aciduria

Dietary restriction of lysine also failed to correct the biochemical abnormalities in some patients (Casey et al. 1978) and has no proven long-term benefit. Administration of pharmaceutical doses of vitamins B_1 and B_6 had no effect on the levels of pathological metabolites (Casey et al. 1978). Specific interventions during intercurrent illnesses do not appear necessary.

12.4 Tryptophanuria

12.5 Hydroxykynureninuria

12.7 Glutaric aciduria I

No.	Symbol	Form	Age	Medication/Diet	Dosage	Doses/day (*n*)
12.1	Vitamin B_6-responsive form[a]	HOGA	< 14 yr	Pyridoxine hydrochloride Diet (see below)	40–200 mg/day[b]	2
			> 14 yr	Pyridoxine hydrochloride Diet (see below)	40–500 mg/day[b]	2
12.1	Vitamin B_6-nonresponsive form[a]	HOGA	All ages	Diet (see below)		
12.4			All ages	Nicotinamide	50–300 mg/day	2
12.5	Vitamin B6-responsive form		< 14 yr	Pyridoxine hydrochloride	40–200 mg/day	2
			> 14 yr	Pyridoxine hydrochloride	40–500 mg/day	2
12.5	Vitamin B6-responsive and nonresponsive forms		All ages	Nicotinamide	50–300 mg/day	2
12.7		GAI	< 6 yr	Carnitine	100 mg/kg per day	3
			> 6 yr	Carnitine	50 mg/kg per day	3
				Riboflavin[c] Diet (see below) Neuropharmaceutical agents[d]	100 mg	2

[a] Target plasma ornithine concentration < 200 µmol/l

[b] 15–20 mg/day might be as effective in some patients as a higher dosage (Weleber and Kennaway 1981)

[c] There is as yet not a single case of proven *riboflavin* responsiveness. Riboflavin may be implemented during the first 6 months of age, then stopped for 4 weeks, and reintroduced in the case of evidence of metabolic effect (acylcarnitines, organic acids)

[d] Several *neuropharmaceutical agents* have been tried to ameliorate neurological symptoms in patients with glutaric aciduria type I. In our experience, baclofen (Lioresal, 1–2 mg/kg daily) or benzodiazepines (Diazepam, 0.1–1 mg/kg daily) reduce involuntary movements and improve motor function. In some patients its use and dosage is limited by worsening of truncal hypotonia. There are single positive reports of treatment with intrathecal baclofen or consecutive botulinum injections. Valproic acid should not be given as it effectively competes with glutaric acid for esterification with L-carnitine and may promote disturbances in the mitochondrial acyl-CoA to CoA ratio (Hoffmann et al. 1991)

Dangers/Pitfalls

1. Acute respiratory failure after institution of vitamin B_6 reported in a few neonates with severe seizure disorder.
2. Peripheral neuropathy associated with long-term ingestion of high dosage vitamin B_6 (> 1000 mg/day)
3. Higher doses of carnitine administration may result in gastrointestinal upset and dysfunction.

12.1 Gyrate atrophy – Dietary treatment

Age	Protein requirement (g/kg per day)	Natural protein (g/kg per day)[a]	Arginine-free essential AAM[b]	
			Type	g/kg per day[c]
Children	1.0–1.7	0.3–0.5	2	0.3–0.5
Adults	0.9	0.25	2	0.25–0.3

[a] Intended arginine intake 15 mg/kg per day

[b] 0.6 g essential amino acids corresponds to 1 g protein equivalent

[c] Spread as evenly as possible through the 24 h

Beware/Pitfalls

Overtreatment by protein restriction

12.7 Glutaric aciduria I – Dietary treatment

	0–12 months	1–6 years	6–14 years	Adults
Lysine (mg/kg per day)	100–80	80–50	n.a.	n.a.
Tryptophan (mg/kg per day)	20–17	17–13	n.a.	n.a.
Protein (formula) (g/kg per day)	1.0–0.8	0.8	n.a.	n.a.
Protein (total) (g/kg per day)	2.3–2.0	2.2–1.9	1.0–1.5	0.8–1.0
Energy (kcal/kg per day)	120–100	100–90	60–70	40–50

n.a. not applicable

Dangers/Pitfalls

1. Overtreatment by protein restriction. Special care must be taken to avoid tryptophan deficiency. Tryptophan-free protein formulas should not be used.
2. Increased muscular tension and sweating, common findings in neurologically injured patients with GAI, require a higher intake of calories and water. Percutaneous gastrostomy often leads to a dramatic improvement of nutritional status, and even reduction of the dystonic-dyskinetic symptoms.

12.5 Alternative Therapies/Experimental Trials

■ *12.1 Gyrate atrophy*

No.	Symbol	Age	Medication/diet	Dosage (g/day)	Doses/day	References
12.1	HOGA	Adults	Creatine monohydrate	1.5–2 (1–1.5 g/m^2 per day)	2–3	Heinanen et al. 1999
		Adults	L-Lysine	10–15 (5 g/m^2 per day)	5[a]	Peltola et al. 2000; Elpeleg and Korman 2001
		Adults	α-Aminoisobutyric acid	0.1	5[a]	Valle et al. 1981

[a] Spread within the diet as evenly as possible through the 24 h

Dangers/Pitfalls

1. Creatine administration corrects skeletal muscle abnormalities but not progress of ophthalmological abnormalities.
2. No studies of the long-term efficacy of these approaches have been reported.

12.6 Follow-up/Monitoring

12.2 Gyrate atrophy

Age	Biochemical monitoring[a]	Clinical monitoring[b]	Opthalmological monitoring and fundus photography
Children	6 monthly	6 monthly	Yearly
Adults	Yearly	Yearly	Yearly

[a] Plasma AA, ammonia, urea, ferritin, folate, vitamin B_{12}, blood cell count

[b] Diet: nutrient intake including micronutrients, body growth, general health. B_6 treatment: check for peripheral neuropathy and ataxia; if in doubt, perform electrophysiological tests (quantitative sensory thresholds, sural nerve electrophysiology)

12.7 Glutaric aciduria I

Age	Biochemical monitoring[a]	Clinical and developmental monitoring[b]	Cranial ultrasound/cranial MRI[c]
Infants	Every 4 weeks	Every 8 weeks	3 monthly
Children < 6 years	3 monthly	6 monthly	At age 24 months
Children > 6 years	6 monthly	6 monthly	
Adolescents/adults	Yearly	Yearly	

[a] Plasma AA, including tryptophan, blood cell count, transaminases, albumin, total protein, Fe, ferritin, folate, vitamin B_{12}, carnitine status in plasma, organic acids in urine

[b] Body growth, general health. Detailed psychomotor and neurobehavioral examination and testing every 2 years until the age of 6, starting from the age of 24 months, e. g., with the Bayley Scales of Infant Development

[c] As long as the fontanelle allows cranial ultrasound, it should be performed quarterly, mainly to detect hygromas. All children shall have a cranial MRI at age 24 months. Neuroradiological investigations at earlier time points are optional; however, they should be performed in the following situations: (a) abnormalities (e. g., hygromas) found by cranial ultrasound, (b) after acute encephalopathic crises, (c) if new clinical symptoms highly suggestive of neurological damage develop (e. g., movement disorders)

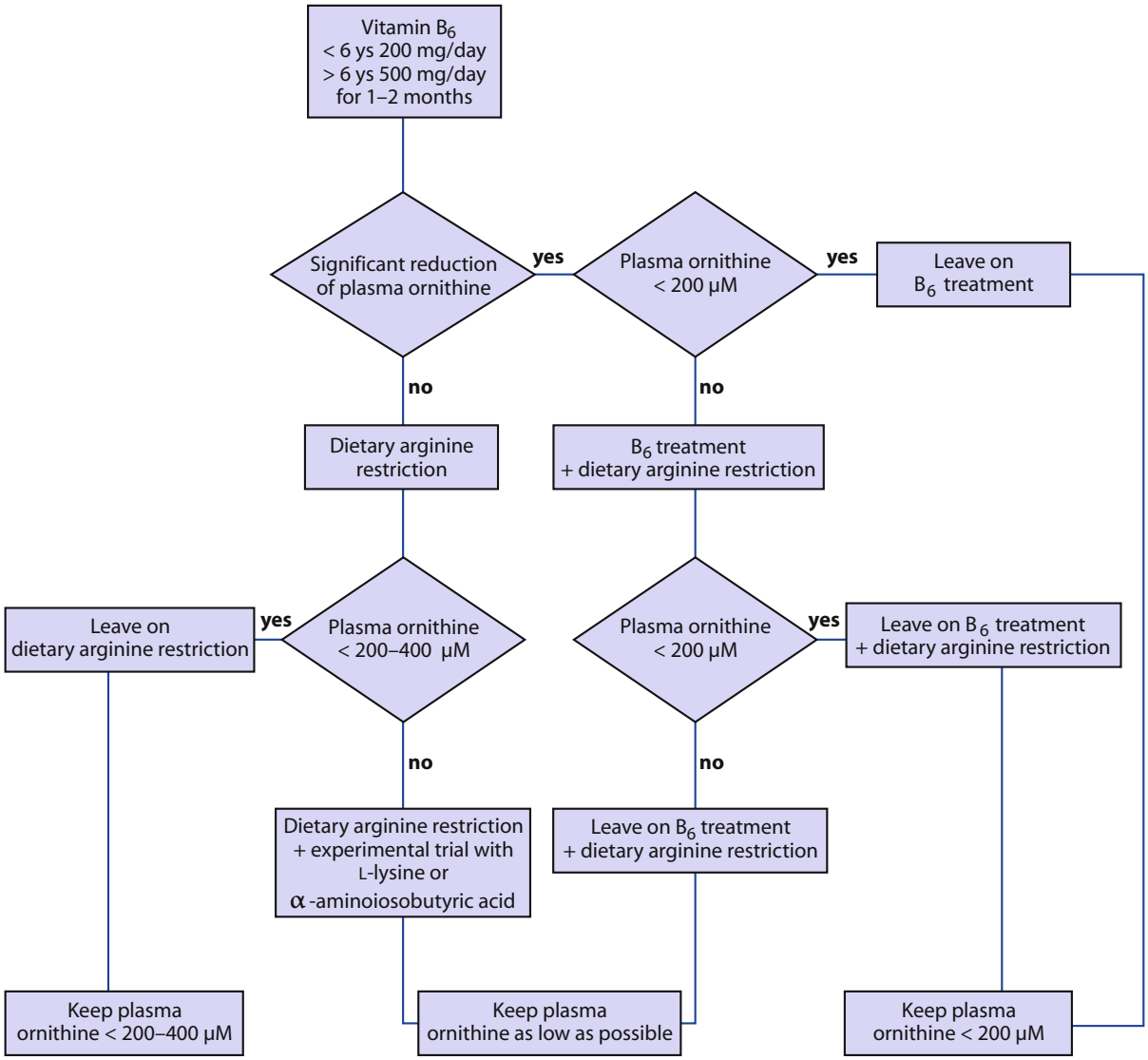

Fig. 12.1. Treatment in gyrate atrophy

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13 Defective Transcellular Transport of Amino Acids

Susanne Schweitzer-Krantz

13.1 Introduction

Transport of Amino Acids

Transcellular transport mechanism are responsible for the transport of free amino acids through epithelial cells and are mainly present in cells of the intestinal mucosa and the renal tubules. A defective transporter may lead to deficient or absent absorption or reabsorption of a single amino acid (e. g., histidine, glycine) or a group of amino acids (e. g., dibasic amino acids, dibasic amino acids and cystine, neutral amino acids, or dicarboxylic amino acids), resulting in only biochemical pathology as "non-disease" or in errors of metabolism with clinical relevance (Kinne et al. 1985).

13.1 Cystinuria

Cystinuria is caused by a defective transport of cystine and the dibasic amino acids lysine, arginine, and ornithine through the brush border epithelial cells of the proximal renal tubules (reabsorption) and the small intestine (absorption) due to mutations in the solute carrier family gene *SLC3A1* encoding the heavy chain rbAT of the renal cystine transport system rbAT/b(0,+)AT on chromosome 2p16.3-p21 (type I) (Byrd et al. 1991; Brodehl et al. 1992; Rosenberg et al. 1965; Botzenhart et al. 2002) or mutations in the *SLC7A9* gene encoding its light chain b(0,+)AT on chromosome 19q13.1-q13.2 (type II and III = type non-I) (Palacin et al. 2001; Byrd et al. 1991). The mode of inheritance is autosomal recessive in the way that heterozygotes reveal either normal amino aciduria (type I) or slight-to-moderate hyperexcretion of cystine and dibasic amino acids (type II or III) (Byrd et al. 1991; Brodehl et al. 1992). According to Rosenberg (Rosenberg et al. 1965), only type III homocygotes, but not type I and II homocygotes, show an increase in plasma cystine levels after oral cystine loading; other authors deny the existence of a type III (Botzenhart et al. 2002; Langen et al. 2000). Homocygotes and compound heterocygotes develop urolithiasis due to the low solubility of cystine ($< 200–300$ mg/l, < 1250 µmol/l). The intestinal malabsorption of cystine and dibasic amino acids has no clinical relevance.

Treatment has to prevent stone formation by high fluid intake during day and night in order to decrease intratubular cystine concentration and by alkalization of the urine to increase cystine solubility (Palacin et al. 2001). Treatment with thiol derivatives such as D-penicillamine or α-mercaptopropionylglycine and the sulfhydryl compound captopril intend to prevent or dissolve stones by forming water-soluble cysteine disulfides with cystine (Stephens 1989; Lindell et al. 1995; Perazella and Buller 1993). Dietary sodium restriction might lead to a contraction of extracellular volume and thus enhance proximal tubular transport of sodium-coupled amino acids (Pewes et al. 1991). Urological techniques should be minimally invasive; they are not able to prevent further stone formation if not combined with medical treatment and permanent increase in fluid intake (Barbey et al. 2000).

For lysinuric protein intolerance (LPI), another transport defect of the solute carrier family (*SLC7A7*), see Chap. 11 (Inherited Hyperammonaemias).

13.2 Dicarboxylic aminoaciduria

Glutamic acid and aspartic acid secretion is highly increased due to a specific renal tubular defect. The few patients described up to now show neurological symptoms (external ophthalmoplegia, deafness, peripheral polyneuropathy), mental symptoms (oligophrenia), or no symptoms (Smith et al. 1994; Teijema et al. 1974; Swarna et al. 1989; Kamoun et al. 1994). A treatment does *not* exist.

13.3 Hartnup disorder

The neutral amino acids alanine, serine, threonine, asparagine, glutamine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, histidine, and citrulline share a common transporter at the luminal border of the epithelial cells in the renal tubuli and the epithelial cells in the small intestine (Levy 2001). In Hartnup disorder an impairment of this tranporter leads to hyperexcretion of these neutral amino acids and to intestinal malabsorption. Excretion of tryptophan metabolites kynurenine and *N*-methyl-nicotinamide is reduced.

Affected persons may be asymptomatic; some demonstrate pellagra-like photodermatitis or cerebellar ataxia due to a nicotinamide deficiency and respond well to the administration of nicotinamide (Levy 2001).

13.2 Nomenclature

No.	Disorder	Definitions/comments	Gene symbol	OMIM No.
13.1	Cystinuria	Defective transport of Cys, Arg, Lys, Orn (intestinal, renal)		
	Type I	Solute carrier family SLC 3A1	*SLC3A1, ATR1 D2H, NBAT*	104614 220100
	Type II (type non-I)	Solute carrier family SLC 7A9	*SLC7A9, CSNU3*	604144
	Type III (type non-I)	Solute carrier family SLC 7A9		600918
13.2	Dicarboxylic aminoaciduria	Defective transport of Glu, Asp (renal)	*SLC1A1, EAAC1*	222730
13.3	Hartnup disorder	Defective transport of neutral amino acids (intestinal, renal)	*HND*	234500

13.3 Treatment

■ *13.1 Cystinuria*

● *Increase in Cystine Solubility by Increase in Fluid Intake*

Age	Fluid intake/24 h (ml)	Fluid distribution
Neonatal	500–1000	Day and night
Infancy	2000	Day and night
Childhood	3000 (–4000)	Day and night
Adolescence	4000[a]	Day and night
Adulthood	4000 (–5000)[a]	Day and night

[a] 2.0 l/m^2/24 h

Dangers/Pitfalls

A high nocturnal fluid intake will delay the achievement of urinary control in childhood.

At least two nocturnal fluid intakes should be the goal. Due to this necessity of several fluid intakes during the night (combined with use of the toilet), good compliance is difficult to achieve in adolescents and adults.

● *Increase in Cystine Solubility by Alkalization of the Urine*

Age	Sodium-potassium citrate (mEq/kg BW ×24 h)	Doses/day
Neonatal	–	–
Infancy	1.5–2.0	3
Childhood	1.5–2.0	3
Adolescence	1.5–2.0	3
Adulthood	8.4 g/24 h	3

Dangers/Pitfalls

One-quarter of the daily dose should be given in the morning, one-quarter at lunchtime, and half in the evening.

The aim is a urinary pH > 7. 5 (self-monitored with indicator paper).

■ *13.2 Dicarboxylic aminoaciduria*

There is no existing therapy.

■ *13.3 Hartnup disorder*

● *Medication of Nicotinamide*

Age	Dosage (mg/24 h)	Doses
Neonatal	–	–
Infancy	50	2
Childhood	100	2
Adolescence	200	2
Adulthood	200	2

Dangers/Pitfalls

Sun-blocking factors should be used, if exposure to sun cannot be avoided.

13.4 Alternative Therapies

■ *13.1 Cystinuria*

● *Forming of Water-Soluble Cysteine Disulfides*

Age	D-Penicillamine (mg every 8 h)	α-Mercaptopropionylglycine (mg/kg every 8 h)	Captopril (mg/24 h)
Neonatal	–	–	–
Infancy	–	–	–
Childhood	< 300	15	6.25–25.0
Adolescence	< 500	15	25.0–50.0
Adulthood	500 (–1000)	15–20 (max. 2000 mg/24 h)	75.0–150.0

Dangers/Pitfalls

The medication is not able to replace high fluid intake.

D-Penicillamine might have several side-effects (rash, fever, immune complex-mediated glomerulonephritis due to antibody formation, leukopenia, thrombocytopenia, taste loss).

α-Mercaptopropionylglycine can lead to fever, proteinuria, and hyperlipidemia.

Captopril reduces blood pressure, inhibiting the conversion from angiotensin I to II and reduces glomerular filtration pressure.

13.5 Follow-up/Monitoring

■ *13.1 Cystinuria*

Age	Biochemical monitoring[a]	Clinical monitoring[b]
Neonatal	Once	Once
Infancy	Monthly	3 monthly
Childhood	3–6 monthly	6 monthly
Adolescence	6 monthly	6 monthly
Adulthood	6 monthly	6 monthly

[a] Urinary pH (daily/weekly), hematuria, leucocyturia, urinary Cys-excretion

[b] Ultrasound of the kidneys

13.2 Dicarboxylic aminoaciduria

Biochemical/clinical monitoring	Frequency	Age
Urinary excretion of Glu, Asp	Once	All ages
Plasma Glu, Asp, Pro	Once	All ages
Neurological examination	Regularly	All ages
Mental development	Regularly	All ages

13.3 Hartnup disorder

Biochemical monitoring	Frequency	Age
Neutral amino acids (U)	Once	All ages
Indolic acids (U)	Once	All ages
Neutral amino acids (P)	Once	All ages

Clinical monitoring	Frequency	Age
Inspection of skin (pellagra-like dermatitis, photodermatitis)	Regularly	All ages

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14 Disorders of Mitochondrial Fatty Acid Oxidation and Ketone Body Metabolism

Hélène Ogier de Baulny, Andrea Superti-Furga

14.1 Introduction

Disorders of mitochondrial fatty acid β-oxidation (FAOD) are a group of inherited metabolic defects that are both clinically and biochemically heterogeneous. Fatty acid oxidation (FAO) is crucial to meet the energy requirement of almost all organs during periods of catabolic stress, and of heart and skeletal muscle at all times. Signs and symptoms in FAOD are mainly due to this inadequacy of energy supply, as well as to potential toxicity of individual metabolites that accumulate secondary to the various enzymatic blocks (for review, Sim et al. 2002).

Therapeutic approaches have two main goals:

- To counteract the accumulation of potentially toxic metabolites such as acyl-CoA esters by preventing lipolysis that occurs during fasting and other catabolic stress, by reducing toxic precursors such as long-chain fatty acids (LC-FA) in long-chain fatty acid oxidation disorders (LC-FAOD), and by promoting detoxification routes such as carnitine esterification
- To circumvent the metabolic block with alternative energetic substrates by providing a high relative amount of carbohydrate, by substituting LC-FA with medium-chain fatty acids in LC-FAOD, by supplying an end-product of β-oxidation such as 3-hydroxybutyrate, or by refilling the Krebs cycle with heptanoate in some disorders, as has recently been described

However, the only two treatment modalities that are undoubtedly beneficial are avoidance of fasting in all FAOD as well as carnitine supplementation for patients affected by carnitine uptake deficiency (OCTN2). The effectiveness of all other therapies has been reported on a case-by-case basis only and provides no firm bases for general recommendations.

14.2 Nomenclature

No.	Disorder	Definition/comment	Gene symbol	OMIM No.
14.1	Carnitine uptake defect	Cardiomyopathy. Reye-like episodes	*OCTN2*	212140
14.2	Carnitine palmitoyl transferase 1	Reye-like episodes/hepatic dysfunction with hypoglycemia. No cardiac, no muscle involvement. Eventually, renal tubular acidosis	*CPT1*	255120
14.3	Carnitine acylcarnitine carrier	Cardiomyopathy, arrhythmia. Liver dysfunction. Unexpected death	*CAC*	212138
14.4	Carnitine palmitoyl transferase 2		*CPT2*	255110
14.4.1	Severe neonatal form	Cardiomyopathy, arrhythmia. Liver dysfunction. Myolysis. Unexpected death. Eventually, renal cysts, multiorgan dysplasias		
14.4.2	Infancy/childhood form	Reye-like episodes. Cardiomyopathy. Myolysis		
14.4.3	Adolescent-adult form	Myopathy, rhabdomyolysis.		
14.5	Very long-chain acyl-CoA dehydrogenase		*VLCAD*	201475
14.5.1	Severe neonatal/early infancy form	Cardiomyopathy, arrhythmia. Liver dysfunction. Myolysis. Unexpected death		
14.5.2	Late infancy/early childhood form	Reye-like episode. Cardiomyopathy. Myolysis. Chronic liver disease		
14.5.3	Adolescent-adult form	Myopathy, rhabdomyolysis		
14.6	Medium-chain acyl-CoA dehydrogenase	Reye-like episodes. Hypoglycemia. A few neonatal/late unexpected deaths	*MCAD*	201450
14.7	Short-chain acyl-CoA dehydrogenase	Poorly defined clinically. Recurrent acute metabolic crises with hypoglycemia, ketoacidosis. Encephalomyopathy, seizures, dysmorphism. Ophtalmoplegia, multicore myopathy (1 case). Ethylmalonate, methylsuccinate (U)	*SCAD*	201470
14.8	Long-chain 3-hydroxyacyl-CoA-dehydrogenase-α		*LCHAD-α*	143450
	Long-chain 3-hydroxyacyl-CoA-dehydrogenase-β		*LCHAD-β*	
14.8.1	Severe neonatal form	Cardiomyopathy, arrhythmia. Liver dysfunction. Myolysis. Unexpected death		
14.8.2	Infancy/early childhood form	Reye-like episodes. Cardiomyopathy. Myolysis. Chronic liver disease (cirrhosis, cholestasis). High incidence of retinopathy, neuropathy. Hypoparathyroidism.		
14.8.3	Adolescent/adult form	Rhabdomyolysis. Neuropathy		
14.9	Medium-/short-chain 3-hydroxyacyl-CoA dehydrogensase	Poorly defined clinically. Fulminant liver disease. Unexpected death (SCHAD in liver). Fasting-induced hypoglycemia (SCHAD in fibroblasts). Hypoglycemia, myopathy, rhabdomyolysis, cardiomyopathy (SCHAD in muscle)	*M/SCHAD*	(600890)

No.	Disorder	Definition/comment	Gene symbol	OMIM No.
14.10	Multiple acyl-CoA dehydrogenation defects		*ETFA* *ETFB* *ETF-DHDH*	231680
14.10.1	Severe neonatal dysmorphic form	Neonatal distress with multiple organ dysplasias (lethal within the 1st week)		
14.10.2	Severe neonatal/early infancy form Milder late infancy/early childhood form	Neonatal distress with hypoglycemia (high mortality rate within weeks) Reye-like episodes. Cardiomyopathy, muscle weakness, myolysis. Progressive leukoencephalopathy		
14.10.3	Late adolescent-adult form	Myopathy, myolysis. Hepatic dysfunction		
14.11	Riboflavin-responsive multiple acyl-CoA dehydrogenation defect	Similar to the milder (14.10.2) or to the late (14.10.3) forms		
14.12	3-Hydroxy-3-methylglutaryl-CoA synthase deficiency	Fasting-induced liver dysfunction with hypoketotic hypoglycemia	*HMGCS2*	246450
14.13	Succinyl-CoA: 3-oxoacid-CoA transferase	Fasting induced ketoacidosis with normal blood glucose levels	*OXCT*	245050
14.14	Long-chain fatty acid transporter protein	Fulminant liver failure (2 cases)	*FATP1*	(600691)
14.15	2,4-Dienoyl-CoA reductase	Myopathy (1 case)	*DECR1*	222745
14.16	Medium-chain 3-ketothiolase	Neonatal distress with hypoglycemia, lactic acidosis, hyperammonemia, myolysis (1 case)	*MKAT*	

14.3 Treatment

■ Management of Life-Threatening Events

No.	Symbol	Therapy	Dosages
14.1	*OCTN2*	L-Carnitine as intravenous infusion	100–400 mg/kg per day
14.2	*CPT1*	Immediate correction of hypoglycemia if present	0.5–1 g/kg per dose
14.3	*CAC*	Constant high-rate glucose infusion (central	
14.4	*CPT2*	intravenous line needed):	
14.5	*VLCAD*	Neonates and infants (<3 years)	10–12 mg/kg per min
14.8	*LCHAD*	Young children (3–10 years)	8–10 mg/kg per min
14.10	*ETF*	Children (> 10 years)	5–8 mg/kg per min
		Insulin infusion (if blood glucose > 6 mmol/l)	0.2–0.3 U/kg per h
		Lipid emulsions are contraindicated	
		L-Carnitine (IV route)	100–200 mg/kg per day
		Once acute problems are resolved, continuous enteral feeding is reintroduced progressively	
14.1	*OCTN2*	For cardiomyopathy and/or cardiac dysrhythmias: conventional cardiac therapy with low NaCl intake, diuretics, cardiotonic and antiarrhythmic drugs	
14.3	*CAC*		
14.4	*CPT2*		
14.5	*VLCAD*		
14.8	*LCHAD*		
14.10	*ETF*		
14.6	*MCAD*	Imediate correction of hypoglycemia if present	0.5–1 g/kg/dose
14.12	*HMGCS2*	Constant high-rate glucose infusion	5–8 mg/kg per min
14.13	*OXCT*	Immediate correction of hypoglycemia if present	0.5–1 g/kg per dose
		Constant high-rate glucose infusion	5–8 mg/kg per min
		Alkalinization if severe acidosis (pH < 7. 20)	Half of daily Na requirement as $NaHCO_3$

During neonatal distress and acute intercurrent decompensations, hypoglycemia, if present, must be corrected immediately by intravenous glucose supply. Subsequently, permanent high-glucose solution is provided in order to maintain blood glucose levels above 5 mmol/l. To meet the recommended glucose infusion rate rapidly, especially in neonates and young children, insertion of a central line catheter should be considered at once. In case of sustained hyperglycemia, insulin infusion is a better choice than decreasing the glucose infusion rate, unless the patient is recovering and continuous enteral feeding can be progressively substituted. In an ETF-DH patient who presented with recurrent life-threatening events with sudden cardiac failure, we have gone further by inserting a permanent central venous line (Port-a-Cath). This measure has allowed immediate high-glucose infusion and rapid recovery in few occasions during the last 3 years.

Lipid emulsions are contraindicated as they contain long-chain fatty acids.

We know now that intravenous carnitine supplementation is well tolerated even by patients with cardiomyopathy or cardiac disrhythmias.

Oral administration of D,L-3-hydroxybutyrate has been successfully used in critically ill ETF patients (disorder 14.10; Van Hove et al. 2003). It could be valuable for all other disorders except OXCT (disorder 14.13).

Cardiomyopathy and dysrhythmias are treated with conventional measures. The potential role of certain antiarrhythmic drugs that inhibit CPT1 activity, such as amiodarone and perhexilline, has been discussed (Bonnet et al. 1999)

It has been proposed to utilize carbamylglutamate (50 mg/kg per day) to treat hyperammonemia that does not regress with high-glucose infusion. However, its usefulness is not proven and one must remember that hyperammonemic states in FAOD are usually not associated with high plasma glutamine levels.

The normalization of glucose, ammonia, plasma free fatty acids, and creatine kinase blood levels is the most valuable indirect marker to indicate that energy metabolism is recovering.

Treatment During Periods of Well-Being

Prevention of Fasting

No.	Symbols	Comments	Therapy
14.2/14.3 14.4.1 14.5.1 14.8.1 14.10.2	CPT1/CAC CPT2 VLCAD LCHAD ETF	In infants <4 months. Severe neonatal/early infancy onset forms	Continuous enteral feeding
(14.2)/14.3 14.4.1/.2 14.5.1/.2 14.8.1/.2 14.10.2	(CPT1)/CAC CPT2 VLCAD LCHAD ETF	Between age 4 months and 24 months; longer in the case of anorexia. Severe early onset forms or milder infant/childhood onset forms	Frequent meals (every 4 h) in daytime + continuous nocturnal enteral feeding
(14.2)/14.3 14.4.1/.2 14.5.1/.2 14.8.1/.2 14.10.2 (14.14.1)	(CPT1)/CAC CPT2 VLCAD LCHAD ETF (FATP1)	Children > 2 years. Severe early onset forms or milder infant/childhood onset forms	Frequent meals in daytime (3 meals and 3 intermeal snacks including a bedtime one) + uncooked cornstarch (1.5–2 g/kg per dose) at midnight
14.2/14.3* 14.4.1/.2* 14.5.1/.2* 14.6/(14.7) 14.8.1/.2* (14.9) 14.10/.2* 14.12 14.13	CPT1/CAC CPT2 VLCAD MCAD/(SCAD) LCHAD (M/SCHAD) ETF HMG-CS2 OXCT	Children older than 4–6 years. Mild childhood-onset forms of FAOD without *signs indicating severe illness such as cardiomyopathy, hepatopathy, or myopathy. Toddlers with ketolysis defects	Normal meal frequency in daytime + a bedtime snack or an uncooked cornstarch dose depending on age (1.5–2 g/kg per dose)
14.2/14.4.3 14.5.3 14.6/14.8.3 14.10.3 14.12 14.13	CPT1/CPT2 VLCAD MCAD/LCHAD ETF HMG-CS2 OXCT	FAOD late adolescent/adult forms. Children with ketolysis defects	Normal meal frequency

Avoidance of fasting is the mainstay of therapy in all FAOD, especially during intercurrent illness. Prescribing increased frequency of meals is a simple preventive measure that allows sufficient glycogen provision that can be used during the first phase of fasting. However, this would not allow infants and young children to cope with night fasting. The maximal time limits for fasting may vary according to age and to the severity of the disorder. Below is some indication of the average tolerance that would be expected in young children,

but the timing should be individualized for each patient, using tolerance tests as described by Morris et al. 1998.

Age	Fasting tolerance (h)
0–4 months	3–4
4–12 months	4–6
1–2 years	6–8
> 2 years	8–12

In young infants with the most severe forms of FAOD, poor appetite, vomiting, and diarrhea may alter the previous scheme. Such cases would benefit from continuous enteral tube feeding for a few months, while others may require nocturnal enteral feeding associated with frequent meals in the daytime. Use of tube feeding in young children has the advantage of allowing prompt nutritional intervention to prevent catastrophic metabolic decompensations during intercurrent illness.

A single dose of uncooked cornstarch given either with a late evening meal or at midnight, depending on individual fasting tolerance, provides a sustained-release source of glucose and may thus delay the fasting period. Usually initiated at 8 months of age, cornstarch is not fully effective before 1 or 2 years. Dosing starts at 1–1.5 g/kg per dose and can be gradually increased to 1.75–2 g/kg per dose by the age of 2 years. It may allow replacement of the nighttime meal or tube feeding in children older than 1–2 years of age (Vockley et al. 2002).

- *Dietary Manipulations*

No.	Disorders (symbols)	Diet (percentage of caloric supply)
14.1, 14.6 14.11 (14.4.3), (14.5.3), 14.7, (14.8.3), (14.10.3) 14.12, 14.13	OCTN2, MCAD ETF-B2+ Mild, late, rhabdomyolytic, asymptomatic forms of (CPT2), (VLCAD), SCAD, (LCHAD), (ETF/ETF-DH) HMGSC2, OXCT	Normal: fat: 30–35%; carbohydrate: 50–55%; proteins: 10–15%
(14.3), (14.4) (14.9) 14.10 (14.14.3)	(CAC), (CPT2) (M/SCHAD) ETF/ETF-DH (MKAT)	High carbohydrate, low fat: fat: 20–25% (including EFA); carbohydrate: 65–75%; proteins: 8–10%
14.2, (14.3), (14.4) 14.5, 14.8, (14.14.1)	CPT1, (CAC), (CPT2) VLCAD, LCHAD, (FATP1)	High carbohydrate, low fat, fat: 20–25%, including: 10% LCT; 10–15% MCT; 1–4% EFA; carbohydrate: 65–75%; proteins: 8–10%

Normal Diet

Many patients do not require a special diet. In a few conditions, namely, OCTN2 (disorder 14.1) and B_2-responsive ETF-DH (disorder 14.11), there are other effective therapies. Patients with MCAD (disorder 14.6), with adult forms of CPT2 (disorder 14.4), with mild-intermittent forms of disorders without chronic expression, with SCAD (disorder 14.7), which clinical expression cannot be clearly linked to the metabolic alteration, and the asymptomatic carriers may tolerate normal diet during periods of well-being. This applies also to ketolysis defect (OXCT, disorder 14.13) and to HMG-CS2 defect (disorder 14.12) that otherwise may require avoidance of protein excesses.

Low-Fat, High-Carbohydrate Diet

A regimen of fat restriction and high carbohydrate (CH) intake, in order to reduce lipolysis, has proven useful for most severe forms of FAOD and is generally recommended. Seventy to seventy-five percent of total energy intakes from carbohydrate are usually recommended.

The ideal proportion of fat intakes has not been studied systematically for each single disease. Many patients are treated with diets providing about 20–25% of total energy intakes as fat (Solis and Singh 2002; Vockley et al. 2002). More severe restriction (<10%) may be applied. It could be an effective means to normalize plasma acylcarnitines profile in deficient LCHAD patients (Gillingham et al. 1999).

Prescription of a fat-restricted diet may put patients at risk of essential fatty acids (EFA) deficiency. Supplementation with EFA can be necessary in order to meet the requirements for age (1–4% of energy intake). Fat-soluble vitamins status has not been studied but may require special attention.

Medium-Chain Triglycerides

Medium-chain triglycerides (MCT) enter mitochondria independently of carnitine. In the LC-FAOD, MCT provision might partially replace the calories that otherwise are provided by LC-FA and thus allow some β -oxidation in the cardiac and skeletal muscles, two tissues that are highly dependent on FAO for their energy requirement. Indeed, a low-fat diet with MCT supplementation, via MCT oil or formulas, is generally used in all LC-FA disorders (Solis and Singh 2002; Vockley et al. 2002). The effectiveness of this approach is controversial and both clinical and biochemical benefits (Parini et al. 1999; Gillingham et al. 1999; Tein 1999) and lack of metabolic alteration have been reported (Lund et al. 2003a).

Some data suggest a role of carnitine acylcarnitine translocase and carnitine palmitoyl transferase 2 in mitochondrial translocation of fatty-acyl esters shorter than C12. Thus, the effectiveness or even the potential harmfulness

roles of MCT-supplementation in CAC (disorder 14.3) and CPT2 (disorder 14.4) patients should be examined carefully (Parini et al. 1999).

Because of the potentially harmful accumulation of toxic metabolites, MCT supplementation is contraindicated in all medium- and short-chain disorders, as well as in ETF/ETF-DH (disorder 14.10), HMG-SC2 (disorder 14.12), and OXCT (disorder 14.13) deficiencies.

There are no universal dosage recommendations for MCT in LC-FA disorders. In LCHAD patients, 10–15% of total energy as MCT (approx. 1.5 g/kg per day), may reduce LC-acylcarnitines accumulation. A higher percentage is not useful, as it would result in medium-chain dicarboxylic aciduria, and MCT in excess would ultimately be stored as LCT in adipocytes (Gillingham et al. 1999).

14.4 Medications

No.	Disorders	Drugs
14.1	OCTN2	100–300 mg carnitine/kg per day
14.2–14.14	All other defects	50–100 mg carnitine/kg per day
14.11	ETF-B2 +	100–300 mg riboflavin (vitamin B_2)/day
14.8	LCHAD α/β	200–400 mg decosahexaenoic acid/kg per day

Carnitine Therapy

In patients affected by OCTN2 (disorder 14.1), L-carnitine therapy is life-saving. It corrects cardiac and skeletal muscle functions within months and allows normal ketogenesis during fasting. With a dosage of 100–300 mg/kg per day divided into three or four doses, plasma carnitine levels can be maintained in the lower normal range (Tein 1999).

In patients with secondary carnitine deficiency, L-carnitine supplementation has long been used. It normalizes plasma carnitine levels and increases urinary excretion of acylcarnitine esters and in this way accelerates the removal of toxic FA intermediates.

In medium- and short-chain FAOD, carnitine levels can be very low as the result of urinary acylcarnitine losses. L-Carnitine supplementation is considered to be beneficial (Wanders et al. 1999; Winter 2003).

In LC-FAOD, L-carnitine supplementation remains controversial because of a theoretical arrhythmogenic risk of LC-acylcarnitine accumulation that has been found in experimental settings. LC-acylcarnitines were also reported to impair the FAO pathway by a substrate/product feedback. In spite of these potential dangers, L-carnitine is commonly prescribed in all FAOD at a median

dose of 75 mg/kg per day, and no deleterious effects have been recognized so far. Direct evidence of a beneficial effect is still lacking, because carnitine is given in combination with other therapeutic measures. However, most patients with LC-FAOD have low plasma free-carnitine levels secondary to increased excretion of LC derivatives, and substitution at pharmacological doses would prevent deficiency and would allow the detoxification process to continue (Gillingham et al. 1999; den Boer et al. 2002; Solis and Singh 2002; Winter 2003).

Riboflavin Supplementation

Because rare patients affected with ETF-DH have been reported with B_2 responsiveness, B_2 supplementation (disorder 14.11), 100–300 mg/day in three divided doses should be systematically tested in these patients.

Docosahexaneoic Supplementation

DHA deficiency has been described with LCHAD defects (disorder 14.8). It has never been described in any other FAOD submitted to low-fat diet. However, conflicting results have been published and not all patients affected with LCHAD (disorder 14.8) are reported to be deficient – even those patients treated with severe restricted-fat diet who have low-to-normal plasma levels of EFA (Gillingham et al. 1999; den Boer et al. 2002). One must, however, remember that EFA should be measured in erythrocytes to conclude on nutritional status (Lund et al. 2003b). Whether putative DHA deficiency could be a contributing factor to the development of neuropathy and retinopathy, exclusively described in LCHAD-deficient patients, is unproven, yet oral supplements are now commonly used.

● *New Therapeutic Approaches*

Triheptanoin

A recent report on this odd-chain triglyceride may open a new pathway to the treatment of LC-FAOD. The rationale for triheptanoin administration relies on the anaplerotic role of the propionyl-CoA obtained during β-oxidation of heptanoate. Propionyl-CoA oxidation forms oxaloacetate and acetyl-CoA that both refill the Krebs cycle, while octanoate and decanoate, as contained in MCT, only give rise to acetyl-CoA. Substitution of triheptanoin for MCT has resulted in dramatic and sustained improvement in three VLCAD patients presenting with severe muscular weakness, rhabdomyolysis and/or cardiomyopathy. It has also allowed the high-carbohydrate diet to be resumed. In theory, a similar improvement might be obtained in other LC-FAOD except for ETF/ETF-DH patients, as in that disorder (disorder 14.10) the generalized dehydrogenation

defect would prevent heptanoate oxidation (Roe et al. 2002). Further studies are underway.

D,L-3-Hydroxybutyrate

The use of 3-hydroxybutyrate is a "product replacement" therapeutic approach in FAOD, during which defective ketogenesis is responsible for energy failure, especially in brain, heart, and muscle.

Beneficial effects have been observed in four patients with the severe infantile form of ETF/ETF-DH (disorder 14.10) who presented with progressive leukodystrophy, or with acute heart failure and myolysis that did not resolve with classic therapy. Oral administration of sodium D,L-3-hydroxybutyrate in increasing doses (100–1000 mg/kg per day) has resulted in sustained clinical and biological improvement (Bonham et al. 1999; Van Hove et al. 2003). This approach might be efficient in all hypoketotic states, especially during acute decompensations. Evidently, it should not be used in patients with ketolysis defect (OXCT/disorder 14.13).

■ Adaptations During Intercurrent Illness

All patients can decompensate rapidly during intercurrent illness and especially during gastroenteritis. To prevent this, a high carbohydrate intake must be maintained during any metabolic stress. Drinks with a 20–25% solution of glucose or cornstarch (patients older than 2 years) should be started at the first sign of illness and then evenly spread over day and night. For those patients usually treated via tube feeding, continuous enteral feeding or repeated bolus of the nutritive solution already used at night can be proposed all through the day. In cases of clinical deterioration with anorexia and gastric intolerance or vomiting, hospital admission is needed for assessment and for intravenous infusion of glucose without delay.

Glucose supply (mg/kg per min)	25% solution	Daily doses
8 (2 years of age)	Maltodextrin	0.8 g/kg/2 h = 12 × 3.2 ml/kg per day
6 (2–6/8 years)	Cornstarch (uncooked)	1.5 g/kg/4 h = 6 × 6 ml/kg per day
5.5 (6/8 years)		2 g/kg/6 h = 4 × 8 ml/kg per day

■ Muscular Forms

Patients who present with late-onset, mild forms with exercise intolerance and vulnerability to rhadomyolysis episodes should, in addition to prevention of fasting, avoid prolonged exercise and cold exposure. A high-carbohydrate diet will replenish muscle glycogen stores and thus help to sustain exercise. Frequent rests and repeated CH loads, via maltodextrin solution or a dose of cornstarch, may be of some benefit (Tein 1999). In practice, it is not easy to plan, and most

patients find their own way to cope with their symptoms. Progressive lethargy with unusual muscular weakness, inability to take oral feedings,and sign of myoglobinuria should prompt rapid hospitalization. Immediate measures to assure energy provision via glucose infusion and/or enteral feeding with a high-carbohydrate, low-fat diet must be taken. Hydration and alkalinization should always be performed to prevent renal failure.

Some beneficial effect of other therapies, such as creatine to prevent recurrent access of myoglobinuria and prednisone in some progressive myopathic forms, has occasionally been reported (Tein et al. 1995; Shortland et al. 2001).

14.5 Follow-up

No.	Disorders	Biological parameter for follow-up
14.1	OCTN2	Free/total carnitine (after an overnight fast)
14.6	MCAD	None available
14.11	ETF-B_2+	None available
14.2 14.3 14.4.1/-2 14.8.1/-2 14.10./-1/-2	CPT1 CAC CPT2 LCHAD α/β ETF*A*/ETFB/ETF-DH	Functional tests to reevaluate fasting tolerance: Blood glucose, lactate, ketones, FA, ammonia, carnitine, acylcarnitines and dicarboxylic acids in urine – Liver function tests, muscle enzymes, EFA/DHA – Cardiac function tests
14.12 14.13	HMGCS2 OXCT	Functional tests to reevaluate fasting tolerance

Clinical assessment will focus on growth, mental development, and cardiac, liver, and muscle function. Regular ophthalmological and neurological evaluations are necessary for LCHAD patients who are susceptible to develop retinopathy and neuropathy. Biological assessment will be regularly planned for those patients affected with severe forms of carnitine shuttle and long-chain mitochondrial spiral defects (Morris et al. 1998; Sim et al. 2002).

14.6 Prognosis

14.1	OCTN2	Good on treatment.
14.6	MCAD	
14.11	ETF-B_2 +	Fasting tolerance would improve with age
14.12	HMG-SC2	
14.13	OXCT	
14.4.3	CPT2 (adult form)	Fairly good, possibly handicapped with myopathy and/or neuropathy
14.5.3	VLCAD (adult form)	
14.8.3	LCHAD α/β(adult form)	
14.10.3	ETF α/β(adult form)	
14.2	CPT1 (infantile/childhood form)	Prognosis uncertain, with high risk of severe sequalae or exitus during intercurrent decompensations
14.3	CAC (infantile/childhood form)	Myopathy, cardiomyopathy
14.4.2	CPT2 (infantile/childhood form)	Myopathy, cardiomyopathy, hepatopathy
14.5.2	VLCAD (infantile/childhood form)	Myopathy, cardiomyopathy, hepatopathy
14.8.2	LCHAD α/β(infantile/childhood form)	Retinopathy, neuropathy, hypoparathyroidism
14.10.2	ETF/ETF-DH (infantile/childhood form)	Myopathy, cardiomyopathy, leukoencephalopathy
14.2	CPT1 (severe neonatal form)	Poor, high risk of sudden death, progressive multi-organ failure, or severe sequelae
14.3	CAC (severe neonatal form)	
14.4.1	CPT2 (severe neonatal form)	
14.5.1	VLCAD (severe neonatal form)	
14.8.1	LCHAD α/β(severe neonatal form)	
14.10.2	ETF/ETF-DH (severe neonatal form)	

As a whole, FAOD are very severe disorders with an unfavorable prognosis. A mortality rate as high as 47% has been reported in a large series of 107 patients. However, in these series and in some LCHAD ones, most of the deaths have occurred at the time of diagnosis and most often before 1 year of age (Gillingham et al. 1999; Saudubray et al. 1999; den Boer et al. 2002). Thanks to better knowledge on clinical presentations, physiopathology, earlier diagnosis and treatment, and novel therapeutic approaches, an increasing number of patients are surviving with a more favorable outcome.

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15 Disorders of Carbohydrate and Glycogen Metabolism

Jan Peter Rake, Gepke Visser, G. Peter A. Smit

15.1 Introduction

The disorders described in this chapter have symptoms varying from mild to severe and life-threatening. The symptoms comprise failure to thrive, hepatomegaly, jaundice and liver failure, hypoglycemia, metabolic acidosis, and (cardio-) myopathy, including muscle pain and exercise intolerance. Four groups of disorders can be distinguished:

A. Disorders of galactose metabolism comprise galactokinase deficiency, galactose-1-*P*-uridyl transferase deficiency (classical galactosemia), and UDP-galactose-4-epimerase deficiency. The primary source of dietary galactose is lactose, the sugar in milk. It is present in human and cow's milk and in most infant formulae. Individuals with one of these enzyme defects are unable to transform galactose into glucose and they accumulate metabolites of galactose after ingesting lactose and/or galactose. Galactitol accumulation accounts for cataract formation. Galactose-1-phosphate is considered to be responsible for the other clinical manifestations, especially liver and kidney failure. Cataracts are the only manifestations of galactose kinase deficiency. The clinical manifestations of classic galactosemia are vomiting, failure to thrive, liver failure with jaundice, kidney failure, cataract, and sepsis, occurring when galactose is introduced in the diet. The severe form of UDP galacose-4-epimerase deficiency resembles classic galactosemia. The main goal of treatment for galactokinase deficiency (more liberal) and classic galactosemia (strict) is the elimination of galactose from the diet. In severe forms of UDP galactose-4-epimerase deficiency, a narrow balance in dietary galactose requirements for biosynthesis (galactosylated compounds) and excess causing accumulation of galactose-1-phosphate should be aimed for.
B. Disorders of fructose metabolism comprise hereditary fructose intolerance, D-glyceric acidemia together with defects in gluconeogenesis. The dietary sources of fructose are fruits, table sugar (sucrose), and sucrose-containing infant formulae. Affected infants with hereditary fructose intolerance (accumulation of fructose-1-phosphate inhibits both hepatic glycogenolysis and gluconeogenesis and results also in depletion of adenosine triphosphate) present with hypoglycemia, vomiting, other gastrointestinal com-

plaints, hepatomegaly, and failure to thrive after ingestion of fructose. Older individuals avoid sweet foods. The main goal of treatment is the elimination of fructose from the diet. Fructose-1,6-diphosphatase deficiency and pyruvate carboxylase deficiency are disorders of gluconeogenesis. Fructose-1,6-diphosphatase deficiency, especially in younger children, presents with moderate hepatomegaly, fasting hypoglycemia, and lactic acidosis. Treatment is aimed at the maintenance of normoglycemia, and fructose ingestion is reduced especially in young children. Pyruvate carboxylase deficiency presents in the first months of life with mild lactic acidemia and delayed psychomotor development. A subgroup of patients with pyruvate carboxylase deficiency present shortly after birth with severe lactic acidemia and die before the age of 3 months. D-Glyceric acidemia, also to be regarded as a defect of serine metabolism, has a relatively large number of healthy unaffected individuals. Affected individuals show a variety of symptoms, mainly neurological. Essential fructosuria, a rare "non-disease" necessitating no specific dietary treatment, and phosphoenolpyruvate carboxykinase deficiency, a very rare disorder of gluconeogenesis with severe psychomotor impairment, are not discussed in this chapter.

C. Disorders of glycogen metabolism affecting mainly the liver comprise glycogen storage diseases (GSDs) 1, 3, 4, 6, 9, 0, and the Fanconi-Bickel form. GSDs 1, 3, 6, and 9 present similarly during infancy, with symptoms of hypoglycemia, marked hepatomegaly, and retarded growth. In all these types, mental development is normal as long as hypoglycemic brain damage is prevented. GSD 1 is the most severe type of these four conditions because, besides impaired glycogen breakdown, also gluconeogenesis is blocked. After a short period of fasting, an overwhelming hypoglycemia and severe lactic acidosis may develop. Two forms of GSD 1 can be distinguished: GSD 1a and GSD 1b. Patients with GSD 1b may also present with infections and symptoms of inflammatory bowel disease related to neutropenia and neutrophil dysfunction. The majority of patients with GSD 3 have a hepatic-myogenic form: a generalized myopathy may include cardiomyopathy. GSD 6 and GSD 9 are the mildest forms: only a mild tendency to fasting hypoglycemia is observed, liver size normalises at adult age, and patients reach normal adult height. A rare hepatic-myogenic form of GSD 9 exists. The main goal of treatment for all these GSDs is to maint normoglycemia by dietary treatment. GSD 4 manifests in the majority of patients in infancy or childhood as hepatic failure with cirrhosis, leading to end-stage liver disease necessitating liver transplantation. In the other patients with GSD 4, all kinds of combinations of hepatic and (cardio-)myogenic forms occur. GSD 0 is in fact not a GSD but a glycogen-synthesis deficiency. It is seen in infancy or early childhood with fasting hypoglycemia and ketosis and postprandial with hyperglycemia and hyperlactacidemia. The Fanconi-Bickel form of GSD has hepatomegaly, hypoglycemia, rickets, and tubulopathy. This type of GSD is discussed separately in Chap. 16.

D. Disorders of glycogen metabolism affecting mainly affecting muscle comprise GSDs 2, 5, and 7. The infantile type of GSD 2 (in fact a lysosomal storage disease) results in cardiac failure, failure to thrive, and death during infancy. Adolescent and adult-onset forms of GSD 2 primarily involve skeletal muscle. GSD 5 (glycogenolytic defect) and 7 (glycolytic defect) involve skeletal muscle and are usually not diagnosed until adolescence or adulthood, when patients present with muscle weakness, exercise intolerance, and myoglobinuria. Patients with GSD 5 may benefit from carbohydrate intake aiming at normoglycemia. In patients with GSD 7, the focus of dietary treatment is aimed at fat enrichment of the diet, since these patients may worsen after high doses of carbohydrates. Some subtypes of the GSDs mainly affecting the liver (GSD 3, GSD 4, and GSD 9) may also affect (heart) muscle. Management of these GSDs including the (cardio-)myogenic symptoms is discussed in the paragraph about liver-related GSDs. Other (very rare) GSDs affecting muscle-related glycogenolytic or glycolytic defects (phosphoglucomutase deficiency, phosphoglycerate kinase deficiency, phosphoglycerate mutase deficiency, lactate dehydrogenase deficiency, and aldolase A deficiency) are not discussed in this chapter.

15.2 Nomenclature

No.	Disorder	Definition/comment	Gene symbol	OMIM No.
15.1	Galactokinase deficiency	Galactose (P,U) ↑, galactitol (U)↑ Cataract	*GALK*	230200
15.2	Galactosemia	Galactose-1-phosphate (P, RBC) ↑, galactose (B,U) ↑ Vomiting, hepatomegaly, jaundice, renal failure, cataracts	*GALT*	230400
15.3	UDPGal-4-epimerase deficiency	Galactose-1-phosphate (P, RBC) ↑ galactose (P) ↑ See galactosemia	*GALE*	230350
15.4	Hereditary fructose intolerance	Fructose ↑ (P), reducing substance (U) Vomiting, liver/renal dysfunction, failure to thrive	*ALDOP*	229600
15.5	Fructose-1,6-diphosphatase deficiency	Glucose ↓(P), lactate ↑ (P) ketones ↑ (P) 2-ketoglutaric acid (U) Seizures, acidosis, hepatomegaly	*FDP 1*	229700
15.7	D-Glyceric acidemia	May vary from mental/motor retardation to no symptoms		220120
15.8	GSD 1a	Glucose ↓ (P), lactate ↑ (P U), ketones ↓ (P), uric acid ↑ (P), cholesterol ↑ (P), triglycerides ↑ (P) Hepatorenomegaly, seizures, acidosis, short stature	*G6PC*	232200
15.8a	GSD 1b	As in GSD Ia and: neutropenia (B) neutrophil dysfunction; infections, inflammatory bowel disease	*G6PT*	232220
15.9	GSD 2 (Pompe)	Infancy: severe cardiomyopathy, hypotonia Juvenile/adult: myopathy	*GAA*	232300
15.10	GSD 3 (Forbe, Cori)	Glucose ↓ (P) ketones ↑↑(P, U), uric acid ↑ (P), cholesterol ↑ (P), CK ↑ (P) 3A Hepatomegaly myopathy 3B Hepatomegaly	*AGL*	232400
15.11	GSD 4 (Andersen)	Hepatosplenomegaly, cirrhosis	*GBE 1*	232500
15.12	GSD 5 (Mc Ardle)	Muscle pain, exercise intolerance, CK ↑ (P)	*PGYm*	232600
15.13	GSD 6 (Hers)	Glucose ↓ (P) ketones ↑↑ (P, U), uric acid ↑ (P), cholesterol ↑ (P), triglycerides ↑ (P) Hepatomegaly	*PGYL*	232700
15.14	GSD 7 (Tauri)	Muscle pain, exercise intolerance, CK ↑ (P)	*PFK-m*	232800
15.15	GSD 9 (GSD 8 by McKusick)	Glucose ↓ (P) ketones ↑↑ (P, U), uric acid ↑ (P), cholesterol ↑ (P), triglycerides ↑ (P) Hepatomegaly	*PHKA/B/G*	306000
15.16	GSD 0	Glucose ↓ (P) ketones ↑↑ (P, U), lactate ↑ (P, U) No hepatomegaly	*GYS 2*	240600
15.17	GSD Fanconi-Bickel type	Glucose ↑ (P,U) galactose ↑ (P,U) Hepatorenomegaly, tubulopathy	*GLUT 2*	227810

15.3 Disorders of Galactose Metabolism

■ Emergency Treatment

No.	Symbol	Therapy
15.2	GALT	Immediate complete restriction of galactose intake, supportive care
15.3	GALE	Immediate complete restriction of galactose intake, supportive care

If GALT (disorder 15.2) or GALE (disorder 15.3) is suspected in a (newborn) child, dietary treatment consisting of a lactose-/galactose-free feeding regimen should be initiated without delay, even before the diagnosis has been confirmed enzymatically or by DNA analysis.

Supportive care depends on the severity of liver, renal, and central nervous system disease and comprises intravenous fluids, plasma, and vitamin K. Initiate treatment with broad-spectrum antibiotics without delay if suspicion of sepsis arises, since, in the event of acute metabolic derangement, patients are at risk for infections due to the compromised response of the immune system.

■ Treatment During Periods of Well-being

● *Dietary Restrictions*

No.	Symbol		Comments
15.1	GALK	Lactose-free/galactose-restricted diet.	Diet for life
15.2	GALT	Lactose-free/galactose-restricted diet.	Diet for life
15.3	GALE	Lactose/galactose-restricted diet.	Diet for life

In GALK (disorder 15.1) minor sources of galactose can probably be disregarded.

In GALT (disorder 15.2) at present it is advised to eliminate galactose intake as much as possible, as very small amounts of galactose may lead to galactose-1-phosphate accumulation.

In severe forms of GALE (disorder 15.3), some dietary galactose intake for biosynthesis is necessary for biosynthesis of galactosylated compounds. Excess, however, should be avoided, as this leads to accumulation of galactose-1-phosphate.

Sufficient calcium intake should be guaranteed to protect patients from osteoporosis.

● *Medications*

No.	Symbol	Medication
15.2	GALT	Ethinyl estradiol therapy in females

Ovarian dysfunction with hypergonadotropic hypogonadism is observed in almost all female GALT (disorder 15.2) patients. Start ethinyl estradiol therapy from age 12–13 years, when gonadotropin levels are high and estradiol levels are low (first 6 months 2 µg daily; 6–12 months 2–5 µg daily; 12–24 months 5 µg daily; 24–36 months 10 µg daily; after 3 years, followed by an oral contraceptive preparation containing ethinyl estradiol and a progestogen daily for 21 days, 7 days abstinence).

No significant effect of additional treatment with uridine could be demonstrated on long-term parameters of development in patients with GALT (disorder 15.2).

■ Follow-up

No.	Symbol	Investigations	Outpatient review
15.1	GALK	Opthalmological investigations. Urine galactose excretion	< 18 years: annually 18+ years: biannually
15.2	GALT	Parameters of growth. Liver size. Opthalmological investigations. Total blood cell count with differential. Hepatic functions, renal functions. Galactose-1-phosphate in red blood cells: aim < 150 µmol/l in red cells; < 50 µg/ml in packed cells; < 0.5 µmol/g hemoglobin. Urinary galactitol excretion. Neurological, psychological, developmental (cognitive functions) investigations. Follicle-stimulating hormone, luteinizing hormone, estradiol (at 6 months, 10 years, 12 years). X-ray left hand for bone age (bone mineral density assessments).	<1 year: 3 monthly 1–4 years: 4 monthly 4–18 years: 6 monthly 18+ years: annually
15.3	GALE	Parameters of growth. Liver size. Opthalmological investigations. Total blood cell count with differential. Hepatic functions, renal functions. Neurological, psychological, developmental (cognitive functions) investigations	< 1 year: 3 monthly 1–4 years: 4 monthly 4–18 years: 6 monthly 18+ years: annually

In milder forms of GALE (disorder 15.3), follow-up can be less extensive.

Follow-up of female GALT patients (disorder 15.2) on hormone treatment should be done on a more regular interval and include, next to physical examinations, blood pressure, bone age, and pelvic ultrasound.

Prognosis

No.	Symbol	Prognosis quoad vitam
15.1	GALK	Undoubtedly good. Normal intellectual development. If treatment has been started in 1st weeks of life, cataracts may clear. Otherwise surgical removal is almost always necessary
15.2	GALT	Variable. After initiation of dietary treatment, liver function and kidney functions will normalize and if started early enough cataracts may clear. However, despite lifelong dietary treatment, long-term outcome is not that favourable: growth retardation, impairment of higher cerebral functions, disorders of motor function and mild intellectual deficit (probably slowly progressive), along with ovarian dysfunction are observed rather frequently in treated patients
15.3	GALE	Poor in severe forms with impairment of psychomotor development/probably good in milder forms

New Therapeutic Approaches

Studies in GALT (disorder 15.2) are underway to investigate the benefits of a selective inhibitor of galactokinase, hereby creating a "GALK" patient and preventing the accumulation of galactose-1-posphate with a much more favorable outcome.

15.4 Disorders of Fructose Metabolism/Deficiencies of Gluconeogenesis

Emergency Treatment

No.	Symbol	Therapeutic means
15.4	FA	Immediate complete restriction of sucrose/fructose/sorbitol intake
15.5	FDP	Immediate (complete) restriction of sucrose/fructose/sorbitol intake

If FA (disorder 15.4); and, to a lesser extent, if FDP, (disorder 15.5) is suspected, dietary treatment consisting of a sucrose-, fructose-, and sorbitol-free feeding regimen should be initiated without delay, even before the diagnosis has been confirmed enzymatically or by DNA analysis. Supportive care depends on the severity of liver and renal disease and comprises intravenous fluids, plasma, and vitamin K.

No.	Symbol	Therapeutic means
15.4 15.5	FA FDP	1. Immediate correction of hypoglycemia by: bolus gift of glucose (in 10 min intravenously): 0–12 months (500 mg glucose/kg);1–6 years (400 mg/kg); 6–12 years (350 mg/kg); adolescents (300 mg/kg); adults (250 mg/kg). Hereafter continuous glucose intravenously: 0–12 months (7–9 mg glucose/kg per min); 1–6 years (6–8 mg/kg per min); 6–12 years (5–7 mg/kg per min); adolescents (4–6 mg/kg per min); adults (2–4 mg/kg per min; increase in amount of glucose in case of fever, 10–30%) 2. Correction of acidosis with (sodium)bicarbonate: number of milliequivalents = 0.3 × weight(kg) × base deficit 3. After correction of hypoglycemia (and acidosis), enteral feedings (fructose-free) should gradually be (re-)introduced

■ Treatment During Periods of Well-being

● *Dietary Restrictions*

No.	Symbol		Comments
15.4	FA	Sucrose/fructose/sorbitol-free diet	Diet for life
15.5	FDP	Sucrose/fructose/sorbitol-restricted diet	
15.7	D-Glyceric acidemia	Sucrose/fructose/sorbitol-restricted diet	

Although in FA (disorder 15.4) tolerance to fructose is very variable, at least till childhood fructose intake should be eliminated completely and not be determined by subjective tolerance.

In FDP (disorder 15.5) fructose intake should be limited (especially during periods of acute illness) but probably need not be eliminated.

Symptomatic patients with D-glyceric acidemia (disorder 15.7) may have the benefit of dietary fructose and sucrose restriction.

● *Prevention of Fasting*

15.5	FDP	During the daytime frequent feedings; at an older age; 3 meals and 2 snacks
15.6	PC	Fasting-tolerance during daytime can be prolonged using uncooked cornstarch. Overnight, at a younger age, continuous gastric drip-feeding may be necessary, depending on age, 8–12 h during the night Alternatively (at a later age) uncooked cornstarch may be given during the night at 4- to 6-h intervals; in late adolescence or adulthood, at 6- to 8-h intervals

Patients with FDP (disorder 15.5) and PC, (disorder 15.6) depend for the maintenance of normal blood glucose concentrations (normoglycemia) on glycogen breakdown from hepatic glycogen stores and on exogenous glucose from intestinal absorption. Especially in young children, the relative amount of hepatic glycogen is limited. Only after a short period of fasting, patients may develop hypoglycemia accompanied by a metabolic acidosis caused by accumulation of lactate. The most important aim of the dietary treatment is therefore maintenance of normoglycemia by avoiding fasting. Although PC (disorder 15.6) is a gluconeogenetic defect and hypoglycemic episodes have been documented, the risk for hypoglycemic episodes is less for PC (disorder 15.6). Intervals between feeds should be determined by glucose profiles and careful fasting studies.

- *Dietary Manipulations*

No.	Symbol	
15.5	FDP	Mild fat restriction (20–25% ER = energy requirement). Protein restriction (10% ER)
15.6	PC	High carbohydrate intake (55–65% ER). Fat restriction (15–20% ER). Triheptanoin

Energy Requirement

Fat intake is restricted in PC (disorder 15.6) in order to reduce the high acetyl-CoA concentrations. It may be necessary to prescribe essential fatty acids to meet with the requirements for age.

Triheptanoin provides the mitochondria after β-oxidation with propionyl-CoA and hence increases the oxaloacetate low concentrations in PC, (disorder 15.6) and acetyl-CoA pool. This would lead to an improved provision of substrate for the Krebs cycle.

- *Medication*

No.	Symbol	
15.4	FA	Vitamin supplements
15.5	FDP	Vitamin supplements
15.7	D-Glyceric acidemia	Vitamin supplements

The benefits of folic acid in FDP (disorder 15.5) have not been proven.

Patients with PC (disorder 15.6) may benefit from biotin (10–40 mg/day); in these patients succinate (2–10 g/day) should also be considered.

Adaptations During Intercurrent Illness

No.	Symbol	Adaptations
15.5 15.6	FDP PC	"Exogenous" glucose delivery should be guaranteed by: repetitive small amounts of glucose solution orally or by nasogastric drip ; continuous drip-feeding; intravenous glucose therapy (+ metabolic correction – lactate – acidosis)

In FDP (disorder 15.5) parents and patients need to recognize different stages of metabolic decompensation: from the impending metabolic situation with paleness, sweating, and abnormal behavior (irritability), to more serious metabolic decompensation with decreased consciousness and hyperventilation, to severe metabolic crisis with coma and convulsions.

Follow-up

No.	Symbol	Investigations	Outpatient review
15.4	FA	Parameters of growth. Liver size. Total blood cell count with differential. Hepatic functions, renal functions. Urine fructose excretion. Neurological, psychological, developmental (cognitive functions) investigations	<12 years: 6 monthly 12–18 years: annually 18+ years: biannually
15.5 15.6 15.7	FDP PC D-Glyceric acidemia	Parameters of growth. Liver size Urine lactate excretion Neurological, psychological, developmental (cognitive functions) investigations 48-h blood glucose curve (at home; preprandial)	Depending on symptomatology

Prognosis

No.	Symbol	Prognosis quoad vitam
15.4	FA	Good. Normal psychomotor/intellectual development. Catch-up growth
15.5	FDP	Benign course after the diagnosis has been made and if intercurrent decompensation can be avoided
15.6	PC	Neonatal and infantile form poorly. Neonatal form rarely survive 3 months of age; infantile form severely mentally retarded Milder (childhood) forms have been described
15.7	D-Glyceric acidemia	Poorly in symptomatic patients with severe neurological abnormalities Good in asymptomatic subjects

In FA (disorder 15.4; intravenous) infusions containing fructose, sorbitol, or invert sugars are life-threatening. Patients (and their parents) should declare their fructose intolerance on every hospital admission.

15.5 Glycogen Storage Diseases – Mainly Affecting the Liver

■ Emergency Treatment

No.	Symbol	Therapeutic means
15.8 15.8a 15.10 15.11 15.13 15.15	GSD 1a GSD 1b GSD 3 GSD 4 GSD 6 GSD 9	1. Immediate correction of hypoglycemia by bolus gift of glucose (in 10 min intravenously): 0–12 months 500 mg glucose/kg; 1–6 years 400 mg/kg; 6–12 years 350 mg/kg; adolescents 300 mg/kg; adults 250 mg/kg Hereafter continuous glucose intravenously: 0–12 months 7–9 mg glucose/kg per min; 1–6 years 6–8 mg/kg per min; 6–12 years 5–7 mg/kg per min; adolescents 4–6 mg/kg per min; adults 2–4 mg/kg per min; increase in amount of glucose in case of fever, (10–30%) 2. Correction of acidosis with (sodium)bicarbonate: number of milliequivalents = 0.3 × weight(kg) × base deficit 3. After correction of hypoglycemia (and acidosis) enteral feedings (galactose-/fructose-restricted, disorders 15.8, 15.8a), should gradually be (re-) introduced

Patients with defects in glycogenolysis (disorders 15.8, 15,8a, 15.10, 15.11, 15.13, 15.15, 15.16) may develop hypoglycemia after only a short period of fasting. This holds especially true for younger patients and patients with GSD 1 (disorders 15.8, 15.8a). The hypoglycemia is often accompanied by a metabolic acidosis caused by accumulation of lactate (disorders 15.8, 15.8a) or ketones (disorders 15.10, 15,11, 15,13, 15.15, 15.16).

Hypoglycemia in GSD 0 needs to be treated; however, excess of glucose (galactose/fructose) may lead to hyperglycemia and/or hyperlactacidemia.

■ Treatment During Periods of Well-being

● *Dietary Restrictions*

No.	Symbol		Comments
15.8 15.8a 15.16	GSD 1a GSD 1b GSD 0	Galactose/fructose/saccharose-restricted	Diet for life

No consensus exists about the extent of avoiding lactate production in GSD 1a and 1b (disorders 15.8, 15.8a) from galactose, fructose, and saccharose. Moderate hyperlactacidemia may prevent cerebral symptoms if blood glucose concentration is low, as lactate may serve as an alternative fuel for the brain. On the other hand, some evidence exists that avoiding lactate production from galactose and fructose intake may favor long-term outcome.

● *Prevention of Fasting*

No.	Symbol	
15.8 15.8a 15.10 15.11 15.13 15.15 15.16	GSD 1a GSD 1b GSD 3 GSD 4 GSD 6 GSD 9 GSD 0	During the daytime frequent feedings; at an older age, 3 meals and 2 snacks. Fasting tolerance during daytime can be prolonged using uncooked cornstarch. Overnight, at a younger age (especially in GSD 1a, 1b, and 3), continuous gastric drip-feeding may be necessary, depending of age 8–12 h during the night. Alternatively, in these patients (at a later age), uncooked cornstarch may be given during the night at 4- to 6-h intervals, in late adolescence or adulthood at 6- to 8-h intervals

Patients with the hepatic glycogenoses (disorders 15.10, 15.11, 15.13, 15.15, 15.16) depend for the maintenance of normal blood glucose concentrations on gluconeogenesis except GSD 1a and 1b, (disorders 15.8, 15.8a, in which also gluconeogenesis is blocked) and on exogenous glucose from intestinal absorption. After a short period of fasting, especially younger patients and patients with GSD 1a and 1b may develop an impending hypoglycemia accompanied by a metabolic acidosis. The most important aim of the dietary treatment is therefore maintenance of normoglycemia by avoiding fasting. Intensive dietary treatment induces catch-up growth, reduces liver size and ameliorates secondary biochemical abnormalities. In GSD 1a and 1b (disorders 15.8, 15.8a) lifelong dietary treatment is necessary. In GSD 3, dietary treatment is less demanding. Intensive dietary treatment with uncooked cornstarch or nocturnal continuous gastric drip-feeding (along with dietary protein enrichment) may ameliorate myogenic symptoms by counteracting increased gluconeogenesis and avoiding a drain from muscle protein. In GSD 4, intensive dietary treatment prevents hypoglycemia and may improve clinical condition before liver transplantation. In GSD 6 and 9, dietary treatment generally is limited to younger children.

The feedings/meals during daytime, including snacks, should contribute to the maintenance of normoglycemia and contain, as a carbohydrate source, preferably precooked cornstarch. In infants it is not necessary to replace breast milk, except for infants with GSD 1a or 1b (disorders 15.8, 15.8a), who may benefit from glucose-enriched lactose-/sucrose-free feedings previous to breastfeeding. Theoretically, uncooked cornstarch should not be started in children less than 1 year of age, as pancreatic amylase activity is insufficiently mature in these children. For continuous gastric drip-feeding, both a glucose/glucose polymer solution or a (galactose-/fructose-free in GSD 1a and 1b) formula enriched with maltodextrin can be used.

- *Dietary Manipulations*

No.	Symbol	
15.8 15.8a	GSD 1a GSD 1b	High carbohydrate intake (55–65% ER = energy requirement). Moderate fat restriction (20–30% ER). Predominantly polyunsaturated fats. Moderate protein restriction (10–15% ER). Sodium restriction
15.10	GSD 3	Carbohydrate enriched (50–55% ER). Protein enriched (20% ER) in patients with the hepatic-myogenic form. Predominantly polyunsaturated fats
15.11 15.13 15.15	GSD 4 GSD 6 GSD 9	Carbohydrate enriched (55–65% ER). Predominantly polyunsaturated fats
15.16	GSD 0	Protein enriched (20% ER)

In GSD 1a and GSD 1b (disorders 15.8, 15.8a), analogous to proteinuric insulin-dependent diabetic mellitus patients, reduction of protein intake should be considered. Furthermore, a reduction in sodium intake may enhance the beneficial renopreservative effects of angiotensin-converting enzyme inhibitors.

In GSD 3 (disorder 15.10), dietary protein enrichment may restore protein loss by amino acid mobilization used as substrates for gluconeogenesis from muscle protein.

- *Medication*

No.	Symbol	
15.8 15.8a 15.10 15.11 15.13 15.15	GSD 1a GSD 1b GSD 3 GSD 4 GSD 6 GSD 9	Allopurinol: initial dose 10 mg/kg/day in 3 dosages (max 900 mg/day). Vitamins and minerals according to WHO standards. Fibrates, for indications, see below. (Statines, for indications, see below)
15.8 15.8a	GSD 1a GSD 1b	Angiotensin-converting enzyme inhibitor (dosage depends on type). (Sodium)Bicarbonate: initial dosage 1–2 mEq/kg in 3–4 doses. (Potassium)Citrate: initial dosage 1–2 mEq/kg in 3–4 doses
15.8a	GSD 1b	Oral antibiotics (prophylactics), for indications, see below. 5-Aminosalicylic acid, for indications, see below. Granulocyte colony-stimulating factor, for indications and dose, see below

In hepatic glycogenosis (disorders 15.8, 15.8a, 15.10, 15.13, 15.15), allopurinol should be started to prevent from urate nephropathy if serum uric acid concentrations exceed the upper normal level for age despite optimal dietary treatment. As uric acid is regarded as a potent radical scavenger (possible protection against premature atherosclerosis), the recommended uric acid concentrations are in the higher normal range.

Supplementation of vitamins should commence when WHO recommendations are not met. Special attention is needed regarding calcium and vitamin D in case the intake of milk and milk-derived products is limited (disorders 15.8, 15.8a). Special attention is also needed regarding vitamin B_1 intake as increased metabolism of carbohydrates needs sufficient vitamin B_1.

In GSD 1a and 1b (disorders 15.8, 15.8a), analogous to proteinuric insulin-dependent diabetic mellitus patients, an ACE inhibitor should be started. Opinions differ about the timing of when to start this renopreservative drug; it is the authors' opinion to start this therapy as soon as microalbuminuria persists and not wait till hypertension develops. Angiotensin II antagonists may elicit comparable results; however, clinical experience in GSD 1a and 1b (disorders 15.8, 15.8a) with this drug is even more limited.

In GSD 1a and 1b patients (disorders 15.8, 15.8a) with, despite intensive dietary treatment, persisting low venous blood base excess (<−5 mmol/l) or persisting low venous blood bicarbonate (<20 mmol/l), it is recommended to correct lactacidemia with (sodium)bicarbonate or (potassium)citrate. Apart from correcting acidemia, it induces also alkalization of the urine, diminishing the risk for urolithiasis and nephrocalcinosis. The use of citrate has the advantage over bicarbonate in the correction of hypocitraturia, another risk factor for urolithiasis. Hypocitraturia is more often seen with increasing age of the patients.

The benefits of prophylactic oral antibiotics in patients with neutropenia have been studied in several groups, but not systematically in GSD 1b (disorder 15.8a). Cotrimoxazol is advised in symptomatic patients or those with neutrophil count $< 500 \times 10^6$ /l.

In mild cases of inflammatory bowel disease in GSD 1b (disorder 15.8a), conservative treatment with 5-aminosalicylic acid might be of benefit.

No controlled trials are available to support G-CSF therapy in GSD 1b (disorder 15.8a). Therefore, the use of G-CSF in GSD 1b should be limited to the following indications: (1) a persistent neutrophil count $< 200 \times 10^6$ /l; (2) a single life-threatening infection requiring intravenous antibiotics; (3) serious complaints of inflammatory bowel disease, including perioral, perianal infections and severe diarrhea requiring hospitalization or disrupting normal life. GSD 1b patients seem to respond to low doses of G-CSF: a starting dose of 2.5 µg/kg subcutaneous daily or every other day is therefor recommended. Determine neutrophil count frequently and adjust the dose in steps of 2.5–5 µg/kg per day (maximum 25 µg/kg) to maintain neutrophils $> 1000 \times 10^6$ /l.

Fibrates are indicated if triglyceride concentrations in patients with hepatic forms of GSD (disorders 15.8, 15.8a, 15.10, 15.13, 15.15) remain above 10.0 mmol/l despite optimal dietary efforts. Fish oil treatment of hyperlipidemia in these patients has limited therapeutic effect, since the beneficial enhancement of fat catabolism on lipids and lipoprotein profile seems to be temporary. Statines may be indicated in adult GSD 1a and 1b (disorders 15.8, 15.8b) patients with deteriorating of hypercholesterolemia despite op-

timal dietary treatment and ACE inhibition as a result of progressive renal disease.

Treatment with growth hormone in patients with the hepatic GSDs (disorders 15.8, 15.8a, 15.10, 15.13, 15.15) and growth retardation is not advocated, since the effect on final height is negligible.

Adaptations During Intercurrent Illness

No.	Symbol	Adaptations
15.8	GSD 1a	"Exogenous" glucose delivery should be guaranteed by: repetitive small amounts of glucose-solution orally or by nasogastric drip; continuous drip feeding; intravenous glucose therapy (+ correction lactate acidosis)
15.8a	GSD 1b	
15.10	GSD 3	
15.11	GSD 4	
15.13	GSD 6	
15.15	GSD 9	
15.16	GSD 0	

Parents and patients with hepatic glycogenosis leading to hypoglycemia and metabolic acidosis need to recognize different stages of metabolic decompensation: from the impending metabolic situation with paleness, sweating, and abnormal behavior (irritability), to more serious metabolic decompensation with decreased consciousness and hyperventilation, to severe metabolic crisis with coma and convulsions.

Especially patients with GSD 1a and 1b (disorders 15.8, 15.8a) and younger patients with GSD 3 and GSD 4 (disorders 15.10, 15.11) have a high risk for metabolic decompensation during intercurrent illness; this risk is lower for younger patients with GSD 6 and GSD 9 (disorders 15.13, 15.15) and adolescent/adult patients with with GSD 3 and GSD 4 (disorders 15.10, 15.11). The risk for metabolic decompensation is nearly absent in adult patients with GSD 6 and GSD 9 (disorders 15.13, 15.15).

In GSD 1a and 1b (disorders 15.8, 15.8a) prior to elective surgery, bleeding time (platelet aggregation) should be normalized by continuous gastric drip feeding (24 h for 2–3 days) or intravenous glucose infusion (24–48 h). Close perioperative monitoring of blood glucose (and lactate) concentration is essential.

Follow-up

No.	Symbol	Investigations	Outpatient review
15.8 15.8a 15.10 15.11 15.13 15.15 15.16	GSD 1 GSD 1a GSD 3 GSD 4 GSD 6 GSD 9 GSD 0	Parameters of growth. Liver size. Spleen size. Hematological parameters. Blood gas analysis. Blood uric acid, cholesterol, triglycerides. Hepatic functions. Renal functions. 48 h blood glucose curve. (at home; preprandial; aim: >3.5–4.0 mmol/l; GSD 0 aim: postprandial <10.0 mmol/l). X-ray left hand for bone age (yearly). Neurological, psychological, developmental (cognitive functions) investigations (on demand) Investigations for detection/follow-up (long-term) complications (see below)	GSD 1a and 1b: 0–3 years: 2 monthly; 3–20 years: 3 monthly; 20+ years: 6 monthly. GSD 0, 3, and 4: 0–3 years: 3 monthly; 3–20 years: 4 monthly; 20+ years: 6 monthly; GSD 6 and 9: 0–3 years: 4 monthly; 3–18 years: 6 monthly; 20+ years: annually
15.8 15.8a	GSD 1a GSD 1b	Urine lactate excretion. Aim: <0.6 mmol/l or <0.06 mmol/mmol creatinine. Investigations for detection/follow-up (long-term) complications (see below)	
15.8a	GSD 1b	Fecal α-1-antitrypsin if, on G-CSF: total blood cell count with differential (monthly). Serological markers of inflammation (every 6 months). Bone marrow investigations (yearly)	
15.10 15.11 15.15	GSD 3 GSD 4 GSD 9	In hepatic-myogenic forms: blood creatinin kinase; electrocardiography, heart ultrasonography; muscle function investigations; lung function measurements	

Investigations for detection or follow-up of complications related to GSD 1a and GSD 1b (disorders 15.8, 15.8a) should include urine sediment analysis (every 6 months); urine microalbumin, protein, creatinine, and calcium concentrations (every 6 months; if microalbuminuria/proteinuria is present or if using ACE-inhibitors every 3 months); creatinine clearance GFR measurement (>5 years, yearly); ultrasonography of the liver, kidneys, spleen, and ovaries (0–10 years, yearly; >10 years every 6 months; if liver adenoma(s) present, every 3 months, CT/MRI on demand and α-fetoprotein every 3 months); ultrasonography of the heart and electrocardiography (>10 years, yearly); bone densitometry (>5 years every 1–2 years); if anemia is present, iron status, vitamin B_{12}, and folic acid status are required; if (acute) abdominal pain is present, blood amylase levels and ultrasonography of the liver, pancreas, and ovaries are recommended.

Investigations for detection or follow-up of complications related to GSD 3 should include blood ASAT, ALAT, AP, γGT, protein, and albumin concentrations, as well as levels of clotting factors (every 6 months); ultrasonography of the liver (0–10 years yearly; >10 years every 6 months; if liver adenoma(s)/fibrosis/cirrhosis are present every 3 months, CT/MRI on demand and αFP, CEA every 3 months).

Investigations for detection or follow-up of complications related to GSD 4 should include blood ASAT, ALAT, AP, γGT, protein, and albumin concentrations, levels of clotting factors (every 3 months); ultrasonography of the liver (every 6 months; if fibrosis/cirrhosis is present every 3 months; CT/MRI on demand).

Prognosis

No.	Symbol	Prognosis quoad vitam
15.8	GSD 1a	Fairly good. Normal psychomotor/intellectual development if acute metabolic decompensation can be prevented for. With intensive dietary treatment, reduction of complications related to secondary metabolic derangement (gouty arthritis, nephrolithiasis, pancreatitis). Long-term complications (liver adenomas (carcinomas), hepcidin-induced anemia, progressive renal disease, osteopenia, pulmonary hypertension) may cause morbidity
15.8a	GSD 1b	See GSD 1a, recurrent infections (ENT, respiratory, pyogenous skin, urinary tract, gastrointestinal, deep abcess) and inflammatory bowel disease in GSD 1b may cause morbidity and mortality
15.10	GSD 3	Good for the purely hepatic form, with normal psychomotor/intellectual development, if acute metabolic decompensation can be prevented. Seldom development of hepatic complications (adenoma, fibrosis/cirrhosis or carcinoma). Less favorable for the hepatic-myogenic form, as severe (cardio-)myopathy and peripheral neuropathy may develop even after a long latency
15.11	GSD 4	In most patients cirrhosis will lead to end-stage liver disease, necessitating liver transplantation before adolescence. More favorable hepatic course in some patients. Intermediate favorable for the hepatic-myogenic form. Rare fatal neuromuscular form exists
15.13	GSD 6	Undoubtedly favorable outcome. Probably less favorable for the hepatic-myogenic form. Typical growth pattern, normal adult height
15.15	GSD 9	
15.16	GSD 0	Probably normal psychomotor/intellectual development if acute metabolic decompensation can be prevented

15.6 Glycogen Storage Diseases – Mainly Affecting Muscle

Treatment During Periods of Well-being

No.	Symbol	Therapy
15.9	GSD 2	Symptomatic. Physiotherapy. Regular physical exercise (at submaximal level); avoid excessive exercise
15.12	GSD 5	
15.14	GSD 7	

In GSD 5 (disorder 15.12) and GSD 7 (disorder 15.14), severe rhabdomyolysis eventually leading to acute renal failure may occur after (short-term) intensive exercise.

Dietary Manipulations

No.	Symbol	
15.9	GSD 2	Protein-enriched (20% ER = energy requirement), supplementation of alanin and branched-chain amino acids
15.12	GSD 5	Carbohydrate enriched (55–65% ER), protein enriched (15–20% ER)
15.14	GSD 7	Fat enriched (30–40% ER), protein enriched (15–20% ER)

Sucrose ingestion before exercise may improve aerobic exercise tolerance in patients with GSD 5 (disorder 15.12). However, it may also lead to overweight and to increased insulin secretion, potentially inhibiting the use of fatty acids. The benefits of using uncooked cornstarch in these patients to guarantee a constant glucose source from blood to muscle as oxidative substrate for glycolysis needs further investigation.

Patients with GSD 7 (disorder 15.14) depend on fatty acid oxidation in muscle as the main energy substrate. Therefore in these patients surplus of dietary carbohydrates should be avoided, since it would enhance the metabolic muscle problems by decreasing the availability of fatty acids for oxidation.

Medication

No.	Symbol	
15.12	GSD 5	Vitamin B6 supplementation (50–100 mg/day). Creatine supplementation (10–20 g/day)

Adaptations During Intercurrent Illness

No.	Symbol	Therapy	Comments
15.9	GSD 2	Supportive care	
15.12	GSD 5	Supportive care	
15.14	GSD 7	Supportive care	

Supportive care of respiratory functions (ventilator) during intercurrent illness may be necessary.

Follow-up

No.	Symbol	Investigations	Outpatient review
15.9 15.12 15.14	GSD 2 GSD 5 GSD 7	Parameters of growth. Blood creatinin kinase, uric acid. Kidney functions. Urine myoglobine. Electrocardiography, heart ultrasonography. Muscle function investigations. Lung function measurements	Depending on symptomatology
15.14	GSD 7	Liver size. Spleen size. Hematological (hemolytic) parameters	

Prognosis

No.	Symbol	Prognosis quoad vitam
15.9	GSD 2	Infantile form very poor: death from cardiopulmonary failure in the 1st year of life. Juvenile form poor: progressive myopathy (seldom cardiac disease); death from respiratory failure before adult age. Adult form poor: progressive myopathy (seldom cardiac disease) leading to wheelchair dependency and respiratory insufficiency; old age can be attained
15.12 15.14	GSD 5 GSD 7	Mostly, normal life-span. However, at adult age, symptoms varying from mild tiredness to severe complaints of exercise intolerance accompanied by cramps and myoglobinuria, to wheelchair dependency and respiratory insufficiency. Very rare infantile forms with very poor prognosis exist

New Therapeutic Approaches

Phase I/II clinical studies in infantile and juvenile patients with GSD 2 (disorder 15.9) with cell-culture derived α-1,4-glucosidase (enzyme replacement therapy) are currently being undertaken, and have shown sofar an improved outcome for the infantile form.

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16 Disorders of Glucose Transport

René Santer, Jörg Klepper

"Disorders of glucose transport" in this chapter refers to congenital defects of membrane proteins that are able to transfer glucose and other monosaccharides from one side to the other of the hydrophobic bilayer of a cellular membrane. Each type of monosaccharide transporter has its characteristic substrate specificity, and this, together with the tissue-specific expression of these proteins, explains the complex clinical picture and the involvement of more than one organ system in some of the disease entities. Two major classes of glucose transporters can be distinguished: *sodium-dependent glucose transporters* (SGLTs) couple the transport of the sugar to the transport of sodium, and the driving force for this type of transporters is the electrochemical gradient of the ion. Members of the *glucose transporter* (GLUT) family mediate so-called facilitative diffusion along an existing glucose gradient.

A common principle in disorders of glucose transport is the lack of glucose in one compartment of the body and/or the accumulation of glucose (with the consequence of osmotic effects) in another. Treatment, in general, is directed toward the dietetic substitution of alternative substrates that are able to use other transport pathways.

In intestinal glucose-galactose malabsorption (disorder 16.1), a condition characterized by severe osmotic diarrhea after the introduction of these two monosaccharides in the diet, symptoms can be circumvented by the use of fructose as the only carbohydrate (Wright 1998).

Renal glucosuria (disorder 16.2), a primary, isolated renal tubular transport defect for glucose, can clinically either present as a mild type (with a daily glucose excretion <10 g/1.73 m^2 body surface area) with dominant inheritance or as a severe type (with a daily glucose excretion >10 g/1.73 m^2) with recessive inheritance. Apart from osmotic diuresis, both conditions show a benign course and do not need any treatment. Only very high glucose loss may be associated by a propensity to hypovolemia and a delay of growth and maturation (Brodehl 1992; Santer 2003).

GLUT1 deficiency syndrome (disorder 16.3) represents the first transport defect across the blood-brain barrier. Sporadic and autosomal-dominant heterozygous mutations in the *GLUT1* gene impair the facilitative glucose transporter GLUT1 and result in a low cerebrospinal fluid (CSF) glucose concentration (hypoglycorrhachia). The lack of glucose as an essential fuel for brain

energy metabolism results in an early-onset epileptic encephalopathy with a variable clinical spectrum. An effective treatment is available by means of a ketogenic diet providing ketones as an alternative fuel for the brain (De Vivo et al. 2002; Klepper and Voit 2002).

Patients with the Fanconi-Bickel syndrome (FBS; disorder 16.4) present with clinical symptoms that result from diminished postprandial hepatic uptake of monosaccharides and an impaired release of glucose in the fasted state. Furthermore, glucose transport is impaired at the basolateral membrane of renal proximal tubular cells, leading to glycogen and glucose overload and a general functional impairment of these cells (which results in the renal Fanconi syndrome). Treatment of disturbed hepatic glucose transport is directed toward a continuous oral supply of carbohydrates or by the use of carbohydrates from which glucose is slowly released. Only symptomatic treatment is available for renal tubular dysfunction (Santer et al. 1998, 2002).

16.1 Nomenclature

No.	Disorder	Definition/comment	Symbol	OMIM No.
16.1	Intestinal glucose-galactose malabsorption	*SGLT1* defect	GGM	182380
16.2	Renal glucosuria	*SGLT2* defect: heterozygous: mild glucosuria (< 10 g/1.73 m^2); homozygous: severe glucosuria (> 10 g/1.73 m^2)	RG	233100; 182381
16.3	GLUT1 deficiency syndrome	*GLUT1* defect	GLUT1 DS	138140
16.4	Fanconi-Bickel syndrome	*GLUT2* defect	FBS	227810; 138160

16.2 Treatment

16.1 Intestinal glucose-galactose malabsorption

Hypertonic dehydration frequently requires intravenous fluid therapy for which glucose-containing solutions can be used. Long-term enteral nutrition has to avoid both glucose and galactose as monomers, as well as disaccharides and polymers of these sugars. Specialized commercial infant formulas containing fat and protein but free of a carbohydrate component can be used. Fructose should be added according to the dietary allowances for carbohydrates to meet caloric needs (Abad-Sinden et al. 1997). High fluid intake is recommeded to prevent renal stone formation, which is repeatedly reported in this condition (Tasic et al. 2004).

16.2 Renal glucosuria

Allow free access to fluid. Caloric intake should compensate for renal losses in the severe cases. No specific treatment is necessary (Scholl-Bürgi et al. 2003).

16.3 GLUT1 deficiency syndrome

The only effective treatment available is the introduction of a ketogenic diet, as ketones enter the brain via the facilitative MCT1 transporter and serve as an alternative fuel for the brain (Nordli and De Vivo 1997). The diet needs to be introduced in a clinical setting and requires a pediatrician and dietician experienced with the diet in order to be successful. A 3:1 (fat vs nonfat) ratio using long-chain triglycerides is usually sufficient. Fluids and calories are not restricted. Supplements (multivitamins, calcium, and often carnitine) are required. Certain anticonvulsive drugs (phenobarbital, chloralhydrate, valproate, topiramate) interfere with the diet (Klepper et al. 1999, 2003) while others (methylxanthines, ethanol) impair GLUT1 function in vitro (Ho et al. 2001).

Ketogenic Diet (3:1): Nutritional Requirements

Age	Fat requirements (g/kg BW per day)	Protein requirements[a] (g/kg BW per day)	Carbohydrates (g/kg BW per day)	Energy demand[b] (kcal/kg BW per day)
0–4 months	9.0	2.2	0.8	93
4–12 months	9.0	1.6	1.4	91
1–3 years	8.7	1.2	1.7	90
4–6 years	7.8	1.1	1.5	80
7–9 years	7.0	1.0	1.3	72
10–12 years	5.8	1.0	0.9	60
13–15 years	5.0	1.0	0.7	52
Adults	5.0	1.0	0.7	52

[a] Recommendations from the German Society for Nutrition (DGE; 1991)

[b] German-Austrian-Swiss (DACH) recommendations (2000)

Dangers/Pitfalls

1. Dangers of contraindications to a ketogenic diet (β-oxidation defects, defects of ketolysis and ketoneogenesis, etc.).
2. Assess compliance by measuring ketones in blood and urine. If ketones are inappropriately low, intensify dietary instructions and be aware that many medications have a high carbohydrate content.
3. The ratio of the ketogenic diet is defined in grams, not in calories or percentages! A 3:1 ratio means that, for 3 g of ingested fat, only 1 g of protein and carbohydrates is allowed. Thus, on a 3:1 ketogenic diet, 87% of kilocalories per day are supplied by fat. Percentages of protein and carbohydrates vary due to age-dependent protein requirements.

16.4 Fanconi-Bickel syndrome

Patients with FBS show signs of a hepatic glycogen storage disease (GSD) with impaired glycogenolysis and gluconeogenesis. Therefore, treatment should be similar to GSD 1 (see disorder 15.6), with frequent feeds and the use of slowly absorbed carbohydrates (Lee et al. 1995). Due to the propensitiy to hypoglycemia of FBS patients, the use of insulin for impaired glucose tolerance has to be considered with extreme caution and only after dietary measures have failed. Doses for nocturnal oligosaccharide or cornstarch treatment can be found in Chap. 15. In contrast to GSD 1, there is no evidence that a fructose-/saccharose-free diet is beneficial to FBS patients. Likewise, there are patients with FBS that have ingested high amounts of galactose/lactose without developing cataracts. Therefore, galactose restriction is not generally recommended, but galactose and galactose-1-phosphate levels should be monitored.

There is no specific treatment for the Fanconi-type nephropathy. Symptomatic treatment is recommended to compensate for losses of water, sodium, potassium, calcium, phosphate, and bicarbonate. Vitamin D should be given for floride rickets; maintenance therapy should be monitored by urinary calcium excretion. Carnitine supplementation should only be performed at low plasma levels or when signs and symptoms of a secondary mitochondrial disorder are observed (Odièvre et al. 2002; see also Chap. 21, Cystinosis).

16.3 Alternative Therapies/Experimental Trials

No.	Symbol	Age	Medication/diet	Dosage (mg/kg per day)	Dosages per day	Reference
16.1	GGM	n.a.	n.a.	n.a.	n.a.	n.a.
16.2	RG	n.a.	n.a.	n.a.	n.a.	n.a.
16.3	GLUT1 DS	All ages	α-Lipoic acid[a]	600–1800	3	De Vivo et al. 1996
16.4	FBS	n.a.	n.a.	n.a.	n.a.	n.a.

[a] Antioxidant, increases glucose transport in cultured muscle cells

16.4 Follow-up/Monitoring

16.1 Intestinal glucose-galactose malabsorption

Age	Clinical monitoring[a]	Biochemical and paraclinical monitoring[b]
Preschool	Every (1–)3(–6) months[c]	Every (1–)3(–6) months[c]
School	Every (3–)6(–12) months[c]	Every (3–)6(–12) months[c]
Adult	Every (6–)12 months[c]	Every (6–)12 months[c]

[a] Nutrient intake, growth, nutritional status, general health

[b] Hemoglobin, total protein, general parameters of liver and kidney function, plasma osmolarity and electrolytes, urinary glucose and RBCs, renal ultrasound

[c] Depending on severity of initial decompensation and/or compliance

16.2 Renal glucosuria

Age	Clinical monitoring[a]	Biochemical and paraclinical monitoring[b]
Preschool	Every (6–)12 months[c]	Every (6–)12 months[c]
School	Every (6–)12 months[c]	Every (6–)12 months[c]
Adult	Every (12–)36 months[c]	Every (12–)36 months[c]

[a] Nutrient intake, growth, nutritional status, general health

[b] Hemoglobin, total protein, kidney function parameters, plasma osmolarity and electrolytes, urinary status

[c] Only in the severe recessive type; patients with mild glucosuria do not need any follow-up

16.3 GLUT1 deficiency syndrome

Investigations on Introduction and Follow-up of a Ketogenic Diet

On admission	Initiation of diet	On discharge	Follow-up every 2–3(–6) months
Clinical[a]	Clinical[a]	Clinical[a]	Clinical[a]
Paraclinical[b]	Paraclinical[b]	Paraclinical[b]	Paraclinical[b]
Glc, OHB, BGA	Glc, OHB, BGA every 4–6 h (bedside)	Glc, OHB, BGA	Glc, OHB, BGA
Electrolytes		Electrolytes	Electrolytes
Liver/kidney parameters		Liver/kidney parameters	Liver/kidney parameters
FBC, CRP		EEG	FBC, CRP
Carnitine		Abdominal sonography	Carnitine
Blood lipids			Blood lipids
Essential fatty acids			Essential fatty acids
Drug monitoring			Drug monitoring
EEG, EKG			EEG (seizure control?)
Abdominal sonography			EKG (long QT?)
			Abdominal sonography (nephrolithiasis?)

[a] Nutrient intake, growth, nutritional status, general health
[b] Glc, Blood glucose; OHB, hydroxybutyrate; BGA, blood gas analysis; FBC, full blood count

Monitoring of Ketosis

Sample	Ketone body	Test	Target value
Urine	Acetoacetate	Test strips	80(++)–160(+++) mg/dl
Blood	Hydroxybutyrate	Test strips	>2 mmol/l
Blood	Total ketone bodies	Enzymatic	3–5 mmol/l

16.4 Fanconi-Bickel syndrome

Age	Clinical monitoring[a]	Biochemical and paraclinical monitoring[b]
Preschool	Every (1–)2(–3) months	Every (1–)2(–3) months
School	Every (2–)6(–12) months	Every (2–)6(–12) months
Adult	Every (6–)12(–24) months	Every (6–)12(–24) months

[a] Nutrient intake, growth, nutritional status, general health
[b] Blood glucose should be checked by patient or parent at least once per day in the morning. The following examinations should be performed at regular intervals: blood glucose profile, blood galactose, galactose-1-phosphate (erythrocytes), blood and urine lactate, hemoglobin, total protein, electrolytes, calcium, phosphate, alkaline phosphatase, vitamine D, parathormone, cholesterol, triglycerides, uric acid, parameters of liver and kidney function (including GFR determination), blood carnitine, α-fetoprotein. Check urine for glucose, protein, microalbinuria, calcium/creatinine ratio. Ophthalmologic examination (cataract?). Ultrasound of liver and kidney. X-ray of left hand (rickets? bone age?)

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17 Disorders of Glycerol Metabolism

Katrina M. Dipple, Edward R.B. McCabe

17.1 Introduction

Disorders of glycerol metabolism include complex glycerol kinase deficiency (cGKD), isolated glycerol kinase deficiency (iGKD), and glycerol intolerance syndrome (GIS) (McCabe 2001a; Dipple and McCabe 2003). Glycerol kinase deficiency (GKD), both complex and isolated, is due to deletions or mutations of the glycerol kinase (*GK*) gene on Xp21. GIS is less well defined and some cases are due to fructose-1,6-diphosphatase (FDP) deficiency (McCabe 2001a; Dipple and McCabe 2003; Beatty et al. 2000). The treatment of acute crises includes intravenous glucose and supportive care (McCabe 2001a). The mainstay of long-term treatment remains a low-fat diet and avoidance of fasting. With cGKD, there can be associated Duchenne muscular dystrophy, adrenal hypoplasia, congenital and mental retardation; therefore, these associated diseases must be recognized and treated, especially the adrenal insufficiency (McCabe 2001a, b; Dipple and McCabe 2003; Vilain 2001). Patients with iGKD are at risk for insulin resistance, glucose intolerance, and type II diabetes mellitus (Gaudet et al. 2000), so individuals with iGKD should be monitored carefully for diabetes. Patients with GIS must avoid glycerol, especially in intravenous infusions (McCabe 2001a). In addition, some patients with GIS have FDP deficiency, and this must be identified and treated appropriately (McCabe 2001a; Beatty et al. 2000). Unfortunately, because disorders of glycerol metabolism are such rare and presumably underdiagnosed diseases, many patients go untreated, and we therefore do not know the efficacy of treatment (Fig. 17.1).

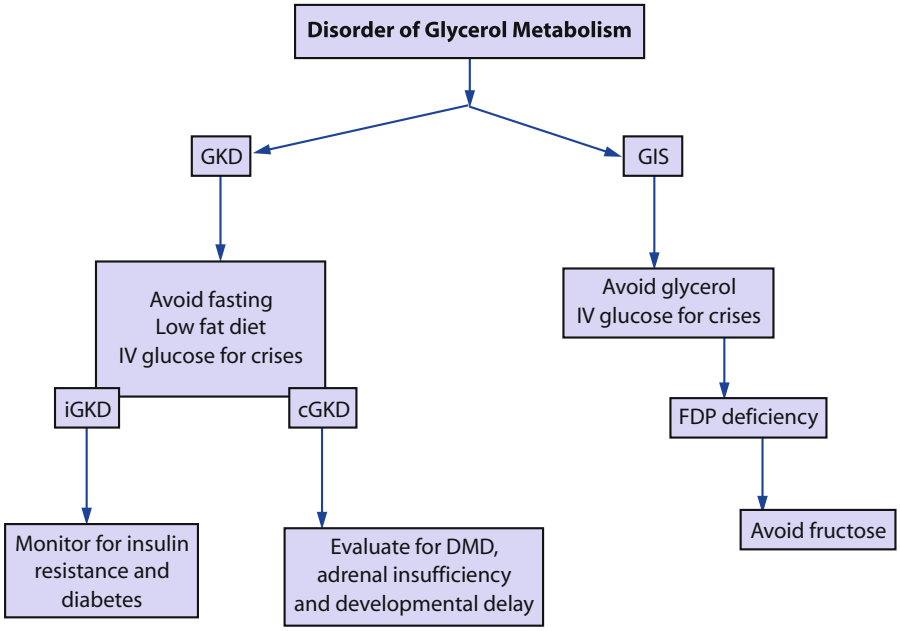

Fig. 17.1. Management if disorders of glycerol metabolism

17.2 Nomenclature

No.	Disorder (symbol)	Definitions/comment	Gene symbol	OMIM No.
17.1	Glycerol kinase deficiency (GKD)	Includes complex GKD (disorder 17.1.1) and isolated GKD (disorder 17.1.2 and 17.1.3)	*GK*	307030
17.1.1	Complex glycerol kinase deficiency (cGKD)	GKD as part of a contiguous gene syndrome	*GK*, *NROB1*, *DMD*	307030, 300200, 310200
17.1.2	Isolated glycerol kinase deficiency (iGKD)	Juvenile, symptomatic form	*GK*	307030
17.1.3	Isolated glycerol kinase deficiency (iGKD)	Adult onset, benign form	*GK*	307030

Adapted from Dipple and McCabe 2003

17.3 Treatment

■ *17.1 Glycerol kinase deficiency*

17.1.1 Complex
17.1.2 Isolated symptomatic (juvenile)
17.1.3 Isolated benign (adult)

No.	Age	Diet	Symbol
17.1	All ages	Acute decompensation – start IV glucose. Check pH, glucose, electrolytes, ACTH	GKD
		Maintenance – avoid fasting, provide low-fat diet[a]	GKD

[a] Treatment may lower hyperglycerolemia and hypertriglyceridemia, but only slightly; may reduce frequency of metabolic decompensation

17.1.1 Complex glycerol kinase deficiency (cGKD)

Diagnose and treat adrenal crisis and DMD if associated. If adrenal crisis, initiate glucocorticoid and mineralocorticoid replacement (McCabe 2001b; Vilain 2001b). Patients are also at risk for developmental delay, mental retardation, and seizures (McCabe 2001a; Dipple et al. 2001). These must be monitored for and intervention started early.

17.1.2 and 17.1.3 Isolated symptomatic glycerol kinase deficiency (iGKD)

Like patients with complex GKD, these patients are at risk for acute, episodic metabolic (acidemia ± hypoglycemia) and central nervous system (stupor, possibly progressing to coma) deterioration (McCabe 2001a; Dipple and McCabe 2003). Monitor for glucose intolerance and type II diabetes mellitus (Gaudet et al. 2000), and consider referral to an endocrinologist.

Dangers/Pitfalls
Patients are at increased risk for metabolic crisis when ill with febrile illness.

17.4 Treatment

Glycerol Intolerance Syndrome

Avoid glycerol ingestions and infusions. Some cases of glycerol intolerance syndrome (GIS) are secondary to FDP deficiency (McCabe 2001a; Beatty et al. 2000), in that case, treatment is based on FDP (see Chap. 15). These patients are at risk for acute, episodic metabolic and central nervous system deterioration (McCabe 2001a; Dipple and McCabe 2003). If patient has associated hypoglycemia, acidosis and ketosis, these should be treated using standard treatment protocols (see Part I: Initial Approaches).

17.5 Alternative Therapies/Experimental Trials

17.1 (disorders 17.1.1, 17.1.2, and 17.1.3).

None.

17.6 Follow-up/Monitoring

- *17.1.1 cGKD*

Age	Biochemical glycerol	Clinical	Developmental assessment
0–3 months	+	Respond rapidly to intercurrent illnesses	+
4–12 months		Respond rapidly to intercurrent illnesses	+
1–2 years		Respond rapidly to intercurrent illnesses	+
2–3 years		Respond rapidly to intercurrent illnesses	
4–6 years		Respond rapidly to intercurrent illnesses	+
7–9 years		Respond rapidly to intercurrent illnesses	
10–12 years		Respond rapidly to intercurrent illnesses	
13–15 years		Monitor for insulin resistance	
Adolescents/ adults		Monitor for insulin resistance	

Standard protocol for intercurrent illness

- Intravenous fluids (glucose) without glycerol. No added fat.
- Treatment of acidosis, hypoglycemia, electrolyte abnormalities, and adrenal crisis (stress-dose steroids).

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18 The Mucopolysaccharidoses

J. Edward Wraith, Joe T.R. Clarke

18.1 Introduction

The disorders described in this chapter are associated with a progressive accumulation of glycosaminoglycans (GAG) within the cells of various organs, ultimately compromising their function. The major sites of disease differ depending on the specific enzyme deficiency, and therefore the clinical presentation and approach to therapy is different for the various disease subtypes.

Patients with the severe form of mucopolysaccharidosis (MPS I; Hurler disease, MPS IH), MPS II (Hunter disease), and MPS VI (Maroteaux-Lamy disease) generally present with facial dysmorphism and persistent respiratory disease in the early years of life. Many patients will have undergone surgical procedures for recurrent otitis media and hernia repair before the diagnosis is established. Infants with MPS III (Sanfilippo A, B, C, or D disease) present with learning difficulties and then develop a profound behavioral disturbance. The behavior disorder is characteristic and often leads to the diagnosis. Somatic features are mild in these patients. Children with MPS IVA (Morquio disease, type A) have normal cognitive functions, but are affected by severe spondoepiphyseal dysplasia, which in most patients leads to extreme short stature, deformity of the chest, marked shortening and instability of the neck, and joint laxity. MPS IVB (Morquio disease, type B) is much more variable in its effects. It has some features of the skeletal dysplasia of MPS IVA; however, most patients also have learning difficulties. MPS VII (Sly disease) often presents as nonimmune hydrops fetalis. Those patients who survive or who present later resemble patients with MPS IH with respect to clinical phenotype and supportive management. So far only one patient with MPS IX (Natowicz disease) has been reported.

The phenotype of patients with more attenuated forms of MPS, e. g., MPS IH/S or MPS IS (Hurler-Scheie or Scheie disease, respectively) is much more difficult to predict, and treatment needs in this group of patients may be very variable. The MPS disorders in general present as a continuum of clinical involvement, and even patients with the most attenuated forms of Scheie syndrome may have severe disabilities, requiring major medical and surgical interventions.

Because of the multisystem involvement in these patients, treatment is multidisciplinary and encompasses both the “curative” and palliative elements.

Those patients with severe central nervous system involvement (MPS III, Sanfilippo disease) or severe bone dysplasia (MPS IVA, Morquio disease) present particular challenges to management, as current therapies are poor in correcting the effects of the genetic lesion in brain and bone, respectively. Table 18.1 summarizes the types of problems experienced by patients with MPS disorders and strategies for their management.

Table 18.1. Supportive or nonspecific symptomatic treatment of MPS

System	Problem	Intervention
Eyes	Corneal clouding	Avoid direct sunlight; corneal transplantation
	Glaucoma	Topical β-blockers; trabecular surgery
	Retinal dystrophy	None
Ears	Recurrent otitis media	Antibiotic therapy; ENT surgery[a]
	Sensorineural deafness	Hearing aids
Dental	Caries, dental abscess	Oral hygiene; dental extractions
Respiratory	Upper-airway obstruction	ENT surgery[a]
	Obstructive sleep apnoea	Oxygen therapy; CPAP
	Restrictive lung disease	Oxygen therapy; CPAP
Cardiac	Cardiomyopathy	Antifailure medication
	Valve lesions	Antifailure medication; valve replacement
	Coronary artery disease	None
Gastrointestinal	Hepatosplenomegaly	None
	Umbilical and inguinal hernia	Surgical repair
	Swallowing problems	Pureed diet, small, frequent meals; gastrostomy
	Diarrhea	antimotility medication
	Drooling	Hyoscine; surgical rerouting of salivary ducts
Central nervous system	Hydrocephalus	Ventriculo-atrial or ventriculo-peritoneal shunt surgery
	Atlantoaxial instability resulting from odontoid dysplasia	Surgical decompression and fusion of cervical spine
	Cervical compression myelopathy	Surgical decompression and fusion
	Seizures	Anticonvulsant medication
	Severe behavior problems	Behavior management, medication
	Sleep disturbance	Medication
	Mental retardation	Appropriate educational support and interventions
Peripheral nervous system	Peripheral nerve entrapment, e. g., carpal tunnel syndrome	Surgical decompression
Skeleton	Degenerative hip dysplasia	Analgesics; orthopedic surgical correction
	Kyphosis or kyphoscoliosis	Bracing or orthopedic surgical correction
	Joint contractures	Physiotherapy and orthoses
	Genu valgum deformities	Osteotomies

[a] Including various combinations of tonsillectomy, adenoidectomy, myringotomy, the insertion of ventilation tubes, and tracheostomy
ENT ears, nose, and throat; *CPAP* continuous positive airways pressure

Attempts at "curative therapy" have previously centered on the use of hematopoetic stem cell transplant (HSCT), using either bone marrow or umbilical cord blood cells. Although all MPS disorders have been treated by HSCT,

evidence for efficacy is strong in only MPS IH (Hurler disease) (Peters et al. 1996, 1998; Fleming et al. 1998) or MPS VI (Krivit et al. 1984; Lee et al. 2000). The procedure is ineffective in MPS III (Sanfilippo disease) (Sivakumar and Wraith 1999), in MPS II (McKinnis et al. 1996), and in MPS IV (Morquio disease); too few patients with MPS VII (Sly syndrome) have received transplants to make a reasonable assessment. The only patient with MPS IX to be described did not undergo HSCT.

The introduction of recombinant human enzyme replacement therapy (ERT) is likely to make a major impact in the area of treatment in the years to come. Laronidase (Aldurazyme) is available for the treatment of MPS I (Kakkis et al. 2001; Wraith 2004; Brooks 2002), and other enzyme strategies are in advanced stages of clinical evaluation, with phase III launched presently for both MPS II (Muenzer et al. 2002) and MPS VI.

Despite these advances in specific therapy, supportive and palliative care are all that can be offered for most patients with various MPS disorders. Management should encompass a holistic approach, with symptom control and enhanced quality of life the main goal of treatment. Many different specialties, both within and allied to clinical medicine, as well as lay members of voluntary organizations, have roles to play. Adequate respite care is important for those families who have children with profound behavioral disturbance.

18.2 Nomenclature

No.	Disorder	Eponym	Enzyme deficiency	Gene symbol	OMIM No.
18.1	MPS IH	Hurler	α-L-Iduronidase	*IDUA*	252800
	MPS IH/S	Hurler-Scheie	α-L-Iduronidase	*IDUA*	252800
	MPS IS	Scheie	α-L-Iduronidase	*IDUA*	252800
18.2	MPS II	Hunter	Iduronate-2-sulfatase	*IDS*	309900
18.3	MPS IIIA	Sanfilippo A	Heparin *N*-sulfatase (sulfamidase)	*SGSH*	252900
18.4	MPS IIIB	Sanfilippo B	α-*N*-Acetylglucosaminidase	*NAGU*	252920
18.5	MPS IIIC	Sanfilippo C	Acetyl-CoA:α-glucosaminide *N*-acetyltransferase	*MPS3C*	252930
18.6	MPS IIID	Sanfilippo D	*N*-Acetylglucosamine-6-sulfatase	*GNS*	252940
18.7	MPS IVA	Morquio A	*N*-Acetylgalactosamine-6-sulfatase	*GALNS*	253000
18.8	MPS IVB	Morquio B	β-Galactosidase	*GLB1*	253010
18.9	MPS VI	Maroteaux-Lamy	*N*-Acetylgalactosamine-4-sulfatase (arylsulfatase B)	*ARSB*	253200
18.10	MPS VII	Sly	β-Glucuronidase	*GUSB*	253220
18.11	MPS IX[a]	Natowicz	Hyaluronidase	*HYAL1*	601492

[a] Only one good description of a patient with hyaluronidase deficiency (MPS IX, Natowicz syndrome) has been reported
MPS, mucopolysaccharidosis

18.3 Treatment

General Considerations

The MPS are all complex multisystem diseases. Irrespective of the type, management of of all of them requires supportive care and multidisciplinary treatment of a variety of systemic complications. Regular evaluation at a major center with special interest and expertise in the management of the diseases is important in the coordination of interdisciplinary input and to coordinate multispecialty treatment strategies. Because of the progressive nature of the diseases, individuals with MPS need to be evaluated regularly in order to identify potential problems early at a time when intervention would decrease morbidity, prevent premature mortality, and enhance the quality of life of affected patients. Every patient with MPS is unique; therefore, treatment options need to be individually based.

In addition to the neurological complications experienced by many, distortion and narrowing of the upper airway and deformities of the chest present potential fatal anesthetic risks for most patients with MPS. Even the most trivial procedures requiring general anesthesia should be done at centers with anesthetists who are experienced with MPS disorders.

Specific Therapies

Specific therapy is available for MPS I, and clinical trials are currently in progress to evaluate specific treatment of MPS II and MPS VI. For the other MPS, no specific therapy exists at present.

Hematopoietic Stem Cell Transplantation

In patients under the age of 2 years who have normal or near-normal developmental scores (DQ >70), HSCT should be considered, using either HLA-matched bone marrow or umbilical cord blood cells as the donor cells. The best results are achieved with HLA-matched sibling donors. Successful engraftment is associated with resolution of hepatosplenomegaly and upper airway obstruction. Corneal clouding usually resolves slowly, but never completely. Intraocular pressures may decrease. Cardiac manifestations attributable to muscle involvement are corrected, but valvular abnormalities are resistant to HSCT and often progress. Improvements in joint mobility are routinely experienced, and growth may approach normal rates for children the same age. However, some skeletal abnormalities, especially abnormalities of the spine, do not respond to HSCT, and most severely affected children still require major orthopedic interventions (Peters et al. 1996, 1998).

- *Enzyme Replacement Therapy*

ERT has been demonstrated in randomized, double-blind, placebo-controlled studies to produce improvements in joint mobility, pulmonary function, and exercise tolerance in patients with MPS IH/S and MPS IS. However, the extent and sustainability of improvement, whether other clinical features of the disease will also response to therapy, and the optimum dosage of laronidase, are unknown. Laronidase (Aldurazyme), is licensed in the European Union and the US to treat the nonneurological aspects of the disease; there is no evidence that the recombinant protein crosses the blood-brain barrier. Dosages and treatment intervals are summarized in Table 18.2). A role as an adjunct to HSCT in patients with MPS IH is currently under investigation. ERT may have the least impact in patients with the most attenuated forms of the disease (Scheie disease). Treatment costs are greater in these patients than in patients with more severe forms of the disease because the dosage of laronidase is based on body weight, and patients with Scheie disease are relatively heavy, compared with patients with Hurler-Scheie or Hurler disease. ERT for both MPS II and MPS VI is currently undergoing clinical trial. Fig. 18.1 shows the approach to the treatment of MPS I.

Table 18.2. Treatment of MPS I by enzyme replacement

Disorder	Age	Medication	Dosage	Route & frequency
MPS IH MPS IH/IS MPS IS	All	Laronidase (Aldurazyme)	100 U/kg (0.58 mgs/kg)	IV weekly

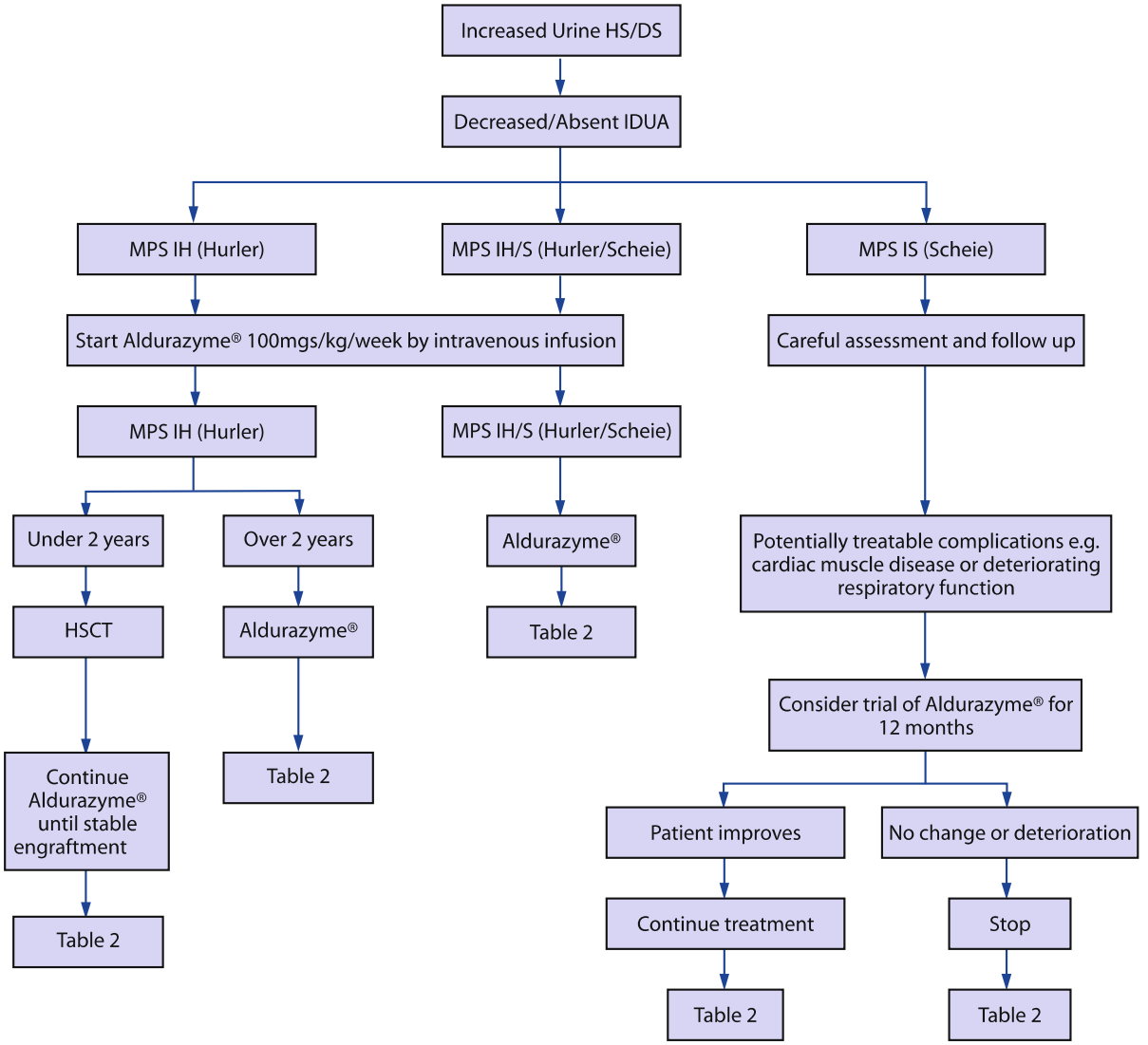

Fig. 18.1. Flow chart for the management of α-L-iduronidase deficiency (MPS IH, -IH/S, -IS). (*HSCT* hematopoietic stem cell transplant by bone marrow or umbilical cord blood cells, *MPS* mucopolysaccharidosis, *HS* heparan, *DS* dematan sulfate)

18.4 Follow-up and Monitoring

The objectives of monitoring patients with MPS disorders are:

1. To provide on-going support for the patient and family
2. To anticipate complications (Table 18.3), identify them early when they occur, and treat them in order to decrease morbidity
3. To monitor specific therapies, such as HSCT and ERT, to assess their effectiveness and, in the case of ERT, to adjust enzyme dosage

Table 18.3. Summary of complications of MPS disorders

System	Problem	MPS IH	MPS IH/IS	MPS IS	MPS II	MPS III	MPS IV	MPS VI	MPS VII[a]	MPS IX[b]
Eyes	Corneal clouding	++++	++++	++++		++	++	+++	+	?
	Glaucoma	++	++	++				++	?	?
	Retinal dystrophy		++	++	+			++	?	?
Ears	Recurrent otitis media	++++	++++	++	++++	+	+	+++	+++	?
	Sensorineural deafness	++	++		+++			++	?	?
Dental	Caries, dental abscess	++++	++	++	++		++		?	?
Respiratory	Upper airway obstruction	++++	+++	++	++++			+++	?	?
	Obstructive sleep apnoea	++++	+++	++	++++			++	?	?
	Restrictive lung disease	++	+++	++	++		++	+	?	
Cardiac	Cardiomyopathy	++[c]	++	++	++			++	?	?
	Valve lesions	+++	++++	++++	+++			++	?	?
	Coronary artery disease	++	++	+++	+			++	?	?
Gastrointestinal	Hepatoplenomegaly	+++	++	+	+++			+	+	?
	Umbilical and inguinal hernias	++++	+++	+	+++			++	+	?
	Swallowing problems	++++	++		+++	++++			?	?
	Diarrhea	+++	++		++	++			?	?
	Drooling	+++			+++	+++			?	?
CNS	Hydrocephalus	+++	+		+++	+			?	?
	Atlanto-axial instability	++			++		++++			?
	Cervical myelopathy	++++[d]	+		+++[d]		++++	+++	?	?
	Seizures	++			+++	++++				?
	Behavior problems	+			+++	++++			++	?
	Sleep disturbance[e]	++			+++	++++			?	?
	Mental retardation	++++			++++	++++			++++	?
Peripheral nerve	Carpal tunnel syndrome	+++	++++	+++	+++			+++	?	?
Skeleton	Degenerative hip dysplasia	++++	++++	++++	+++	+	+++	+++	++	++++
	Kyphosis or kypho-scoliosis	++++	++		++		++	++	++	++
	Joint contractures	++++	++++	++	+++		[f]	+++	++	++
	Genu valgum deformities	+	+		+		++++			?

[a] MPS VII is rare and clinically heterogeneous. It may present as nonimmune fetal hydrops
[b] Only one good description of a patient with hyaluronidase deficiency (MPS IX, Natowicz syndrome) has been reported
[c] May be the presenting problem progressing rapidly to death in early infancy
[d] A late complication in almost all patients with severe disease
[e] Not caused by upper-airway obstruction
[f] Joint laxity and the resulting instability, rather than joint contractures, is a major problem in MPS IV

A general schedule of assessment and reassessment is shown in Table 18.4. What is shown represents a minimum follow-up schedule; adjustments are always necessary in individual cases, as unanticipated problems arise.

Table 18.4. Recommended follow-up and monitoring of MPS disorders

	Initial	Every 6 months	Every 12 months	Every 2 years
General				
Medical history and physical examination[a]	•	•		
Neurological	•	•		
Developmental assessment	•		•	
MRI of brain	•			•
MRI of spine	•			•
Ophthalmologic			•	
Visual acuity	•		•	
Retinal examination	•		•	
Corneal examination[b]	•		•	
Auditory			•	
ENT consultation	•		•	
Audiometry	•		•	
Cardiac	•		•	
Chest radiograph (for heart size)				
ECG	•			•
Echocardiogram	•		•	•
Respiratory	•			
Pulmonary function tests[c]	•	•		
Sleep study	•		•	
Gastrointestinal				
Spleen & liver volumes[d]	•			•
Musculoskeletal				
Skeletal radiographs[e]	•			•
Laboratory studies				
Leukocyte α-L-iduronidase[f]	•			
Urinary GAG level[g]	•	•		
Urine analysis	•	•		

[a] Including measurement of height, weight, head circumference, and blood pressure

[b] Including measurement of intraocular pressures

[c] Forced vital capacity (FVC) and1-s forced expiratory volume (FEV_1)

[d] Best measured by MRI or CT scan

[e] AP and lateral views of the skull, PA view of the chest, lateral views of the spine (including the cervical spine), AP view of the hips and pelvis, single AP view of both hands together. In the case of MPS IV, include lateral views of the neck in flexion and extension to assess stability of the atlanto-axial joint, and a single AP view of the upper cervical spine through the open mouth to assess the integrity of the odontoid process. These studies are primarily for the asssessment of disease in children; the menu and schedule for radiographic studies in adults would be more limited, emphasizing the assessment of osteoarthritis

[f] In patients who have undergone hematopoietic stem cell transplantation (HSCT), leukocyte α-L-iduronidase assays and VNTR analyses on DNA extracted from peripheral blood should be done monthly from the time of transplantation, then every 6 months, to assess engraftment

[g] For assessment of the response to enzyme replacement therapy or HSCT

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19 Oligosaccharidoses and Related Disorders

Generoso Andria, Giancarlo Parenti

19.1 Introduction

During the past 15 years, remarkable progress has been made in the treatment of lysosomal storage disorders (LSD), including the group of oligosaccharidoses and related disorders discussed in this chapter. Different therapeutic strategies have been introduced for a number of these diseases, resulting in a significant impact on the prognosis and quality of life of patients.

These innovative approaches include bone marrow transplantation or hematopoietic stem cell transplantation (HSCT), enzyme replacement therapy (ERT), and substrate reduction, which have already been tested in humans with encouraging results. Other promising approaches such as gene therapy and chaperone-mediated enzyme enhancement are still under investigation.

A major breakthrough in the care of patients with LSD has been the development of ERT for Gaucher disease (Barton et al. 1991). The bulk of information and experience deriving from the treatment of a large number of Gaucher patient for more than a decade is proving of great value for the treatment of other disorders, including mucopolysaccharidoses (see Chap. 18), glycogenosis type II (see Chap. 15), and other sphingolipidoses, such as Fabry disease (see Chap. 22), for which ERT has recently become available.

Sufficient experience and validated follow-up protocols are presently available only for Gaucher disease, which has been treated for a sufficiently long period and will be reported in the present chapter. For other disorders clinical trials are still in progress and it is reasonable to expect that several years will be necessary to develop standardized protocols for treatment and monitoring of therapy.

An important issue is the need for a careful assessment of the natural history of LSD to evaluate the efficacy of novel therapeutic approaches. In this respect, efforts to enroll the largest number of patients affected by individually rare disorders and to develop standardized follow-up and monitoring protocols both in treated and nontreated patients are of crucial importance.

19.2 Nomenclature

No.	Disorder (symbol)	Definitions/comment	Gene symbol	OMIM No.
19.1.1	α-Mannosidosis type I	α-Mannosidase deficiency	*MAN2B1*	248500
19.1.2	α-Mannosidosis type II			
19.2.1	β-Mannosidosis infantile	β-Mannosidase deficiency	*MANBA*	248510
19.2.2	β-Mannosidosis juvenile/adult			
19.3	Fucosidosis	α-Fucosidase deficiency	*FUCA1*	230000
19.4.1	Sialidosis severe infantile	α-Neuraminidase deficiency	*NEU1*	256550
19.4.2	Sialidosis mild infantile, mucolipidosis I (MLI)			
19.4.3	Sialidosis adult			
19.5.1	Galactosialidosis, early infantile	"Protective protein"/cathepsin A deficiency (secondary β-galactosidase and α-neuraminidase deficiencies)	*PPGB*	256540
19.5.2	Galactosialidosis, late infantile			
19.5.3	Galactosialidosis, juvenile/adult			
19.6	Aspartylglucosaminuria	Aspartylglucosaminidase deficiency	*AGA*	208400
19.7.1	α-NAGA deficiency type I, Schindler disease	α-N-acetylgalactosaminidase deficiency	*NAGA*	104170
19.7.2	α-NAGA deficiency type II, Kanzaki disease			
19.8.1	GM_1 gangliosidosis early infantile	β-Galactosidase deficiency	*GLB1*	230500
19.8.2	GM_1 gangliosidosis late infantile			
19.8.3	GM_1 gangliosidosis adult			
19.9.1	GM_2 gangliosidosis variant B, infantile, Tay-Sachs disease	β-Hexosaminidase A deficiency (α-subunit)	*HEXA*	272800
19.9.2	GM_2 gangliosidosis variant B, late onset			
19.9.3	GM_2 gangliosidosis variant 0, infantile, Sandhoff disease	β-Hexosaminidase A and B deficiency (β-subunit)	*HEXB*	268800
19.9.4	GM_2 gangliosidosis variant 0, juvenile/adult			
19.9.5	GM_2 gangliosidosis variant AB	β-Hexosaminidase activator deficiency	*GM2A*	272750
19.10	Mucolipidosis II, -I cell disease (ML II)	*N*-Acetylglucosamine 1-phosphotransferase deficiency (secondary multiple lysosomal enzyme deficiencies)	*GNPTA*	252500
19.11	Mucolipidosis III (ML III)	*N*-Acetylglucosamine 1-phosphotransferase deficiency (secondary multiple lysosomal enzyme deficiencies)	*GNPTA*, *GNPTAG*	252600 252605
19.12	Mucolipidosis IV (ML IV)	Mucolipidin deficiency (receptor-stimulated cation channel)	*MCOLN1*	252650
19.13.1	Gaucher disease type 1 "adult," chronic nonneuronopathic	β-Glucocerebrosidase deficiency	*GBA*	230800
19.13.2	Gaucher disease type 2 acute neuronopathic			

No.	Disorder (symbol)	Definitions/comment	Gene symbol	OMIM No.
19.13.3	Gaucher disease type 3 subacute neuronopathic			
19.13.4	Gaucher disease, SAPC deficiency	SAPC deficiency	*PSAP*	176801
19.14.1	Niemann-Pick disease type A	Sphingomyelinase deficiency	*SMPD1*	257200, 607616
19.14.2	Niemann-Pick disease type B			
19.14.3	Niemann-Pick disease type B adult			
19.15.1	Niemann-Pick disease type C acute	Abnormal intracellular cholesterol transport	*NPC1, HE1 (NPC2)*	257220
19.15.2	Niemann-Pick disease type C classic			
19.15.3	Niemann-Pick disease type C adult			
19.16.1	Krabbe disease infantile	β-Galactocerebrosidase	*GALC*	245200
19.16.2	Krabbe disease late onset			
19.17	Multiple sulfatase deficiency (MSD)	FGE (formylglycine generating enzyme – absent posttranslational modification of a cysteine in at least 13 sulfatases)	*SUMF1*	272200

19.3 Treatment

Different strategies for the treatment of LSD have been explored with variable success. Some of them are based on increasing the availability of a specific lysosomal hydrolase and include HSCT and ERT.

An alternative approach is based on substrate deprivation, using iminosugars that inhibit substrate synthesis. For all these strategies Gaucher disease has been the most extensively studied LSD.

Hematopoietic Stem Cell Transplantation

HSCT is aimed at replacing hematopoietic cells with wild-type cells secreting normal enzyme. A critical point is the efficacy of HSCT in preventing the progression of neurological disease. It has been shown that donor-derived microglial cells are present in the recipient brain, but it is questioned whether they are able to deliver enough functional enzyme to central nervous system cells. It is therefore advisable that transplantation be attempted early, before extensive neurological involvement occurs. Careful setting of patients' conditions before transplantation is also of critical importance.

Clinical experience on the efficacy of HSCT in lysosomal storage disorders has been obtained in patients with mucopolysaccharidoses, Gaucher disease, Krabbe disease, Niemann-Pick disease types A, B, and C, fucosidosis, α-mannosidosis, aspartylglucosaminuria, mucolipidosis II, GM_2-gangliosidoses (Hoogerbrugge et al. 1995; Krivit 2002; Krivit et al. 1999; Malatack et al. 2003).

Experience has been also obtained in animal models that provided useful information on HSCT effects on central nervous system manifestations of lysosomal storage diseases. In Krabbe disease (twitcher mouse) and α-mannosidase deficiency models, HSCT has proved effective in improving brain pathology, whereas, in a GM_2-gangliosidosis feline model, the procedure was ineffective (Malatack et al. 2003).

In Gaucher disease HSCT has been effective in type 1 nonneuronopathic forms, resulting in the correction of the enzymatic defect and elimination of the manifestations of the disease (Malatack et al. 2003). The effectiveness of this procedure in the neuronopathic forms (types 2 and 3) is poor. In Gaucher disease type 2, in spite of reversal of peripheral neurological involvement, the progression of central nervous system disease remained unchanged. In chronic neuronopathic (type 3) Gaucher disease stabilization of central nervous system manifestations was observed.

HSCT has been effective in preventing or reverting brain disease in patients with late-onset Krabbe disease and in a few patients with infantile Krabbe disease in whom a prenatal diagnosis was available and HSCT was done in the 1st weeks of life (Malatack et al. 2003). However, infantile Krabbe disease has a rapid course and in nonfamilial cases it is not possible to perform HSCT before extensive brain involvement occurs.

HSCT failed to prevent neurological deterioration in Niemann-Pick disease type A. In principle this approach should be effective in Niemann-Pick disease type B, but there is little experience published in the literature (Victor et al. 2003).

Enzyme Replacement Therapy

At the beginning of the 1990s, the availability of new technologies for protein expression in eukaryotic cells, enzyme purification, and cell targeting, made ERT a feasible approach to the treatment of LSD. ERT is based on the periodic infusion of a specific wild-type recombinant lysosomal enzyme in the systemic circulation. The enzyme is internalized by the patient's cells and targeted via the mannose-6-phosphate pathway (or via the mannose receptor for mannose-terminated recombinant beta-glucocerebrosidase) to lysosomes, where it exerts its catalytic activity.

This approach proved to be effective in nonneuronopathic Gaucher patients in improving hematologic and biochemical parameters and growth, and in reducing hepatosplenomegaly (Charrow et al. 2004). Clinical and radiological evidence of improvement of skeletal disease has also been obtained (Charrow et al. 2004; Poll et al. 2002; Maas et al. 2002).

Since exogenous enzyme is unable to cross the blood-brain barrier, the efficacy of this approach in the treatment of LSD showing severe neurological involvement is poor (Vellodi et al. 2001).

Substrate Reduction

Recently, the use of iminosugars such as miglustat (*N*-butyl deoxynojirimycin), inhibiting glycosyltransferases involved in the synthesis of accumulating substrates, was tested in Gaucher disease (Cox et al. 2000, 2003). The rationale of this approach is to reduce the synthesis of glycosphingolipids to rates at which the residual enzyme activity can catabolize stored and newly-formed lysosomal substrate. This approach has been studied in clinical trials showing improvement of liver and spleen size and of hematological variables, although some adverse events such as weight loss, gastrointestinal symptoms, diarrhea, and peripheral neuropathy were reported (Cox et al. 2000, 2003).

It is currently accepted that substrate reduction therapy should be restricted to patients with mild or moderate Gaucher disease unwilling or unable to continue ERT (Platt et al. 2001). The combination of enzyme replacement and substrate deprivation is also a therapeutic option that deserves further investigation (Cox et al. 2000, 2003; Cox et al. 2000, 2003)

Standardized and validated protocols for ERT and substrate deprivation have been published only for the treatment of Gaucher disease and are reported in Table 19.1.

Table 19.1. Treatment of Gaucher disease (GD)

GD type	Patients	Miglustat (mg/day divided into 3 doses)	Imiglucerase (U/kg per month)	Comment
Nonneuronopathic GD	All		30–120	Decrease dose when improvement of symptoms occurs. Increase dose if no improvement is seen after 6 months. Individualize dosage
	Patients unsuitable for Imiglucerase treatment	300		In case of diarrhea reduce dose to 100–200 mg/day
Chronic neuronopathic GD	Patients at risk of neurological involvement		120	Careful monitoring for neurological signs
	Patients with neurological involvement		240–480	Start with 240 U; if neurological involvement progresses, increase dose to 480 U/kg per month for a short period (no more than 6 months); if neurological involvement progresses after 6 months, the dose should be reduced to a level that controls systemic disease; if patients reach adulthood and neurological involvement is stable, dose reduction *may* be considered
Acute neuronopathic GD	Type A		240 U/kg per month	6-month trial with monthly follow-up
	Type B		Not recommended	

Definition of the different forms of GD: (1) nonneuronopathic: patients without neurological involvement and risk factors indicated in 3b. "Adult GD", onset after 2 years. The *N370S* mutation prevents the occurrence of neurological involvement; (2) chronic neuronopathic: (a) GD patients with neurological signs or symptoms; (b) GD patients with risk factors, including: sibling of patients with proven neuronopathic GD; high-risk genotypes, including *L444P/L444P*, *D409H/D409H* or *L444P/D409H*; onset of severe systemic GD before or at 2 years of age; (3) acute neuronopathic: onset before or at 1 year with progressive bulbar involvement (stridor, squint, swallowing difficulty); pyramidal (opisthotonus, head retroflection, spasticity, trismus) and cognitive impairment are variably present: type A, little or no pyramidal involvement; type B, marked pyramidal involvement, cognitive impairment

19.4 Alternative Therapies/Experimental Trials

It has been proposed that the approach based on substrate deprivation can be extended to LSD other than Gaucher disease. Miglustat may act as an inhibitor of substrate synthesis for Fabry disease, GM_1 and GM_2 gangliosidoses.

An experimental trial on ERT in patients with Niemann-Pick disease type B is currently in progress.

The observation that substrate synthesis inhibitors may be effective as putative chaperones in enhancing β-glucocerebrosidase and α-galactosidase in Gaucher and Fabry cells, respectively, is of interest in developing a chaperone-mediated enzyme enhancement therapy (Desnick and Schuchman 2002; Sawkar et al. 2002; Asano et al. 2000; Frustaci et al. 2001).

19.5 Follow-up and Monitoring

Protocols for follow-up of patients with Gaucher disease are available in the literature (Charrow et al. 2004; Vellodi et al. 2001; Baldellou et al. 2004; Grabowski et al. 2004) and are reported in Tables 19.2 and 19.3.

Table 19.2. Follow-up and monitoring of nonneuronopathic Gaucher disease (GD)

Assessment		Patients not receiving therapy		Patients receiving enzyme therapy			
				Not achieved therapeutic goals		Achieved therapeutic goals	At time of dose change or significant complication
		Every 12 months	Every 12–24 months	Every 3 months	Every 12 months	Every 12–24 months	
Physical examination[a]		Every 6 months			Every 6–12 months		x
Hematology	Hemoglobin	x		x		x	x
	Platelets	x		x		x	x
Biochemistry	Chitotriosidase and/or TRAP and/or ACE	x		x		x	x
Visceral	Spleen volume (MRI/ultrasound)		x		x	x	x
	Liver volume (MRI/ultrasound)		x		x	x	x
	Pulmonary function tests	x			x	x	
	Cardiovascular function (echocardiography, ECG)	x			x	x	
Skeletal	MRI[b]		Every 24 months		x	x	x
	X-rays of chest, spine[c], pelvis, long bones		x		x	x	x
	DEXA of spine and hip		x		x	Every 24 months	x
Other	Pain	x			Every 6–12 months	x	x
	Quality of life[d]	x			x		x

Therapeutic goals should be individualized, based on the results of a comprehensive evaluation of patients that considers signs associated with the viscera, blood, and skeleton and a full assessment of quality of life. In pediatric patients normal growth and development should be achieved

[a] Physical examination should include evaluation of: skin (bruising, petechiae, palor); abdomen (liver and spleen enlargement); growth (weight, height, head circumference) using standardized growth charts, pubertal staus using the Tanner staging system); lung function; range of joint movement and gait

[b] Sagittal T1-weighted scan of spine, coronal T1-weighted scan of femora

[c] Only when the patient is symptomatic (e. g., back pain), in cases the disease is severe and poor growth or kyphosis are present

[d] Quality-of-life scoring system

TRAP tartrate-resistant acid phosphatase, *ACE* angiotensin-converting enzyme, *MRI* magnetic resonance imaging, *ECG* electrocardiography

Table 19.3. Neurological follow-up and monitoring of chronic neuronopathic Gaucher disease

		Initial assessment	Follow-up Every 3 months	Every 6 months	Every 12 months
Clinical examination	Neurological examination	x	In the 1st year	x	
	Eye movement examination	x		x	
	Additional neuro-ophthalmologic examination with direct ophthalmoscopy	x			x
	Audiometry	x			x
Neurophysiology	EEG	x	Only if clinically indicated (e. g., presence of seizures)		
	BSER	x			x
Neuroimaging	Brain MRI (or CT scan)	x	Only if clinically indicated		
Neuropsychometry	IQ	x			x

EEG electroencephalography, *BSER* brain stem evoked responses, *MRI* magnetic resonance imaging, *CT* computerized tomography

For most LSD, follow-up and monitoring protocols are based on the clinical presentation and organ involvement of the single patients or are derived from the local experience of the specific lysosomal disorder.

Baseline and follow-up assessment of patients with oligosaccharidoses and related disorders should be based on a multidisciplinary evaluation of the different systems and organs, together with laboratory tests. Such an approach should include careful evaluation of central nervous system (physical examination, IQ, neurophysiology, neuroimaging), respiratory function (lung functional tests, presence of sleep apneas, oxymetry, chest X-ray), heart (clinical evaluation, ECG, echography), abdominal viscera (physical examination, ultrasound, CT, MRI), eye (fundoscopy, slit-lamp examination), bone (standard X-ray, bone mass density, bone marrow MRI), growth, and nutritional status.

Experience on large series of patients will probably be of help in defining more appropriate and precise protocols.

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20 Congenital Disorders of Glycosylation

Jaak Jaeken

20.1 Introduction

Among the 19 identified disorders of *N*- and *O*-glycan synthesis, only two are amenable to treatment: phosphomannose isomerase deficiency (CDG-Ib) is efficiently treatable by mannose, while GDP-fucose transporter deficiency (CDG-IIc) can be partially treated by fucose. Symptomatic treatment mainly consists of antithrombotic therapy in CDG-Ia, and management of epilepsy.

20.2 Nomenclature

No.	Disorder	Definitions/Comment	Gene symbol	OMIM No.
20.1	Phosphomannomutase 2 (PMM2) deficiency (CDG-Ia)	Deficient mannose-1-phosphate and GDP-mannose	*PMM2*	212065
20.2	Phosphomannose isomerase (PMI) deficiency (CDG-Ib)	Deficient mannose-6-phosphate and GDP mannose	*MPI*	602579
20.3	Glucosyltransferase I deficiency (CDG-Ic)	Deficient $Glc_3Man_9GlcNAc_2$ P_2 dolichol and downstream metabolites	*hALG6*	603147
20.4	Mannosyltransferase VI deficiency (CDG-Id)	Deficient $Man_6GlcNAc_2$ P_2 dolichol and downstream metabolites	*hALG3*	601110
20.5	Dolichol-P-Man synthase I deficiency (CDG-Ie)	Deficient $Man_6GlcNAc_2$ P_2 dolichol and downstream metabolites	*DPM1*	603503
20.6	Lec 35 deficiency (CDG-If)	Increased $Man_5GlcNAc_2$ P_2 dolichol and $Man_9GlcNAc_2$	*MPDU1*	604041
20.7	Mannosyltransferase VIII deficiency (CDG-Ig)	Deficient $Man_8GlcNAc_2$ P_2 dolichol and downstream metabolites	*hALG12*	607143
20.8	Glucosyltransferase II deficiency (CDG-Ih)	Deficient $Glc_2Man_9GlcNAc_2$ P_2 dolichol and downstream metabolites	*hALG8*	608104
20.9	Mannosyltransferase II deficiency (CDG-Ii)	Deficient $Man_2GlcNAc_2$ P_2 dolichol and downstream metabolites	*hALG2*	607906
20.10	UDP-GlcNAc: dolichol phosphate *N*-acetylglucosamine-1-phosphate transferase deficiency (CDG-Ij)	Deficient $GlcNAc_2$ P_2 dolichol and downstream metabolites	*DPAGT1*	608093
20.11	Mannosyltransferase I deficiency (CDG-Ik)	Deficient Man_1 $GlcNAc_2$ P_2 dolichol and downstream metabolites	*hALG1*	608540
20.12	*N*-Acetylglucosaminyltransferase II (GnT II) deficiency (CDG-IIa)	Accumulation of $Sia_1Gal_1GlcNAc_3Man_3$ protein	*MGAT2*	212066
20.13	Glucosidase I deficiency (CDG-IIb)	Accumulation of Glc_3 Man_9 $GlcNAc_2$ protein; presence of Glc_3Man in urine	*GCS1*	606056
20.14	GDP-fucose transporter 1 deficiency (CDG-IIc)	Generalized fucose deficiency	*FUCT1*	266265
20.15	β-1,4-Galactosyltransferase 1 deficiency (CDG-IId)	Accumulation of $GlcNAc_4Man_3$ protein	*B4GALT1*	607091
20.16	β-1,4-Galactosyltransferase 7 deficiency	Decrease in glycosaminoglycans	*B4GALT7*	130070
20.17	Glucuronyltransferase/*N*-acetyl-D-hexosaminyltransferase deficiency (multiple exostoses syndrome)	Decrease in glycosaminoglycans	*EXT1/ EXT2*	133700
20.18	*O*-Mannosyltransferase 1 deficiency (Walker-Warburg syndrome)	Decrease in *O*-mannosylglycans	*POMT1*	236670
20.19	*O*-Mannosyl-β-1,2-*N*-acetylglucosaminyltransferase 1 deficiency (muscle-eye-brain disease)	Decrease in *O*-mannosylglycans	*POMGnT1*	253280

20.3 Treatment

20.1 Phosphomannomutase 2 deficiency

A minority of these patients present recurrent strokes (at least in part due to hyperaggregability of blood platelets). These strokes can be prevented more or less efficiently by small doses acetylsalicylic acid (∼ 1 mg/kg per day).

20.2 Phosphomannose isomerase deficiency

Oral mannose, 1 g/kg BW per day, divided into five doses per day. The clinical symptoms disappear rapidly, but it takes several months for the serum transferrin pattern to improve or normalize.

20.14 GDP-fucose transporter deficiency

Oral fucose, 150 mg/kg BW, five times a day, abolishes or prevents infections and normalizes neutrophil counts in some patients (depending on genotype).

Dangers/Pitfalls

- 20.2 Higher mannose doses can induce osmotic diarrhea
- 20.14 Higher fucose doses can induce autoimmune neutropenia

20.4 Alternative Therapies/Experimental Trials

None

20.5 Follow-up/Monitoring

20.2 Phosphomannose isomerase deficiency

- Clinical monitoring: 3–6 monthly
- Biochemical monitoring: serum transaminases, albumin, transferrin isoelectrofocusing, clotting factor XI: according to clinical and biochemical data.

20.14 GDP-fucose transporter deficiency

- Clinical monitoring: 3–6 monthly
- Biochemical monitoring: leukocytosis and formula: weekly until normalization; thereafter 3–6 monthly.

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21 Cystinosis

Erik Harms

21.1 Introduction

Renal Fanconi syndrome leads to early clinical symptoms of infantile, nephropathic cystinosis, with failure to thrive, growth retardation, and hypophosphatemic rickets. Most patients show also polyuria, salt craving, and excessive drinking. At this stage clinical chemistry shows characteristic changes, with glucosuria, generalized hyperaminoaciduria, hyperphosphaturia in urine, and hypophosphatemia, hypokalemia, and renal acidosis in blood. The degree of tubular dysfunction is variable in any patient, but also dependent on glomerular filtration. There is no clear distinction between infantile and late-onset type of the disease; any transitional type might exist. In late-onset nephropathic cystinosis (adolescent cystinosis), the first sign of tubular dysfunction might be tubular proteinuria.

Patients with nephropathic cystinosis need free access to fluids. In the case of gross polyuria, a trial of indomethacin could be undertaken with the dosage 1–2 mg/kg per day. It might be sufficient to provide indomethacin as a single evening dose of 1–2 mg/kg per day to reduce polyuria and excessive drinking overnight.

The goal of electrolyte supplementation is to keep the serum electrolytes and bicarbonate within normal limits. Values should not be overcorrected, because this might result in overexpansion of extracellular volume. For every patient the mixture of potassium phosphate and sodium phosphate, potassium bicarbonate and sodium bicarbonate, potassium citrate and sodium citrate, potassium lactate and sodium lactate has to be titrated. In severe renal acidosis, which cannot be corrected by oral bicarbonate alone, hydrochlorothiazide (1 mg/kg per day) can be tried, but potassium should be monitored carefully. Oral calcium should not be given as a routine measure, but only during healing of rickets and abnormal calcium losses.

Vitamin D can be given as vitamin D_3 (starting dose 5, 000 IU daily, maintenance dose after healing of rickets 1000–2000 IU daily) or 25-(OH)-vitamin D_3 (0.5 µg starting dose, up to 1 µg/day) or 1,25-$(OH)_2$-vitamin D_3 (starting dose 0.25 µg daily, dose correction according to Ca-P-levels; urinary Ca excretion should not exceed 0.5 mmol Ca/mmol creatinine).

Due to excessive drinking and eating problems, nutrition might be difficult, especially in infants and young children below 3 years of age. On the other hand, high-calorie nutrition is the basis for growth. Therefore for children with eating and swallowing difficulties, permanent tube feeding or percutaneous gastroenterostomy (PGE) might be necessary.

In any illness – in particular those with vomiting and/or diarrhea – cystinotic patients need immediate and close supervision, with frequent examination and mostly parenteral correction of electrolytes and blood gases.

Cysteamine has been proven to preserve the kidneys from further glomerular damage. Cysteamine should be administered orally as cysteamine bitartrate (Cystagon). In contrast to cysteamine, HCl cysteamine bitartrate is not hygroscopic. Cysteamine in solution has a foul taste. Fruit juice might help to reduce the nasty taste of cysteamine. Cysteamine should be given in five equal doses over 24 h, starting with 10 mg/kg per day and weekly increases of 10 mg/kg per day up to 50 mg/kg per day or 1.3 g/m^2 per day. After reaching this dosage, leukocyte cystine should be measured again. If the leukocyte cystine is still too high, cysteamine can be increased at least up to 70 mg/kg per day.

Although many adolescent and adult patients after renal transplantation are presently treated with cysteamine, the effectiveness of depleting agents in preventing late sequelae is still unproved. However, any older patient should receive cysteamine eye drops to reduce corneal damage.

Photophobia is a common feature in cystinosis. Therefore any patient, even younger patients, need prescription of sunglasses (80% reduction). Cysteamine eyedrops (0.5% cysteamine, HCl in isotonic saline) effectively remove corneal cystine crystals. These eyedrops need to be applied four times daily over months before a therapeutic effect is noticed.

Successful nutrition, supplementation therapy, and early institution of cysteamine therapy might result in an almost normal-for-age growth velocity, but most cases are below the 3rd percentile. Use of growth hormone (rhGH) in cystinotic children before renal transplantation yields improved growth and catch-up growth. Growth hormone should be especially considered in patients growing with diminished growth velocity and being below the 3rd percentile. In growth hormone-treated patients, Ca and P supplementation should be monitored carefully to avoid reappearance of rickets. After transplantation rhGH can be used in cystinotic children in the same way as in other transplanted children.

The loss of carnitine varies widely among cystinotic children. It is still being debated whether low carnitine values in cystinotic children are of clinical importance. Although reports on lipid droplets in muscle of cystinotic patients exist, no impairement of fatty acid oxidation could be demonstrated in stable isotope experiments. Overtreatment with carnitine is expensive and has no clinical benefit. Only in patients with extremely low serum carnitine levels can a low-dose therapy with 50–100 mg/kg per day be considered.

Dialysis should be started early, because plasma creatinine could be spuriously low due to low muscle mass. Both hemo- and peritoneal dialysis can be used as suitable to the individual patient. However, with respect to possible diabetes mellitus, the enhanced glucose load is a disadvantage of peritoneal dialysis. If necessary, renal transplantation should be carried out as early as possible, preferably preemptive, without prior dialysis. After transplantation steroid dosage should be lowered rapidly to avoid induction of diabetes mellitus. Posttransplantation therapy uses lifelong immunosuppression and the same control measures as in any other transplanted patient. But in cystinotic patients ocular and cerebral function needs special attention. It is undecided so far whether cystine-depleting therapy should be recommended in all transplanted patients, since there are no clear data to prove that this treatment could postpone or prevent late sequelae of cystinosis.

21.2 Nomenclature

No.	Disorder	Definitions/comments	Gene symbol	OMIM No.
21.1	Infantile nephropathic cystinosis	Infancy or early childhood	*CTNS*	219800
21.2	Adolescent nephropathic cystinosis	Late childhood to adolescence	*CTNS*	219900
21.3	Benign non-nephropathic cystinosis	Corneal cystine crystals only (diagnosis by chance)	*CTNS*	219750

The three disorders are allelic due to different mutations of the cystinosin gene (17p)

21.3 Treatment

No.	Age/stage	Medication/diet	Dosage	Doses per day
21.1	Renal-tubular	Free fluid intake	Ad lib	
21.2	dysfunction	Cysteamine (cysteamine bitartrate, Cystagon)	50–70 mg/kg per day	(4)–5
		Sodium, potassium, or phosphorus bicarbonate	Compensate for renal losses	3–4
		Calcium (only during healing of rickets)	Individual dosage	3
		Hydrochlorothiazide	1 mg/kg per day	1
		Vitamin D:		
		Vitamin D_3	1, 000–2, 000 IU/day or	1
		25-(OH)-Cholecalciferol	0.5–1.0 µg/day	1
		L-Carnitine	50–100 mg/kg per day	1
		Indomethacin	1–3 mg/kg per day or	2
			1–2 mg/kg per day	1 (evening)
		Cysteamine eyedrops (0.5% cysteamine·HCl in 0.9% saline)	1 drop/eye	4
		Thyroxine (T_4)	100 µg/m^2 per day	1
		Recombinant growth hormone (rGH)	0.045–0.050 mg/kg per day or	1
			1.4 mg/m^2 per day	1
		High-calorie nutrition, if necessary by PEG tube feeding		
21.1	Renal-tubular	Free fluid intake	Ad lib	
21.2	and glomerular dysfunction	Cysteamine (cysteamine bitartrate, Cystagon)	50–70 mg/kg per day	(4)–5
		Sodium, potassium, or phosphorus bicarbonate	Compensate for renal losses	3–4
		Hydrochlorothiazide	1 mg/kg per day	1
		Vitamin D		
		1,25-$(OH)_2$-cholecalciferol	0.25–0.5–1.0 µg/day	1
		L-Carnitine	50–100 mg/kg per day	1
		Cysteamine eyedrops (0.5% cysteamine · HCl in 0.9% saline)	1 drop/eye	4
		Thyroxine (T_4)	100 µg/m^2 per day	1
		Recombinant growth hormone (rGH)	0.045–0.050 mg/kg per day or	1
			1.4 mg/m^2 per day	1
		High-calorie nutrition		
21.1	Endstage renal	Cysteamine (cysteamine	50–70 mg/kg per day	(4)–5
21.2	failure	bitartrate, Cystagon)		
		Sodium bicarbonate	Compensate for losses	3–4
		Calcium	Individual dosage	3
		Vitamin D:		
		1,25-$(OH)_2$-cholecalciferol	0.25–0.5–1.0 µg/day	1
		L-Carnitine	50–100 mg/kg per day	1

No.	Age/stage	Medication/diet	Dosage	Doses per day
		Cysteamine eyedrops (0.5% cysteamine · HCl in 0.9% saline)	1 drop/eye	4
		Thyroxine (T_4)	100 µg/m^2 per day	1
		Recombinant growth hormone (rhGH)	0.045–0.050 mg/kg per day or 1.4 mg/m^2 per day	1
		Erythropoeitin (rhEPO; renal anemia)	1,000–3,000 IU weekly	1
		High-calorie nutrition		

Dangers/Pitfalls

1. Cysteamine dosage is calculated for cysteamine as free base.
2. Avoid overcorrection of electrolytes resulting in overexpansion of extracellular volume. In the stage of decreasing glomerular function or endstage renal failure, electrolyte supplementation needs to be reduced, especially phosphorus and potassium.
3. In patients with hyperphosphaturia, calcium supplementation leads to a high risk of nephrocalcinosis. When calcium is given to cystinotic patients, urine should be monitored carefully for Ca excretion. Ca excretion should not exceed 0.5 mmol/mmol creatinine.
4. Hyrochlorothiazide should only be tried in severe renal acidosis, which cannot be corrected by oral bicarbonate alone. When using hydrochlorothiazide, potassium should be monitored carefully.
5. Carnitine supplementation is recommended only in patients with very low plasma carnitine levels (e. g., total carnitin levels < 10 µmol/l).
6. The use of indomethacin should be restricted to patients presenting with gross polyuria. A single evening dose might help prevent enuresis nocturna.
7. Cysteamine eyedrops can be used at all ages. However, younger children do not tolerate regular application well. At school age all patients should be put on cysteamine eyedrops. Removal of cystine crystals effectively reduces the risk of damage to the corneal epithelium. Cysteamine eyedrops are of limited stability and should be kept in a refrigerator.
8. Thyroxine supplementation is necessary only in cases with proven hypothyroidism.
9. Recombinant growth hormone is indicated in patients growing with diminished growth velocity below the 3rd percentile.
10. Use of 1,25-$(OH)_2$-cholecalciferol implies the risk of hypercalciuria. In order to avoid nephrocalcinosis, urinary calcium should carefully be monitored. Ca excretion should not exceed 0.5 mmol/mmol creatinine.
11. Due to excessive drinking and eating problems, good nutrition can be difficult, especially in infants and young children below 3 years of age, but high-calorie nutrition is essential for growth. Therefore permanent tube feeding or PGE might be necessary.

21.4 Alternative Therapies/Experimental Trials

No.	Age/stage	Measure
21.1 21.2	Endstage renal failure	Renal replacement therapy: continous peritoneal dialysis; hemodialysis; kidney transplant

Dangers/Pitfalls

Dialysis should be started early, because plasma creatinine could be spuriously low due to low muscle mass. Both, hemo- or peritoneal dialysis can be used as suitable for the individual patient. However, the increased glucose load is a disadvantage of peritoneal dialysis in diabetic patients. If necessary, renal transplantation should be carried out as early as possible, preferably preemptive, without prior dialysis. After transplantation steroid dosage should be lowered rapidly to avoid induction of diabetes mellitus. Posttransplantation immunosuppression and control measures are the same as in any other transplanted patient, but ocular and cerebral function needs special attention in cystinotic patients.

21.5 Follow-up/Monitoring

■ *21.1 and 21.2*

Test	Age	Frequency	Comments
Cystine in leukocytes	All ages	After reaching therapeutic dosis: every 3 months	Goal: ~ 0.5 nmol/mg protein
Clinical monitoring	<6 years	Every 3 months	Regular control of growth and nutrition, calculate growth velocity
	6–10 years	Every 4 months	Depending on compliance
	>10 years	Every 6 months	Depending on compliance; more frequent monitoring with decreasing glomerular function
Electrolytes, phosphorus, blood gases, creatinine, alkaline phosphatase, liver function, hemoglobin, blood count	All ages	Every 1–3 months	Immediate control in GI disease (vomiting, diarrhea); more frequent controls when close to endstage renal failure
Creatinine clearance	>4 years	6 monthly	
Carnitine	All ages	6 monthly to yearly	
Parathormone	All ages	6 monthly	More frequent controls when close to endstage renal failure
Thyroid function	All ages	Yearly	
Glucose tolerance	>10 years	Yearly	
Hypogonadism	Pubertal boys		
Ultrasound kidneys	All ages	Yearly	Check for nephrocalcinosis
X-ray bones (left hand)	During healing of rickets	Every 3 months until healing	
	In endstage renal failure	6 monthly	Check for renal osteopathy
Ophthalmologist (split lamp)	>4 years (without local treatment)	6 monthly to yearly	
	>4 years (with local treatment)	6 monthly	
Brain imaging (MRI, CT)			Only in neurological, psychointellectual, or psychiatric deterioration

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22 Other Storage Disorders

Joe T.R. Clarke

22.1 Introduction

This chapter covers a group of conditions that are all characterized by accumulation of metabolites, either as a result of defects in catabolism, transport of metabolites across lysosomal membranes, or overproduction of a metabolite owing to a breakdown in feedback inhibition of its synthesis. All but one are defects in lysosomal enzymes or membranes. In most of them, primary involvement of the central nervous system is prominent, posing a major challenge to the development of effective treatments. In general, specific treatment for those in which central nervous system (CNS) involvement is the principal cause of morbidity is nonexistent or inadequate. Although it is of central importance, supportive and symptomatic treatment in these cases is complex, involving participation by a variety of medical and surgical specialists, and often only marginally effective.

22.2 Nomenclature

No.	Disorder	Enzyme defect	Gene symbol	OMIM No.
22.1	Fabry disease	α-Galactosidase A	*GLA*	301500
22.2.1	Farber disease (classic type)	Ceramidase	*ASAH*	228000
22.2.2	Farber disease (intermediate and mild type)	Ceramidase	*ASAH*	228000
22.3.1	Metachromatic leukodystrophy, infantile form	Arylsulfatase A	*ARSA*	250100
22.3.2	Metachromatic leukodystrophy, juvenile form	Arylsulfatase A	*ARSA*	250100
22.3.3	Metachromatic leukodystrophy (SAP B defect)	Saposin B	*PSAP*	249900
22.4.1	Infantile neuronal ceroid lipofuscinosis	Palmitoyl protein thioesterase 1	*CLN1*	256730
22.4.2	Late infantile neuronal ceroid lipofuscinosis	Tripeptidyl peptidase 1	*CLN2*	204500
22.4.3	Juvenile neuronal ceroid lipofuscinosis	Membrane protein	*CLN3*	204200
22.5.1	Sialic acid storage disorder (infantile form)	Sialin (sialic acid transporter)	*SLC17A5*	604322
22.5.2	Sialic acid storage disorder (Salla disease)	Sialin (sialic acid transporter)	*SLC17A5*	604369
22.6	Sialuria	UDP-*N*-acetylglucosamine 2-epimerase		269921

22.1 Fabry disease

Fabry disease is an X-linked lysosomal storage disease caused by deficiency of α-galactosidase A, resulting in accumulation of the principal glycosphingolipid substrate globotriaosylceramide (ceramide trihexoside, CTH, Gb3), primarily in the walls of small arteries, the kidneys, and small unmyelinated nerves. The disease is characterized clinically by onset in the first decade of life of chronic and episodic neuritic pain in the hands and feet, recurrent abdominal pain and diarrhea, and joint pain often misdiagnosed as acute pauciarticular rheumatoid arthritis. Young adult patients often develop a characteristic angiokeratomatous skin rash distributed primarily in the genital area and lower trunk and back. Kidney involvement is usually heralded by the appearance of persistent proteinuria and urosthenia progressing eventually to chronic renal failure. Accumulation of Gb3 in the myocardium is associated with progressive hypertrophic cardiomyopathy. Involvement of cerebral blood vessels commonly causes transient ischemic attacks and stroke.

The disease is clinically highly heterogenous, varying markedly in the constellation and severity of symptoms (MacDermot et al. 2001a). It is characteristically more severe in affected males than in carrier females. However, a small but significant number of carrier females may develop symptoms and complications indistinguishable from those in affected males, though generally at an older age (MacDermot et al. 2001b). Patients of either sex often experience problems referable to numerous tissues and organs, with any combination of painful crises, fatiguability, abdominal pain and diarrhea, palpitations, ankle edema, hearing impairment, tinnitus and vertigo, as well as signs of renal impairment and transient ischemic attacks. The protean, multisystem nature of the disease, along with the extraordinary emotional stress experienced by affected patients, generally requires a coordinated team approach to management, involving a number of medical specialists and other health professionals.

Milder clinical variants have been reported in which problems may be limited to one organ or system. The only significant clinical manifestation of the disease in patients with these variants may be symptoms caused by progressive hypertrophic cardiomyopathy or by progressive renal failure.

22.3 Treatment

Table 22.1 gives details of the treatment of Fabry disease.

Table 22.1. Treatment of Fabry disease

Treatment objective	Medication or procedure	Dosage
Primary		
Enzyme replacement therapy[a]	Agalsidase-alfa	0.2 mg/kg IV biweekly
	Agalsidase-beta	1.0 mg/kg IV biweekly
Symptomatic		
Relief of pain	Phenytoin	100 mg PO tid
	Carbamazepine	200–400 mg PO bid
	Amitriptylline	25–100 mg PO daily
	Gabapentin	300–400 mg PO tid
Abdominal distress	Pancreatic enzymes	Various
	Bismuth subsalicylate	2 tabs PO q 1 h prn
	Ranitidine	150 mg PO bid
	Loperamide	4 mg PO stat, then 2 mg per loose stool to max of 16 mg
	Octreotide	50–100 µg SC, once daily to tid
Renal insufficiency[b]	Dietary protein restriction	
	Angiotensin-converting enzyme inhibitors	Various
	Chronic ambulatory peritoneal dialysis, chronic hemodialysis, or renal transplantation	Treatment of ESRD (Ojo et al. 2000)
Hypertrophic cardiomyopathy[b]	Beta-blockers, carvedilol	Various
	Calcium channel blockers, e. g., diltiazem	Various
	Antihypertensives	Various
	Cardiac transplantation	
Transient ischemic attacks and stroke[b]	Aspirin	80 mg/day PO

IV intravenous, *PO* orally, *SC* subcutaneously, *ESRD* end-stagerenal disease

[a] The safety and effectiveness of enzyme replacement therapy has been demonstrated in randomized, double-blind, placebo-controlled studies (Eng et al. 2001; Schiffmann et al. 2001; Pastores and Thadhani 2002; Germain 2002)

[b] These complications are best managed by specialists in the area, such as nephrologists, cardiologists, and neurologists, with experience of the management of Fabry disease

22.4 Alternative or Investigational Treatments

A single report has appeared of treatment of Fabry disease by weekly intravenous infusions of galactose (Frustaci et al. 2001), which was shown in vitro to enhance mutant α-galactosidase A activity, presumably by stabilization of a catalytically active but unstable enzyme protein. The patient, a middle-aged man with severe cardiomyopathy, showed significant improvement in cardiac

function after several weeks' treatment. The long-term effectiveness of this treatment and the role it might have to play in the treatment of other patients with the disease remains to be established.

Clinical trials are currently underway to evaluate the safety and efficacy of substrate reduction therapy (SRT) in Fabry disease (Lachmann 2003). The rationale for SRT derives from the principle that accumulation is controlled, in part, by the rate of synthesis of the glycosphingolipid substrates. As long as the mutant enzyme retains some residual hydrolytic activity, substrate accumulation is controllable, at least in theory, by inhibiting biosynthesis of the accumulating substrate itself or a biosynthetic precursor. Miglustat (*N*-butyldeoxynojirimycin) is a potent, competitive inhibitor of UDP-glucose:ceramide glucosyltransferase, which catalyzes the biosynthesis of glycosylceramide (glucocerebroside). The safety and efficacy of miglustat treatment of Gaucher disease has been demonstrated in clinical trials (see Chap. 19). The treatment of Fabry disease with miglustat is still under investigation. Diarrhea, weight loss, and tremor are common side-effects of treatment.

22.5 Follow-up/Monitoring

All patients with Fabry disease should be followed-up regularly, regardless of sex, age, or apparent disease severity. After comprehensive initial evaluation, detailed history and physical examination should be undertaken in all patients at least annually (Desnick et al. 2003). The frequency and extent of other follow-up assessments will depend on the severity of disease manifestations and complications. The extent and frequency of suggested follow-up studies are shown in Table 22.2.

Table 22.2. Follow-up and monitoring of Fabry disease

Examination	Initial	6 months	12 months	24 months
Adults (> 18 years old)				
Detailed history & physical examination	x		x	
Routine urinalysis	x		x	
24-h urinary protein	x	x[1]	x	
Endogenous creatinine clearance	x	x[1]	x	
Plasma urea, creatinine, electrolytes	x	x[1]	x	
Plasma homocysteine	x			
Plasma total, LDL- and HDL-cholesterol	x			x
Ocular examination (by ophthalmologist)	x			x
Electrocardiogram	x	x[2]	x	
Echocardiogram	x	x[2]		x
Audiogram	x		x	
Brain MRI	x			x[3]
Children (≤ 18 years old)				
Detailed history & physical examination	x		x	
Routine urinalysis	x		x	
Ocular examination (by ophthalmologist)	x			
Audiogram	x			x
Electrocardiogram (> 10 years old)	x		X	

[1] If the results of previous kidney function tests were abnormal
[2] If previous test results show evidence of cardiomegaly, arrhythmia, or other potentially progressive abnormality
[3] Abnormalities should be followed up with more extensive assessment of renal function, including plasma urea, creatinine, 24-h protein excretion, and endogenous creatinine clearance

22.2 Farber disease

Farber lipogranulomatosis is an autosomal recessive lysosomal storage disease caused by deficiency of acid ceramidase. In severe forms of the disease, the resulting accumulation of ceramide in tissues throughout the body causes the appearance in the first few weeks or months of life of painful swelling and stiffness of joints, palpable subcutaneous nodules around affected joints areas of skin exposed to pressure, hoarse cry, interstitial pulmonary infiltration, developmental delay, feeding difficulty and failure to thrive, intermittent fever,

and marked irritability. Some patients also exhibit enlargement of the liver, and corneal clouding and cherry-red spots in the fundi have also been observed in some patients. The subcutaneous nodules increase in number and size as the disease progresses. The development of granulomas in the pharynx and larynx often produce dysphagia and upper airway obstruction, often prompting gastrostomy and tracheostomy. Developmental delay and hyporeflexia are common, but seizures are relatively uncommon. The most severe form is characterized by death by age 2 years, usually as a result of pulmonary complications of the disease.

In children with rare, milder, variants, flexion contractures of the knees, wrists, and fingers, along with subcutaneous nodules, are the main clinical features of the disease. The lungs and liver are spared, and the majority of patients have normal intelligence. Survival into middle childhood or the late teens is usual, with death generally due to severe malnutrition and pneumonia.

A small number of patients have been described in which hepatosplenomegaly and massive pulmonary infiltration are present from the newborn period, without the characteristic subcutaneous nodules. Affected infants do not survive more than a few months. Another rare variant of the disease has been reported in which the clinical presentation is dominated by developmental delay and regression from 12–24 months of age. Ataxia, tremors, rigidity, depressed deep tendon reflexes, and seizures are prominent. Careful physical examination in these cases shows the presence of subcutaneous nodules and joint stiffness. The average age of death of affected children is around 3 years.

22.6 Treatment

Treatment of Farber lipogranulomatosis is entirely symptomatic and supportive. Treatment with systemic corticosteroids may relieve some of the discomfort of the subcutaneous nodules. Surgical excision of nodules affecting feeding or causing airway obstruction may significantly improve the quality of life of affected infants. Pulmonary and airway complications may require tracheostomy and continuous oxygen administration. Gastrostomy may be necessary for management of feeding difficulties.

Treatment by hematopoietic stem cell transplantation (HSCT) by bone marrow transplantation has been attempted in a small number of patients with milder forms of the disease (Souillet et al. 1991). It may produce some amelioration of nonneurological complications of the disease, but does not appear to affect the brain in those patients with significant central neurological involvement. HSCT should be considered to be investigational and offered only to patients in whom central nervous system involvement is absent or minimal.

22.7 Follow-up Monitoring

The rapidity of the progression of this disease makes frequent monitoring essential. Clinical evaluation, with ancillary investigations and therapeutic interventions as indicated, should be repeated at least every 3 months.

22.3 Metachromatic leukodystrophy

Metachromatic leukodystrophy (MLD) is an autosomal recessive neurodegenerative disorder caused by deficiency of lysosomal arylsulfatase A, resulting in accumulation of sulfatide ((6-*O*-sulfate)galactosylceramide) in the brain, peripheral nerves, gall bladder mucosa, and urinary sediment. The late-infantile variant is characterized by the onset in the 2nd year of life of unsteadiness of gait and muscle weakness, progressing to marked spasticity, rapid developmental regression, and seizures, culminating in death within 3–10 years.

Juvenile-onset MLD is characterized clinically by slowly developing developmental arrest and regression, often manifested as deteriorating school performance. Muscle weakness progressing to spasticity occurs later. Survival for many years with advanced neurological impairment is common.

MLD caused by mutations in the prosaposin gene (PSAP), causing deficiency of saposin B, a noncatalytic activator protein required for the hydrolysis of sulfatide by arylsulfatase A, is clinically indistinguishable from classic late-infantile MLD. Measurements of the enzyme with the use of synthetic substrates, such as *p*-nitrophenylsulfate, show no deficiency of enzyme activity. The diagnosis is often suspected by the typical appearance of the brain on magnetic resonance (MR) imaging, the demonstration of the accumulation of metachromatic inclusions in Schwann cells, or the demonstration of sulfatide accumulation in urinary sediment.

22.8 Treatment

Therapeutic efforts to arrest or reverse the course of the disease in symptomatic infants with classic late-infantile MLD have been uniformly disappointing. Treatment of presymptomatic infants, usually identified on the basis of a history of the disease in a sibling, by HSCT appears at least to delay the onset of neurological symptoms of the disease (Krivit et al. 1990, 1999; Peters et al. 1997). In children with juvenile MLD, HSCT by bone marrow transplantation has been reported to arrest the disease (Krivit et al. 1999), though experience is not uniformly positive (Kapaun et al. 1999; Malm et al. 1996). A single case of HSCT treatment of a patient with MLD caused by saposin-B deficiency did poorly (Landrieu et al. 1998). Allogeneic mesenchymal stem cell infusion has been proposed as an improved approach to primary treatment of MLD; however, experience is still very limited (Koç et al. 2002). Most of the published

information on the treatment of MLD by HSCT is in the form of single-case reports, small series (less than 5 cases), or review articles. No systematic clinical trials have been conducted, and data collection from centers undertaking this treatment is still haphazard and incomplete.

Supportive and symptomatic therapy is particularly important in MLD. Some of the major problems and treatments are shown in Table 22.3.

Table 22.3. Treatment of metachromatic leukodystrophy

Treatment objective	Medication or procedure	Dosage and comments
Primary		
Enzyme replacement therapy	Hematopoietic stem cell transplantation	Patients with presymptomatic late-infantile or early symptomatic juvenile MLD
Symptomatic		
Relief of spasticity	Baclofen, systemic	Up to 5 mg by mouth tid; benefit is variable and generally incomplete
	Baclofen, intrathecal[1]	Little experience
	Gabapentin	Start 10–15 mg/kg per day by mouth, increasing to a maximum of 40 mg/kg per day divided tid; improvement is sometimes dramatic
	Botulinum toxin, type A[1]	Benefit is variable
Seizures	Anti-convulsants, e. g., carbamazepine	Various
Constipation	Dietary manipulation	Ensuring adequate fluid intake; high-fiber diet; high-pectin fruits
	Lactulose	15–30 ml by mouth once or twice (max 60 ml) daily; improvement is often dramatic; may cause flatulence and cramps
	Stool softeners, e. g., docusate sodium	50–250 mg by mouth divided once to 4 times daily; benefit variable
	Stool lubricants, e. g., mineral oil, glycerin	Benefit variable
	Bowel stimulants, e. g., bisacodyl	10 mg per rectum daily; limit administration to 1–2 days weekly
Feeding difficulties	Dietary manipulation	Soft or pureed foods of uniform texture
	Gastrostomy	

[1] Should be considered investigational

22.9 Follow-up Monitoring

Patients with MLD should be seen at least every 6 months for management of spasticity, seizures, constipation, and nutritional support.

22.4 Neuronal ceroid lipofuscinosis

Neuronal ceroid lipofuscinosis (NCL) is a genetically and clinically heterogeneous group of neurodegenerative diseases characterized clinically by prominent involvement of gray matter: developmental arrest and regression, visual impairment progressing to early blindness, and seizures. The causes of the three most common variants of NCL are summarized in Table 22.1.

22.10 Treatment

No treatment for any variant of NCL has been reported to materially affect the natural history of the disease. However, supportive treatment of visual impairment and intellectual deterioration, as well as control of seizures by administration of appropriate anticonvulsants, significantly adds to the quality of life of affected patients. Seizure control may be difficult to achieve, requiring the use of anticonvulsants that are not commonly used in the treatment of idiopathic epilepsy (Åberg et al. 2000). Optimum management generally requires close consultation with neurologists with experience in the management of intractable seizure disorders.

22.11 Alternative or Investigational Treatments

A variety of experimental treatments for NCL have been proposed and, in some cases, evaluated systematically. Some of these, including a few that are still under investigation, are summarized in Table 22.4. None has been shown unambiguously to affect the long-term outcome for patients with NCL.

Table 22.4. Alternative or investigational treatments of neuronal ceroid lipofuscinosis

Treatment or procedure	Comments	References
Hematopoietic stem cell transplantation	Very small number of cases, mostly negative; no formal clinical trials	Lönnqvist et al. 2001
Flupirtine	Preclinical evidence of efficacy; clinical trials currently in progress	Dhar et al. 2002
Cysteamine	Preclinical evidence of potential efficacy in infantile NCL caused by PPT1 deficiency; phase I clinical trial underway	Zhang et al. 2001
Dietary supplementation with polyunsaturated fatty acids	No formal clinical trials assessment; benefit doubtful	Bennett et al. 1994
Carnitine	No formal clinical trials assessment; benefit doubtful	Katz et al. 1997
Enzyme replacement therapy[a]	Pre-clinical evidence of potential efficacy	Lin and Lobel 2001
Neurotrophic factors[b]	Pre-clinical evidence of potential efficacy	Cooper and Mobley 2001

NCL neuronal ceroid lipofuscinosis, *PPT1* palmitoyl protein thioesterase 1, *TPP-1* tripeptidyl peptidase-1

[a] Treatment of late-infantile NCL by infusions of TPP-1

[b] Polypeptides that support the growth, differentiation, and survival of neurons, such as nerve growth factor (NGF)

22.12 Follow-up Monitoring

Follow-up monitoring by a neurologist experienced in the management of this group of disorders, especially the management of seizures, is important. Patients should generally be seen at least semiannually for assessment of seizure control and supportive management of visual impairment and intellectual deterioration. Active involvement of support agencies, such as associations for the visually impaired, and those involved in the education of affected children, is imperative. The emotional and psychological toll of these diseases on parents, as well as on affected children, is enormous.

■ *22.5 Sialic acid storage disease*

Sialic acid storage disease is a rare autosomal recessive neurodegenerative disorder caused by a defect in lysosomal membrane transport resulting in intralysosomal accumulation of sialic acid. The most severe form of the disease is

characterized clinically by early onset of coarse facial features, hypopigmentation, hepatosplenomegaly, and severe psychomotor retardation in all patients, and nephrotic syndrome in most (Lemyre et al. 1999). Many cases present as nonimmune fetal hydrops. Hypertrophic cardiomyopathy may be present. Radiographic evidence of mild dysostosis multiplex is found, but the corneas are clear. Death between 6 and 24 months of age is generally caused by respiratory infections occurring as a complication of progressive neurodegeneration.

A clinically milder, allelic variant of the disease, which is common in Finland, where it has been called Salla disease, is characterized by slowly progressive mental retardation, ataxia, central hypotonia, and spasticity in the lower extremities (Varho et al. 2002). Affected patients show no organomegaly or skeletal abnormalities, and life expectancy is generally normal. Most Finnish patients are homozygous for a single missense mutation, R39C. Compound heterozygous patients generally have clinically more severe disease.

22.13 Treatment

There is no effective treatment for the primary defect in sialic acid storage disease. However, patients benefit from long-term supportive management of the neurological and intellectual disabilities.

22.14 Follow-up Monitoring

Follow-up of infantile sialic acid storage disease is dictated by the demands of the complications of a rapidly progressive neurodegenerative disease. Supportive treatment of refractory nephrotic syndrome generally requires participation of pediatric nephrologists in the care.

Follow-up care of patients with Salla disease is directed primarily at the monitoring and supportive management of neurological problems, especially intellectual impairment. This generally requires a multidisciplinary approach involving a range of social and educational supports, in addition to periodic specialized neurological consultation. The scheduling of follow-up will depend on the severity of the complications and the individual circumstances of the patient.

■ *22.6 Sialuria*

This extremely rare condition, sometimes called “French sialuria”, is an autosomal dominant disorder caused by failure of allosteric feedback inhibition of uridinediphosphate-*N*-acetylglucosamine (UDP-GlcNAc) 2-epimerase by cytidine monophosphate (CMP)-*N*-acetylneuraminic acid, resulting in overproduction of *N*-acetylneuraminic acid (sialic acid) and the excretion of vast

amounts of sialic acid in the urine. The small number of patients reported so far have presented with mental retardation, seizures, hepatosplenomegaly, and dysmorphic features (Enns et al. 2001).

22.15 Treatment

There is no effective treatment for sialuria.

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23 Inborn Errors of Purine and Pyrimidine Metabolism

Albert H. van Gennip, Jörgen Bierau, William L. Nyhan

23.1 Introduction

Purines and pyrimidines are vital components of all living cells. Not only are purines and pyrimidines the precursors of DNA and RNA and not only do they provide energy in the form of adenosine triphosphate (ATP), they are also involved in the biosynthesis of phospholipids and glycolipids. Furthermore, purines and pyrimidines are involved in signal transduction pathways.

A total of 30 defects of enzymes involved in the metabolism of purines and pyrimidines have been described. Some of these enzyme defects are relatively benign or nondiseases. A total of 15 of these defects in the metabolism of purines and pyrimidines are known to cause human disease. One defect, dihydropyrimidine dehydrogenase deficiency, becomes important to recognize in patients treated for cancer with fluorinated pyrimidine analogs. Administration of these drugs can then be catastrophic, as a consequence of the inability of the patient to degrade these compounds, which results in severe toxicity. In thiopurine methyltransferase deficiency, there may be enhanced toxicity of mercaptopurines.

A major advance in the management of the hyperuricemic disorders was the discovery of allopurinol, which inhibits xanthine oxidase. Effective therapy has eliminated the consequences of overproduction of uric acid, including gouty arthritis, tophaceous deposits, urate calculi, and urate nephropathy.

23.2 Nomenclature

No.	Disorder (symbol)	Definitions/comment	Gene symbol	OMIM No.
23.1	ADA	Adenosine deaminase deficiency	*ADA*	102700
23.2	PNP	Purine nucleoside phosphorylase deficiency	*NP*	164050
23.3	HPRT	Hypoxanthine phosphoribosyltransferase deficiency	*HPRT1*	308000
23.4	PRPS	Phosphoribosylpyrophosphate synthetase superactivity	*PRPS1*	311850
23.5	APRT	Adenine phosphoribosyltransferase deficiency	*APRT*	102600
23.6a	XDH	Xanthine dehydrogenase/oxidase deficiency	*XDH*	607633
23.6b	XDH/SO	Combined XDH/sulphite oxidase deficiency		
23.6c	XDH/AO	Combined XDH/aldehyde oxidase deficiency		
23.7	ADSL	Adenylosuccinate lyase deficiency	*ADSL*	608222 103050
23.8	MAD	Myoadenylate deaminase deficiency Adenosine monophosphate deaminase deficiency	*AMPD1*	102770
23.9	TPMT	Thiopurine methyltransefrase deficiency	*TPMT*	187680
23.10	UMPS	UMP synthetase deficiency Oroticaciduria	*UMP*	258900
23.11a	UMPH1	UMP hydrolase deficiency 5′-Nucleotidase deficiency pyrimidine 5′-nucleotidase deficiency	*UMPH1* *NT5C3* *P5N1*	266120 606224
23.11b	UMPHS	UMP hydrolase superactivity		
23.12	TP	Thymidine phosphorylase deficiency Mitochondrial Neurogastronintestinal encephalopathy (MNGIE)	*ECGF1*	131222 603041
23.13	DPD	Dihydropyrimidine dehydrogenase deficiency	*DPYD*	274270
23.14	DHP	Dihydropyrimidinase deficiency	*DPYS*	222748
23.15	UP	β-Ureidopropionase deficiency	*UPB1*	606673

23.3 Treatment

23.1 Adenosine deaminase deficiency

No.	Symbol	Age	Medication	Initial dosage	Maintenance dosage[a]	Maintain plasma ADA actively
23.1	ADA	Any	PEG-ADA	60 U/kg per week	30 U/kg per week	25–150 µmol/h per ml

[a] After several months

The treatment of choice of adenosine deaminase (ADA) deficiency is transplantation of bone marrow (BMT) from an human leukocyte antigen (HLA)-identical sib. In the absence of identical sib BMT with T-cell depletion or hematopoietic stem cells:

- Enzyme replacement with polyethylene glycol-modified bovine adenosine deaminase (PEG-ADA; Adagen, Enzon; intramuscular injections)
- Somatic gene therapy

Dangers/Pitfalls
Bone marrow transplant: graft-versus-host disease
Gene therapy: immunity to gene-transfer system; the effect of gene therapy is difficult to assess, because treatment with PEG-ADA was continued in the patients who received gene therapy

23.2 Purine nucleoside phosphorylase deficiency

Bone marrow transplantation (BMT).

Dangers/Pitfalls
BMT: beware of graft-versus-host disease.

23.3 Hypoxanthine phosphoribosyltransferase deficiency

No.	Symbol	Age	Medication	Dosage	Monitor	Target[a]
23.3	HPRT	Child	Allopurinol	20 mg/kg per day	Blood uric acid	Blood uric acid < 3 mg/dl
		Adult	Allopurinol	200–600 mg/kg per day		

[a] Once target blood level is achieved, monitor urine oxypurines to maximize hypoxanthine and minimize xanthine and uric acid

Allopurinol is sufficient therapy for variants with partial deficiency of hypoxanthine phosphoribosyltransferase deficiency (HPRT). In patients with Lesch-Nyhan syndrome, allopurinol does nothing for the neurological and behavioral features of the disease. Most patients require some muscle relaxant, valium or baclophen, doses adjusted individually. Self-injurious behavior usually requires the removal of teeth. Physical restraint is usually required to prevent self-mutilation. This often requires physician advocacy and intervention when authorities consider restraint an infringement of liberties.

Stones already formed may be treated by lithotripsy.

Dangers/Pitfalls

Urinary tract calculi may be composed of urate or xanthine, so allopurinol will not always prevent their formation. They are radiolucent. Ultrasound is therefore the usual approach to diagnosis.

BMT or stem cell transplantation has been of no benefit in this disease, and there have been a number of deaths.

In general, surgical interventions such as for hip dislocation or gastric fundoplication have been disastrous in this disease.

Uricosuric agents such as probenecid are contraindicated; they may induce acute renal shut down.

In the presence of renal insufficiency, dosage of allopurinol may have to be reduced; monitoring of levels in the blood is useful.

23.4 Phosphoribosylpyrophosphate synthetase abnormality

No	Symbol	Age	Medication	Dosage	Target
23.4	PRPPS	Child Adult	Allopurinol	20 mg/kg per day 200–600 mg/kg per day	Blood uric acid <3 mg/dl

It is not necessary to monitor urinary purines in this disease. In the presence of normal HPRT activity and inhibition of xanthine oxidase, the total purine to be excreted decreases.

Some kindred have associated deafness, which is often recognized late. Hearing aids facilitate normal development.

See disorder 23.3.

Dangers/Pitfalls

Uricosuric agents such as probenecid are contraindicated in any overproduction hyperuricemia.

See disorder 23.3.

23.5 Adenine phosphoribosyltransferase deficiency

No.	Symbol	Medication	Dosage	Target
23.5	APRT	Allopurinol	Child: 10 mg/kg per day Adult: 200–300 mg/kg per day	Urine 2,8 DHA virtually 0

2,8-Dihydroxyadenine (2,8-DHA) stones may be radiolucent.

In case of acute or chronic renal failure, the dosage of allopurinol needs to be lowered.

Lithotripsy.

Dangers/Pitfalls

See disorder 23.3.

23.6a Xanthine dehydrogenase deficiency, isolated

No.	Symbol	Medication	Dosage
23.6a	XDH	Allopurinol Child Adult	 10–20 mg/kg per day 100–300 mg/day

23.6b Combined xanthine dehydrogenase/sulfite oxidase deficiency, molybdenum cofactor deficiency

In cofactor deficiency (xanthine dehydrogenase/sulfite oxidase deficiency, XDH/SO) the use of dextromethorphan (an *N*-methyl-D-aspartate receptor agonist) may be useful as an anticonvulsant.

23.6c XDH/AO combined xanthine dehydrogenase/aldehyde oxidase deficiency (see disorder 23.6a)

In any XDH, partial activity is required for any benefit from allopurinol. In the presence of HPRT, any hypoxanthine is recycled, and this may reduce total purine excretion, virtually all of which is xanthine.

In SO deficiency a low-methionine/-cystine diet may be of benefit. Therapy is facilitated by the use of Homimex.

Treatment may be monitored by measuring levels of sulfocysteine or sulfate in the urine. Target levels have not been established.

Cysteamine may be helpful in absorbing excess sulfite in patients with SO deficiency. Thiamine should be supplemented to avoid deficiency.

23.7 Adenylosuccinate lyase deficiency

Oral supplementation of D-ribose at a dose of 10 mmol/kg per day has been reported to be beneficial.

Oral administration of adenine 10 mg/kg per day with allopurinol 5–10 mg/kg per day.

Dangers/Pitfalls

Adenine is converted to 2,8-DHA by XDH, raising the risk of kidney stone formation. Allopurinol is an inhibitor of XDH and serves to prevent formation of 2,8-DHA.

23.8 Myoadenylate deaminase deficiency

No.	Symbol	Age	Medication	Dose/day
23.8	MAD	Any Any	D-Ribose Xylitol	< 200 mg/kg 15–20 g

23.9 Thiopurine methyltransferase deficiency

In patients treatd with mercaptopurines (MP), dosage of MP to be lowered dependent on residual thiopurine methyltransefrase (TPMT) activity.

23.10 Orotic aciduria – UMP synthase deficiency

No.	Symbol	Age	Medication	Dose mg/kg per day	Divided times/day	Monitor	Target reduction
23.10	UMPS	Any	Uridine	50–300	1–5	Hematology	Urinary orotic acid

Clear relationship between urinary orotate and uridine dosage has not been established. The major target is zero megaloblastosis and a normal complete blood count.

Susceptibility to infection may remain after hematological findings are normal.

Uridine dosage may be limited by diarrhea.

Triacetyluridine has not been tried in this disease, but it should be more effective than uridine because of greater bioavailability following oral administration.

23.11a UMP hydrolase deficiency (UMPH1); synonyms: 5'-nucleotidase deficiency, pyrimidine 5'-nucleotidase deficiency (NT5C3, P5N1)

Splenectomy has been reported to cure the life-long hemolytic anemia associated with UMPH1 deficiency.

23.11b UMP hydrolase superactivity (UMPHS); synonyms: 5'-nucleotidase superactivity

No.	Symbol	Age	Medication	Dosage mg/kg per day	Target
23.11b	UMPHS	Any	Uridine	1,000	Seizures, infection

Treatment with uridine has led to cessation of seizures and reduced susceptibility to infection, as well as improvement in neurological findings.

Triacetyluridine is more effective than uridine in this disease. Dosages have not been published.

23.12 Thymidine phosphorylase deficiency

No specific treatment is available.

23.13 Dihydropyrimidine dehydrogenase deficiency

Anticonvulsant therapy should be used for seizures.

The use of 5-halogenated pyrimidines such as 5-fluorouracil should be avoided.

23.14 Dihydropyrimidinase deficiency

See disorder 23.13.

23.15 β-Ureidopropionase deficiency

No specific treatment is available.

23.4 Alternative Therapies/Experimental Trials

23.1 Adenosine deaminase deficiency

Gene (transfer) therapy.

A clinical trial is currently being conducted by the National Institutes of Health, Bethesda, Maryland, USA, in which patients suffering from severe combined immunodeficiency (SCID) due to adenosine deaminase deficiency are being treated with autologous cord blood or bone marrow CD34+ cells transduced with a human ADA gene. (NIH protocol number 01-HG-0189.)

Carrier erythrocyte-entrapped ADA has been employed with ADA deficiency.

23.3 Hypoxanthine phosphoribosyltransferase deficiency

An adult patient with HPRT deficienicy has been treated with bilateral direct stereotactic stimulation of the globus pallidum and self-injurious behavior has been extinguished.

23.10 Orotic aciduria – UMP synthase deficiency

Allopurinol has been used in orotic aciduria, and it has been found to increase activity of OPRT and ODC, and in some patients to reduce orotic acid excretion. In other patients it had no effect.

23.7 Adenylosuccinate lyase deficiency

D-Ribose has been employed in adenylosuccinate lyase deficiency.

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24 Disorders of Creatine Metabolism

Sylvia Stöckler-Ipsiroglu, Roberta Battini, Ton DeGrauw, Andreas Schulze

24.1 Introduction

Three inborn errors affecting creatine metabolism are known in humans: two disorders of creatine synthesis including arginine:glycine amidinotransferase (AGAT) deficiency (Item et al. 2001) and guanidinoacetate methyltransferase (GAMT) deficiency (Stoeckler et al. 1996b); and one disorder of cellular creatine transport, namely the X-linked creatine transporter (CRTR, *SLC6A8*) deficiency (Salomons et al. 2001). Cerebral creatine deficiency is the common biochemical feature, and therefore these disorders are also described as creatine deficiency syndromes (CDS) in the literature. So far, only four patients with AGAT deficiency and about 30 patients with GAMT and 100 patients with CRTR deficiency have been diagnosed. Therefore, studies in a sufficient number of patients are widely lacking and recommendations on treatment and follow-up remain preliminary. Principles of treatment and critical discussion of the experience obtained so far are given in this Introduction. In the tables, guidelines for the practical management of a patient are given that might allow comparison of data obtained from single patients and finally find out evidence for the most effective treatment strategies.

■ Clinical and Biochemical Phenotype

Common clinical denominators of CDS are mental retardation, speech impairment, and epilepsy (Stromberger et al. 2003). The most severe clinical phenotype occurs in GAMT deficiency, including intractable epilepsy and progressive extrapyramidal symptoms and signs.

Common biochemical denominators are cerebral creatine deficiency and, because of intracellular depletion of creatine, reduced production and low urinary excretion of creatinine. GAMT deficiency is additionally characterized by accumulation of guanidinoacetate (GAA), the immediate precursor of creatine and substrate to the deficient GAMT activity. In affected patients, concentrations of GAA are elevated in urine and plasma tenfold and even elevated 100-fold in cerebrospinal fluid (CSF; Stoeckler et al. 1997). GAA is neurotoxic (Hiramatsu 2003) and its accumulation may significantly contribute to the clinical phenotype. In AGAT deficiency, accumulation of nonconvertible sub-

strates (arginine and glycine) has not been found (Battini et al. 2002; Bianchi et al. 2000). In CRTR deficiency, creatine deficiency is only limited to tissues expressing the active CRTR-linked creatine transport (mainly brain), without additional primary biochemical abnormalities (Cecil et al. 2001).

Principles of Treatment

In general, treatment of CDS is based on the classic approach, including substitution of deficient creatine and reduction of accumulating small molecules by dietary means. In particular, treatment of CDS includes:

1. Oral substitution of deficient creatine in GAMT and AGAT deficiency
2. Dietary reduction of accumulating GAA in GAMT deficiency.

CRTR deficiency is not treatable by any of these classic approaches. Therefore alternative strategies need to be developed, such as: enhancement of passive creatine transport to the brain by substitution of extremely high doses of creatine or of modified molecules; and/or substitution of substances that might serve as substrates for intracerebral creatine synthesis.

Oral Substitution of Creatine in GAMT and AGAT Deficiency

In GAMT and AGAT deficiency, oral creatine substitution is effective in replenishing the cerebral creatine pool (Stoeckler et al. 1996a; Bianchi et al. 2000). However, despite administration of high doses, the replenishment takes months to complete. In GAMT deficiency, accumulation of GAA, which is a competitive inhibitor of active creatine transport (Ohtsuki et al. 2002), might contribute to the delayed creatine replenishment. A preliminary comparison of the slope of brain creatine replenishment by the same dose of creatine between GAMT- and AGAT-deficient patients has revealed a faster rise of brain creatine and a nearly complete replenishment in AGAT patients; whereas, in GAMT patients, replenishment takes more than 24 months to complete (Schulze 2004).

Creatine is substituted as creatine monohydrate. As a first estimate for the dosage, the 15- to 20-fold of the normal daily creatine requirement has been taken. In children aged from 4 to 12 years, this corresponds to 350–400 mg/kg per day. For other age groups, values are derived from the daily urinary creatinine excretion, which is equivalent to the daily creatine requirements (Borsook and Dubnoff 1947). Higher dosages up to 2000 mg/kg per day have been reported (Ganesan et al. 1997; Schulze et al. 1998). The maximum dosage given to an adult was 25 g/day, 4 days/week (Schulze et al. 2003).

In a single patient, it has been shown that doubling the 400 mg/kg per day dosage does not result in an increased velocity of replenishment of the cerebral creatine pool (Stoeckler et al. 1997). In most of the other patients, dosage and time-dependent increase in cerebral creatine stores has not been sufficiently documented. Therefore the optimal dosage of creatine monohydrate

for recovery and maintenance of the cerebral creatine pool has still to be determined.

It is also unclear in how many daily doses creatine monohydrate has to be administered. Constantly high blood creatine concentrations as achieved by frequent administration (8 times a day) of creatine monohydrate are certainly favorable with respect to passive transport of creatine across the blood-brain barrier (BBB; Stoeckler et al. 1997). Greater time intervals or pulsatile administration seem not to be more favorable to further enhance active transport of creatine though the BBB (Schulze 2004).

In GAMT patients, clinical response to oral creatine supplementation includes resolution of extrapyramidal sings and symptoms and improvement of epilepsy. However, none of the patients have achieved normal development. In particular, mental retardation, absent speech development, and autistic and self-aggressive behavior may constitute significant residual handicap.

In the three patients reported with AGAT deficiency, clinical response included significant improvement of abnormal developmental scores (Battini et al. 2002; Bianchi et al. 2000). Diagnosis and long-term observation of more patients will allow the description of the natural course and of the potential prevention of neurological sequelae in early-treated patients.

Reduction of Accumulating GAA in GAMT Deficiency

Within the group of CDS, GAMT deficiency plays a particular role, as the pathobiochemical background of the disease is determined not only by deficiency of creatine but also by accumulation of GAA. GAA levels are almost exclusively determined by AGAT activity and can be controlled by the following means (Walker 1979):

1. Repression of AGAT activity at a translational level via creatine substitution and thus enhancement of the creatine-dependent negative feedback
2. Reduction of AGAT activity by competitive inhibition via ornithine substitution (K_m = 300 mol/l)
3. Reduction of AGAT activity via restriction of the rate-limiting substrate (arginine)

Repression of (highly expressed) AGAT activity by exogenous creatine leads to a decrease but not to normalization of GAA concentrations in body fluids (Stoeckler et al.1997). Further reduction of GAA concentrations via additional substitution with high-dose ornithine fails (Stoeckler et al. 1997). In one GAMT patient with epileptic seizures refractory to oral creatine substitution, combined restriction of dietary arginine/protein and substitution of ornithine and creatine has resulted in a significant decrease in urinary and plasma GAA concentrations and in a significant improvement of epilepsy and electroencephalogram (EEG) findings (Schulze et al. 2001). Sodium benzoate is given in addition in order to reduce the nitrogen load in the urea cycle which due

to arginine restriction might function at a lower than normal capacity level (Schulze et al. 2003).

Taking into account the various neurotoxic effects of GAA (Hiramatsu 2003), therapeutic reduction of this compound will have an important role on the long-term outcome of GAMT patients.

Potential Treatment Strategies in CRTR Deficiency

Cellular creatine uptake is affected mainly by an active transporter-mediated, high-capacity process. In muscle tissue, an additional passive, low-capacity process has been demonstrated (Loike et al. 1988). Whether and to what extent passive transport is also effective across the BBB has not yet been elucidated. Patients with CRTR deficiency have a reduced or absent activity of the high-capacity creatine uptake. Therefore, unlike in patients with GAMT and AGAT deficiency, conventional oral creatine substitution does not result in an increase in brain creatine levels within an observation period of a few weeks in the index patient (Cecil et al. 2001). Since uptake studies in fibroblasts show creatine uptake at high concentrations of creatine in the culture medium, it was decided to treat several more patients (DeGrauw et al. 2003). Three male, hemizygous patients were treated with a maximal dose of 750 mg/kg per day of creatine monohydrate for 12–18 weeks without any clinical or spectroscopic improvement. However, a female heterozygous patient with learning disabilities and mildly decreased creatine concentration in brain magnetic resonance spectroscopy (MRS) showed mild improvement on neuropsychological testing after 18 weeks of treatment with creatine monohydrate (250–750 mg/kg per day; unpublished results). Other experimental treatment approaches have not been published so far.

Adverse Effects of Specific Treatments

In patients with GAMT deficiency, the longest observation period of creatine monohydrate substitution is 6–8 years and no obvious long-term side-effects have been reported. However, in one patient urinary excretion of creatine crystals has been observed upon short-term administration of extremely high dosages (1.5 g/kg per day) of creatine monohydrate (Schulze 2004). In individuals supplemented with creatine, intake of high doses (20 g/day in adults) has been associated with weight gain (due to intracellular edema), muscle cramps, and impairment of renal function (for review see Wyss and Schulze 2002). In one patient with MELAS and preexisting renal disease, further impairment of renal function has been observed upon oral creatine substitution (Barisic et al. 2002). Creatine monohydrate is freely available in drug stores, and attention has to be paid to the purity of the various products. In particular, after chemical synthesis from sarcosine and cyanamide, contamination with dicyanamide, which liberates HCN in the acidic conditions of the stomach, may

occur as a result of incomplete purification (for review see Wyss and Schulze 2002).

Arginine is essential for the functional maintenance of the urea cycle, and its dietary restriction in GAMT deficiency should be closely monitored by measurement of plasma amino acids and ammonia concentrations. As in other protein-restricted diets, deficiency of a single amino acid due to overtreatment might lead to atrophic skin and mucosa lesions, as well as to general impairment of growth and development. Determination of the individual protein tolerance and supplementation of essential amino acid mixtures might prevent the latter problems to a certain degree.

High ornithine levels are primary metabolic abnormalities in HHH (hyperammonemia, hyperornithinemia, homocitrullinuria) syndrome and in hyperornithinemia and gyrate atrophy syndrome. These disorders accompany various degrees of developmental retardation, myopathy, and retinopathy, respectively. High ornithine levels due to exogenous ornithine substitution have not been associated with obvious side-effects in GAMT patients, but there is still no long-term experience with this treatment.

24.2 Nomenclature

No.	Disorder	Definition/comment	Gene symbol	OMIM No.
24.1	Guanidinoacetate methyltransferase deficiency	Defect in creatine synthesis. Biochemical phenotype: deficiency of creatine and accumulation of GAA. Clinical phenotype: mental retardation, epilepsy, extra pyramidal symptoms and signs; most severe phenotype within the group of CDS. About 30 patients known	*GAMT*	601240
24.2	L-Arginine:glycine amidinotransferase deficiency	Defect in creatine synthesis. Biochemical phenotype: deficiency of creatine without accumulation of specific substrate. Clinical phenotype: mental retardation, epilepsy. Three patients reported in literature	*AGAT*	602360
24.3	X-linked creatine transporter deficiency	Defect in creatine transport. Biochemical phenotype: brain creatine deficiency and renal loss of creatine (high urinary creatine/creatinine ratio). Clinical phenotype: mental retardation, epilepsy. About 100 patients known	*CRTR*	300036

24.3 Treatment

■ *24.1. GAMT deficiency*

● *Overview*

No./symbol	Medication/diet	Dosage (mg/kg per day)	Doses per day
24.1 GAMT	Creatine monohydrate	400	3–6
	L-Ornithine hydrochloride		3–6
	Low dose	100[a]	
	High dose	800[a]	
	Sodium benzoate	100	3
	L-Arginine intake	15–25[b]	3–5 daily meals
	Essential amino acid mixture (arginine free)	0.2–0.7 g essential amino acids/kg	3–5 daily meals

[a] Aim of low-dose substitution is to provide sufficient amounts of ornithine to the urea cycle (target plasma ornithine concentration 100–200 µmol/l). Aim of high-dose substitution is to potentially inhibit competitively AGAT activity by high intracellular ornithine concentrations (K_m = 300 µmol/l)

[b] Corresponds to 0.4–0.7 g/kg natural protein. Essential amino acid mixture has to be substituted in order to meet age-dependent physiological amino acid/protein requirements

● *Instruction for Arginine-Restricted Diet*

Age	Minimal protein requirement (g/kg per day)[a]	Arginine intake by natural protein (mg/kg per day)	Corresponding intake of natural protein (g/kg per day)	Essential amino acid mixture	
				Type[b]	protein equivalent/day (g)[c]
0–3 months	2.7–1.6	15	0.4	1	2–5
4–12 months	1.4–1.1	15	0.4	1	2–5
1–2 years	1.0	15	0.4	2	10–25
2–3 years	1.0	15	0.4	2	10–25
4–6 years	0.9	15	0.4	2	10–25
7–9 years	0.9	15	0.4	2	10–25
10–12 years	0.9	15	0.4	2	25–45
13–15 years	0.9	15–25	0.4–0.7	2	25–45
> 15 years	0.8	25	0.7	2	30–75

[a] According to Dewey et al. (1996)

[b] Type 1: infantile formula; type 2: childhood formula

[c] Spread as evenly as possible through the 24 h

24.2 AGAT deficiency

No./symbol	Medication	Dosage (mg/kg per day)	Doses per day
24.2 AGAT	Creatine monohydrate	300–400[a]	3–6

[a] Due to absence of GAA accumulation and subsequent competitive inhibition of creatine uptake, lower dosages of creatine monohydrate might be sufficient for restoration of the cerebral creatine pool in AGAT deficiency

24.3 CRTR deficiency

So far, no treatment available.

24.4 Follow-up

24.1 GAMT deficiency

No./ symbol	Biochemical assessment	Frequency/method	Clinical assessment	Frequency/method
24.1 GAMT	Brain creatine levels	Quantitative single voxel proton MRS of brain (standardized voxles in white and/or gray matter) 0, 3, 6, 12 months after treatment and then at greater intervals	General status	Close monitoring of weight and skin/mucosa especially during arginine-/protein-restricted diet
			Neurological examination	Document movement disorder by video record
	GAA in urine/plasma	Quantitative methods For urine, preferably 24-h urine, give values as µmol/l, and as mmol/mol creatinine 0, 3, 6, 12 months after treatment, longer intervals later on	Developmental score	Use common tests in order to make multicenter data comparable
			Assessment of degree of mental retardation	Use ICD 10 definitions
	Plasma ammonia & amino acids/urinary amino acids, vitamins and micronutrients[a]	Plasma: use samples (e. g., 6 h) prior to intake of food and amino acids Weekly to twice a month until dietary intake is stabilized, longer intervals later on	EEG	Depends on severity of epilepsy and clinical response to treatment Check at least 0, 1, 3, 6, and 12 months after treatment
			Magnetic resonance imaging	Together with MRS

[a] Monitoring of these compounds is necessary on dietary arginine restriction and ornithine supplementation

24.2 AGAT deficiency

No./ symbol	Biochemical assessment	Frequency/method	Clinical assessment	Frequency/method
24.2 AGAT	Brain creatine levels	Quantitative single voxel proton MRS of brain (standardized voxles in white and/or gray matter) 0, 3, 6, 12 months after treatment and then in greater intervals	General status & neurological examination	Frequency according to clinical status
			Developmental score	Use common tests in order to make multicenter data comparable
			Assessment of degree of mental retardation	Use ICD 10 definitions
			EEG	Depends on pretreatment findings. Check at least prior to and once a year during treatment
			MRI	See MRS

24.3 CRTR deficiency

Because of a lack of treatment, no protocols for follow-up are established.

Experimental Follow-up Protocols

No./ symbol	Biochemical assessment	Indication	Method/frequency
24.1 GAMT	GAA and amino acids in CSF	In particular on arginine-restricted diet	Take first sample prior to arginine-restricted diet; take second sample when plasma GAA levels have fallen down to a low steady-state level
	Creatine in muscle	[a]	Phosphorus magnetic resonance spectroscopy; prior to and on oral creatine substitution
24.2 AGAT	Creatine in muscle	[a]	Phosphorus magnetic resonance spectroscopy; prior to and on oral creatine substitution
24.3 CRTR	Brain creatine levels	Upon different experimental treatment strategies: long-term substitution of high dosages of creatine monohydrate; substitution of arginine as a substrate for intracerebral creatine synthesis; modified creatine molecule transported via an alternative way across BBB	Quantitative single voxel proton MRS of brain (standardized voxels in white and/or gray matter). 0, 3, 6, 12 months after treatment and then in greater intervals
	Creatine in muscle	[a]	Phosphorus magnetic resonance spectroscopy; prior to and on oral creatine substitution

[a] Results on muscle creatine metabolism have been published for only one GAMT patient so far (Schulze et al. 2003), and have not been published for AGAT and CRTR patients. Clinically patients with CDS do not have signs of severe myopathy

- *General Protocol for Biochemical Evaluation of Effects of Oral Creatine Substitution*

Assessement	Aim	Method
Urinary creatine crystals	Measure for creatine overdose resulting in creatine precipitation within the urinary tract	Macroscopic and microscopic urine analysis
Renal function	Measure for monitoring potential adverse effects on kidney function	Plasma creatinine, urea, electrolytes
		Renal creatinine clearance[a] Chrome EDTA clearance Tubular function tests
24-h urinary creatinine excretion	Indirect measure for intracellular creatine levels and thus efficiency of creatine substitution	Use methods that do not cross-react with creatine (e. g., HPLC)
		Monthly until steady state, longer intervals later on

Protocol should be applied in any patient substituted with creatine in supraphysiological dosages in addition to the specific monitoring protocol. Apart from CDS, creatine monohydrate has been substituted (mainly on an experimental basis) in the following diseases/disease groups: mitochondrial disorders, myopathies, muscular dystrophies, neurodegenerative disorders, fatty acid oxidation disorders (LCHAD)and others (for review see Wyss and Schulze 2002)

[a] Plasma creatinine may increase as an effect of creatine substitution and subsequent augmentation of the body (muscle) creatine pool, and renal creatinine clearance my not specifically reflect renal function in this condition. Therefore, in patients on creatine substitution, chrome EDTA clearance is recommended for determination of renal glomerular function

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25 Peroxisomal Disorders

Hanna Mandel

25.1 Introduction

Peroxisomes are highly complex organelles, present in all mammalian cells except mature erythrocytes. They participate in a multitude of essential catabolic and biosynthetic functions, including β-oxidation of very long chain fatty acids (VLCFA), fatty acid α-oxidation, formation of plasmalogens, bile acids, polyunsaturated fatty acids (PUFA), cholesterol and leukotrienes, glyoxylate detoxification, and metabolism of H_2O_2 (Purdue and Lazarow 2001). The process whereby peroxisomal membranes are assembled and peroxisomal matrix proteins are targeted from the cytosol and then imported into the organelle is a highly complex mechanism dependent on a series of specialized proteins termed "peroxins," encoded by more than one *PEX* gene. Mutations in *PEX* genes are responsible for peroxiosmal biogenesis disorders (PBD), characterized by absence of morphologically identifiable peroxisomes and loss of multiple or generalized peroxisomal functions. Another category of peroxisomal disorders includes disorders with a single peroxisomal enzyme or protein defect, with intact peroxisomes and preservation of other peroxiosmal functions.

25.2 Nomenclature

No.	Disorder	Protein defect	Gene symbol	OMIM No.
25.1	Zellweger syndrome (ZS)	Peroxins	*PEX1, PEX2, PEX3, PEX5, PEX6, PEX12, PEX14, PEX26*	214100
25.2	Neonatal adrenoleukodystrophy (NALD)	PTS1 receptor or peroxin-1	*PXR1, PEX1, (PEX10, PEX13, PEX26)*	202370
25.3	Infantile Refsum disease (IRD)	Peroxins	*PEX1, PEX2*	266510
25.4	Hyperpipecolic acidemia (HPA)[a]	?	?	239400
25.5	Rhizomelic chondrodysplasia punctata (RCDP) type I	Peroxisomal biogenesis factor-7	*PEX7*	215100
25.6	(Rhizomelic) chondrodysplasia punctata (RCDP) type 2	Dihydroxyacetonephosphate (DHAP) acyltransferase	*GNPAT, DHAPAT*	222765
25.7	(Rhizomelic) chondrodysplasia punctata (RCDP) type 3	Alkyl-DHAP synthase	*AGPS*	600121
25.8	X-linked adrenoleukodystrophy	ATP-binding cassette, subfamily D, member 1	*ABCD1*	300100
25.9	Pseudo-NALD	Peroxisomal acyl-CoA oxidase 1	*ACOX1*	264470
25.10	D-Bifunctional enzyme deficiency	Peroxisomal bifunctional protein	*HSD17B4*	261515
25.11	Pseudo-Zellweger syndrome[b]			261515
25.12	α-Methylacyl-CoA racemase deficiency	α-Methylacyl-CoA racemase	*AMACR*	604489
25.13	Refsum disease (adult form)	Phytanoyl-CoA hydroxylase Peroxin 7	*PHYH, PAHX, PEX7*	266500

[a] This condition probably does not exist as a separate entity.

[b] Reclassified as D-bifunctional enzyme deficiency.

25.3 Treatment

Peroxisomal Biogenesis Disorders

The potential of treatment of individuals with peroxisomal biogenesis disorders (PBD) is restricted, involving mainly symptomatic and supportive therapy, steroid-replacement therapy to correct adrenal insufficiency, and supplementation of fat-soluble vitamins (Table 25.1). The treatment of isolated acyl-CoA oxidase deficiency and D-bifunctional protein deficiency is also mainly supportive. The treatment of 2-methylacyl-CoA racemase deficiency by dietary restriction of phytanic acid and supplementation with cholic acid may prevent progression of symptoms (see also Chap. 32). Efforts to induce hepatic peroxosomal proliferation by administration of clofibrate and other drugs have failed in Zellweger disease patients (McGuinness et al. 2000; Wei et al. 2000). The effectiveness of treatment is difficult to assess because of the small number of patients, the variability of the diseases, and the absence of a control patient-group. This chapter focuses mainly on the management of two isolated peroxisomal defects, X-linked adrenoleukodystrophy (X-ALD) and Refsum disease (Fig. 25.1).

Table 25.1. Experimental treatment of peroxisomal biogenesis disorders (PBD)

Defect/deficiency	Medication/diet	Dosage	References
Vitamin A deficiency	Vitamin A	2500 U/day, PO	
Vitamin D deficiency	1,25-Dihydroxycholecalciferol	0.25–1 µg/day, PO	
Vitamin E deficiency	Alpha-tocopherol acetate	50 mg, PO	
Vitamin K (phytomenadione) deficiency	Vitamin K (phytomenadione)	1 mg/day, IM or IV	
Docosahexaenoic acid (DHA) deficiency	Docosahexaenoic acid (DHA, C22:6ω3)	100–500 mg/day, PO	Martinez 1996; Martinez and Vaquez 1998
Accumulation of bile acids intermediates	Cholic and/or chenodeoxycholic Ursodecholic acids	100 mg or 5 mg/kg/day, PO	Setchell et al. 1992; Maeda et al. 2002
Plasmalogen deficiency	Ether lipid (a mix of batyl alcohol)	10 mg/kg, PO	Holmes et al. 1987
Adrenal insufficiency	Steroid replacement therapy		

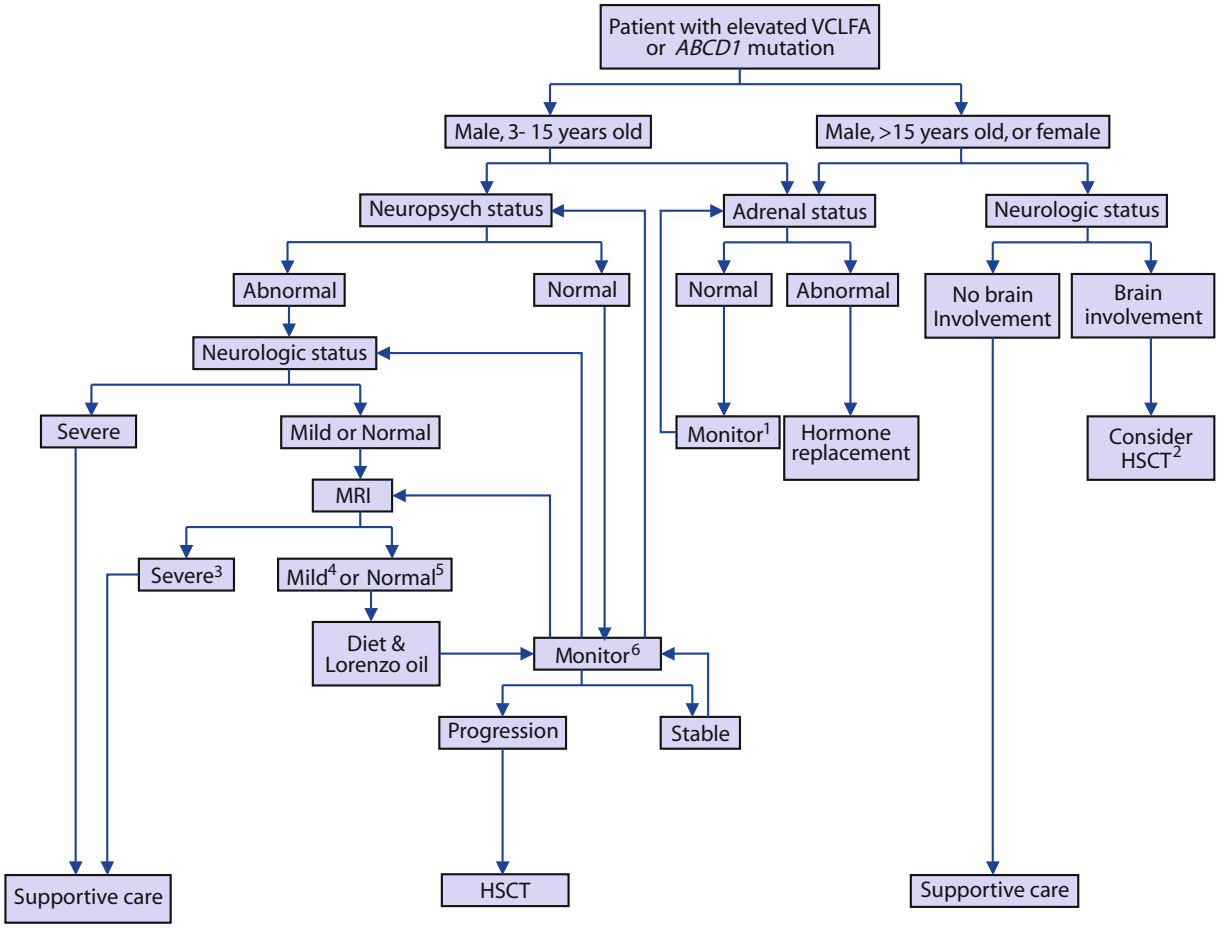

Fig. 25.1. Treatment and follow-up monitoring of X-linked adrenoleukodystrophy (X-ALD). (*ACTH* Adrenocorticotrophic hormone, *HSCT* hematopoietic stem cell transplantation, *VLCFA* very longchain fatty acids) 1, annual ACTH stimulation testing; 2, considered experimental at this time; 3, Loes score > 10; 4, Loes score 5–10; 5, Loes score < 5; 6, neuropsychological testing, neurological examination, and MRI every 6 months, increasing to every 2–3 months with the new appearance of subtle evidence of neurodegeneration

25.8 X-linked adrenoleukodystrophy

X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal disorder due to mutations in the *ABCD1* gene that encodes a peroxisomal ATP-binding cassette protein. Phenotypes vary in severity from the rapidly dementing and fatal childhood-onset cerebral form, through the insidious adult-onset form adrenomyeloneuropathy (AMN), adolescent- and adult-onset cerebral X-ALD, to the pure addisonian presentations without obvious central nervous system (CNS) involvement. Approximately 40% of boys with X-ALD will develop childhood cerebral disease, usually between 4 and 12 years; and 40–45% of hemizygotes are

likely to develop AMN during the 3rd or 4th decades, with or without cerebral involvement. Note, there is no genotype-phenotype correlation even among members of the same kindred, and it is not possible to predict the future course in young asymptomatic boys on the basis of mutation analysis, the concentrations of VLCFA in plasma or cultured skin fibroblasts, or the phenotype in affected family members.

The adrenal insufficiency in X-ALD is correctable by steroid replacement therapy, but this does not alter the progression of the neurological disease. Hematopoietic cell transplantation (HCT) is considered the only effective long-term treatment of cerebral X-ALD in boys and adolescents if performed at an early stage of inflammatory cerebral myelinopathy (Shapiro et al. 2000; Baumann et al. 2003; Peters et al. 2004).

In patients who have developed progressive neurological disease, the ALD-Disability Rating Scale (ALD-DRS) identifies requirements for services; levels range from 0 to IV with increasing disability (Table 25.2).

Table 25.2. X-linked adrenoleukodystrophy-disability rating scale

Level	Disability
0	No difficulties
I	Mild learning or coordination difficulties no requiring support or intervention
II	Moderate learning, sensory, and/or neurological abnormalities requiring support or intervention in a few areas
III	Severe learning, sensory, and/or neurological abnormalities requiring support or intervention in many areas
IV	Loss of cognitive ability and disorientation; patients require constant supervision

- *Boys Less Than15 Years Old with X-ALD*

The treatment of X-ALD by dietary fat restriction and administration of Lorenzo oil (LO) is controversial. LO is a 4:1 mixture of glyceryl-trioleate (GTO) and glyceryl trierucate (GTE). The results of a recent multicenter clinical study show a positive association between the degree of lowering of C26:0 levels and clinical outcome in asymptomatic boys 2–10 years of age (Moser et al. 2003, 2004). Lowering the mean annual C26:0 level by 0.2 µg/ml reduces the risk of neurological involvement (either clinical or magnetic resonance imaging, MRI) by 50%; lowering by 0.4 µg reduces the risk by 75%; and, by 0.6 µg/ml, by 90%. The diet and LO should be prescribed and monitored by a multidisciplinary team, including a clinical nutritionist and a metabolic specialist. LO is taken orally in a dosage that provides approximately 20% of caloric intake. Intake of other dietary fats, including supplemental essential fatty acids, should be reduced to 10–15% of total calories. Taking the oil without substantial lowering of C26:0 level, or dietary fat restriction without supplemental LO, is of no benefit.

Monitoring is essential to prevent complications such as reduction of platelet count and the rare and moderate disturbances of liver function. Adrenal function must be monitored and deficiency treated by steroid replacement therapy. It is also essential to monitor plasma levels of polyunsaturated VLCFA such as docosahexaenoic acid (DHA) and arachidonic acid. It is essential that patients be monitored (Fig. 25.1), to identify those for whom hematopoietic stem cell transplantation (HSCT) is indicated by current criteria. It is unclear how long LO therapy should be continued in patients who remain neurologically uninvolved.

Clearly, additional therapies are needed for all forms of X-ALD. Several new approaches such as new immunosuppressive agents for the rapidly progressive cerebral forms of X-ALD, phenylbutyrate, arginine butyrate, lovastatin, neuroprotective or neurotrophic agents, coenzyme Q, stem cell and gene therapy are under investigation in several laboratories, but require further study.

Boys less than 15 years of age, diagnosed with X-ALD because of positive family history, yet still symptom-free, should be monitored serially for the earliest evidence of demyelination (see Fig. 25.1). Monitoring should include T2-weighted gadolinium-enhanced brain MRI, MRI spectroscopy, neurological examination, neuropsychological evaluation, and evoked potentials. Brain MRIs should be evaluated by a neuroradiologist experienced with X-ALD, using a scale ranging from 0 to 34 devised by Loes et al. (Loes et al. 2003) specifically for X-ALD. It has been shown to correlate with severity of neurological deficits and to be predictive of disease progression. Different brain regions are considered in the MRI severity score. Each of several areas in the brain is scored as 0 if normal, 0.5 if unilaterally abnormal, and 1 if the lesion or atrophy is bilateral. The maximum severity score is 34. If the MRI is abnormal, without clinical deficits, repeat MRI in 3 months is indicated in order to assess the trend (see Follow-up and Monitoring).

At the first indication of progressive neurodegeneration, patients under 15 years of age should be considered candidates for HSCT. HSCT is not recommended in patients with a Loes score of more than 10, severe neurological involvement, or marked neuropsychological decline and dysfunction (Fig. 25.1).Candidates with the greatest benefit are patients with a Loes score of less than 5, with no or only mild impairment on neuropsychological resting and absent neurological symptoms However, even an MRI Loes severity score as low as 2–3 and/or gadolinum enhancements in a X-ALD boy less than 15 years of age is highly predictive of subsequent progressive cerebral demyelination. It is strongly suggested that such boys undergo HSCT as soon as possible. Boys with advanced cerebral X-ALD and the associated neurological deficits and neuropsychological dysfunction (especially Performance IQ < 80) are poor candidates for HSCT. In the group of patients with Loes scores between 5 and 10, the prognosis is uncertain. Patients who have not developed neuropsychological or neurological symptoms seem to have a more favorable prognosis. The outcome after HSCT can usually be determined within the first year after

the procedure. Longer follow-up of X-ALD patients who have undergone HSCT is needed to confirm that it may halt or prevent AMN, because the onset of spinal-cord signs may be delayed until the 4th or 5th decade.

Men with Adrenomyeloneuropathy

Neurological progression in most patients with AMN is slow, and general support and vocational counseling is often helpful (Fig. 25.1). The early identification and treatment of adrenal insufficiency is imperative. Treatment of adrenal insufficiency is by hormone replacement, using dosages of hydrocortisone similar to those used in the treatment of any adult with adrenal insufficiency, irrespective of the cause.

Treatment of men with AMN by dietary fat restriction and LO may slow the progression of the disease in patients without brain involvement. Dietary fat restiction alone, or the use of LO without control of plasma C26:0 levels, appears to be without value. However, since the treatment regimen involves a considerable change of lifestyle for adults and the benefit has not yet been clearly established, it is not recommended at present for men with AMN. Treatment of AMN by HSCT when the disease is confined to the spinal cord has not been shown to alter the natural history of the disease, and the risks of the procedure are considerable. It is not recommended for the treatment of patients with this variant of the disease. On the other hand, HSCT has been considered for treatment of patients with AMN showing evidence of rapidly progressive inflammatory brain involvement.

Follow-up and supportive care include management of adrenal insufficiency, physiotherapy, urological consultation for impaired bladder control, prevention and treatment of urinary infection, avoidance of constipation, psychological counseling. Oral baclofan, dantrolene, or tizanidine may aid management of spasticity and quality of life. Behavioral disturbances, frequent in the AMN-cerebral form, require psychiatric consultation.

Heterozygous Women with AMN-Like Syndrome

AMN in women generally begins later and is somewhat milder than the disease in men. No specific therapy is available at this time. Adrenal insufficiency occurs in less than 1%. Medications such as gabapentin may aid the neuropathic leg pain that is a frequent feature in symptomatic heterozygotes. At this time, the benefit of dietary therapy is not sufficient to warrant undertaking the major inconvenience and changes in diet it requires.

Refsum Disease

Excessive accumulation of phytanic acid in plasma lipids, fatty tissues, myelin sheaths, retina, heart, liver, and kidneys is the hallmark of Refsum disease.

The retinitis pigmentosa, cerebellar ataxia, polyneuropathy, ichthiosis, cardiac arrhythmias, and kidney malfunction are directly related to the plasma level of phytanic acid (Wanders et al. 2001). Phytanic acid is derived solely from the diet, and the mainstay of management is a drastic restriction of dietary of the compound. Current knowledge on the content of phytanic acid level in different lipids is limited, and the phytanic acid concentrations in similar food items may differ in different countries. Thus, it is difficult to give precise dietary rules. Ideally, the goal is to maintain phytanic acid intake below 10 mg/day. Information on dietary management is available in several publications (for review see 10). Therapeutic dieatry phytanic acid restriction involves some risk of malnutrition and should only be undertaken with the active involvement of a dietitian. Despite strict adherence to an apparently appropriate therapeutic diet, there may be a time lag before serum levels of phytanic acid start to fall, owing probably to release from adipose stores. Patients who respond with a fall in plasma phytanic acid levels may exhibit an arrest in the progression of the peripheral neuropathy, improved muscle strength, regression of ichthyosis, and correction of electrocardiographic aberrations. The visual and hearing impairments are less responsive to treatment (Wills et al. 2001). Rapid weight loss due to rigorous low-phytanic diets, pregnancy, surgery, or intercurrent infections might cause precipitate mobilization of phytanic acid from hepatic lipid and body adipose stores, resulting in severe clinical relapse or "Refsum disease crisis," which may cause sudden death.

Plasmapheresis has been used in conjunction with diet to lower plasma phytanic acid levels in acutely ill patients with phytanic acid storage disease. The decision to initiate plasmapheresis should be a clinical one. In general, a patient with rapidly worsening symptoms may be considered for therapeutic plasma exchange. Periodic plasmapheresis can be useful as a supplementation to the dietary treatment. Several groups have reported successful lowering of plasma phytanic acid levels using various schedules of plasmaphereses (Weinstein 1999).

A low phytanic acid diet, with adequate caloric intake to maintain or increase weight, along with plasma exchange procedures averaging 1–1.25 volume of plasma removed twice weekly, may be effective in removing several grams of phytanic acid from the body. The return fluid should be plasma-free colloid, such as 5% human serum albumin, and 0.9% NaCl. The treatment should be guided by the patient's plasma phytanic acid level and the extent to which exacerbations of disease are prevented.

About 65% of plasma phytanic acid and also pristanic acid are localized within VLDL, LDL, and HDL lipoprotein particles. Thus, LDL- and VLDL-bound phytanic and pristanic acids can be effectively eliminated from plasma using extracorporal LDL-apheresis using membrane differential filtration (MDF) (Straube et al. 2003). In contrast to plasma exchange where plasma with essential immunoglobulins and coagulation factors is discarded, selective MDF can be performed long term with high frequency and good tolerability

in medical centers with expertise in this technology. Dialysis is ineffective for lowering phytanic acid levels, because the compound in plasma is bound to lipoproteins.

25.4 Follow-up and Monitoring

25.8 X-linked adrenoleukodystrophy

In presymptomatic boys with X-ALD, under 15 years of age, clinical, neurological, neuropsychological, and neuroradiological assessment should be performed every 6 months from 3 until 10 years of age and yearly thereafter (Fig. 25.1). Endocrinological evaluation should include assessment of adrenal function by ACTH stimulation testing. Neurological function should be evaluated by an experienced pediatric neurologist by assessing vision, hearing, speech, gait, fine motor skills, and the patient's daily activities. A detailed neurological score, adapted from Baumann et al. (2003), is shown in Table 25.3. Neuropsychological assessment is valuable in the early detection of patients with risk of progressive cerebral involvement. Neuropsychological function may be assessed by use of the Wechsler Intelligence Scale for Children, third edition (WISC-III), or the Wechsler Preschool and Primary Scale of Intelligence.

Newly recognized brain lesions must be interpreted in the context of other evidence of progressive disease, including expanding lesions on follow-up MRI, typical gadolinium enhancement, characteristic changes in MR spectra, progressive neuropsychological impairment, or new neurological symptoms. HSCT is recommended for patients whose cognitive abilities exceed a verbal or performance IQ of 80 (Shapiro et al. 2000). If MRI abnormalities increase over a 3- to 6-month period, HSCT should be considered even in the absence of neurological or neuropsychological deficits. Boys without evidence of abnormality on brain MRI should be monitored closely for signs of progression of the disease before HCT is undertaken.

Patients with AMN should be monitored for adrenal insufficiency and steroid replacement therapy should be initiated as necessary. This is effective, but often neglected, and several patients have died in adrenal crisis. Performance of brain MRI is recommended yearly or every other year to identify early the 20–30% of AMN patients who also develop inflammatory brain involvement and who may be candidates for HSCT.

Table 25.3. Neurological score (Baumann et al. 2003)

Neurological signs		Score
Motor signs	Mild motor signs: hyperreflexia, fine motor difficulties, mild dystonia, running difficulties, mild cerebellar symptoms, nystagmus or others	1
	or walking difficulties (spasticity and/or cerebellar symptoms), no assistance necessary	2
	or walking difficulties, assistance required	3
	or wheelchair required	4
	or no voluntary movements	5
Hearing or auditory processing problems	Mild hearing impairment	1
	or severe hearing/auditory processing problems	2
	or deafness	3
Visual problems	Mild visual impairment, decreased visual acuity, field cuts, reading problems or others	1
	or severe visual problems	2
	or cortical blindness	3
Speech problems	Mild dysphasia, dysarthria	1
	or severe dysphasia, dysarthria	2
	or loss of speech	3
Swallowing problems	Dysphagia	1
	or tube feeding	2
Incontinence	Episodic incontinence	1
	or total incontinence	2
Seizures	Non-febrile seizures (more than one)	1
	Maximum	19

■ Refsum Disease

The monitoring and follow-up of the treatment of Refsum disease requires a close collaborative relationship between a metabolic specialist familiar with the natural history of the disease and the clinical signs of malnutrition, a neurologist, and a dietitian. Clinical assessment, including careful neurological examination, should be done every 3 months for the 1st year, then semiannually. Monitoring of plasma phytanic acid levels and appropriate modifications of the diet should be done monthly for the 1st year, then every 3 months.

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26 Hyperoxaluria

Bernd Hoppe, Ernst Leumann

26.1 Introduction

The autosomal-recessive inherited *primary* hyperoxalurias (PH) types 1 and 2 are defects of glyoxylate metabolism leading to endogenous (primary) overproduction of oxalic acid. Further types of PH are likely to exist (atypical PH). Urinary excretion of oxalate is strongly elevated (> 1 mmol/1.73 m^2 BSA/day, normal < 0.5), resulting in recurrent stone formation and/or nephrocalcinosis and in progressive kidney damage with systemic calcium oxalate deposition (systemic oxalosis). Plasma oxalate and plasma calcium oxalate saturation (β_{PCaOx}) correlate inversely with the glomerular filtration rate (GFR). Calcium oxalate (CaOx) supersaturation leads to systemic CaOx crystal deposition. The clinical spectrum of PH 1 is extremely large, ranging from severe renal failure in infants (infantile oxalosis) to first symptoms at the age of 50 years.

Systemic oxalosis is a catastrophic situation that must be prevented by all means. Yet, diagnosis of PH is all to often missed or delayed until endstage renal failure (ESRF) occurs (in up to one-third of adult patients). This is particularly unfortunate, because progressive renal damage can be delayed or even prevented by early intervention.

The management greatly depends on the degree of renal function. One-third of patients with PH 1 respond to pharmacological doses of pyridoxine. In the case of renal failure, the waiting time until renal transplantation has to be kept as short as possible, as no form of dialysis is able to keep pace with the extreme amounts of endogenous oxalate production. Thus, systemic oxalosis develops, which greatly reduces the success of transplantation. Isolated kidney transplantation in PH 1 is only a reasonable option in fully pyridoxine responsive patients or, perhaps, in patients older than 50 years. The transplantation treatment of choice in all other patients with PH 1 (except in infantile oxalosis) is combined liver-kidney transplantation. Preemptive liver transplantation as enzyme replacement therapy may be considered in patients with stable residual kidney function (GFR 50–70% of normal). PH 2 is rarer than PH 1 and its clinical course is less severe.

Distinction between PH and *secondary* hyperoxaluria may be difficult. The latter is due either to excessive dietary oxalate intake (dietary hyperoxaluria, SDHyOx) or to increased intestinal oxalate absorption (enteric, SEHyOx). Patients

with intestinal disease have an increased risk of hyperoxaluria, particularly after bowel resection (short-bowel syndrome), after bypass surgery, in chronic inflammatory bowel disease or cystic fibrosis, and in other malabsorption syndromes. Although the urinary oxalate excretion is usually < 1 mmol/1.73 m^2 BSA/24 h, it may nevertheless lead to significant morbidity, i. e., to recurrent urolithiasis or progressive nephrocalcinosis with renal failure. Therapy is primarily directed toward the underlying disease, but additional measures are very important.

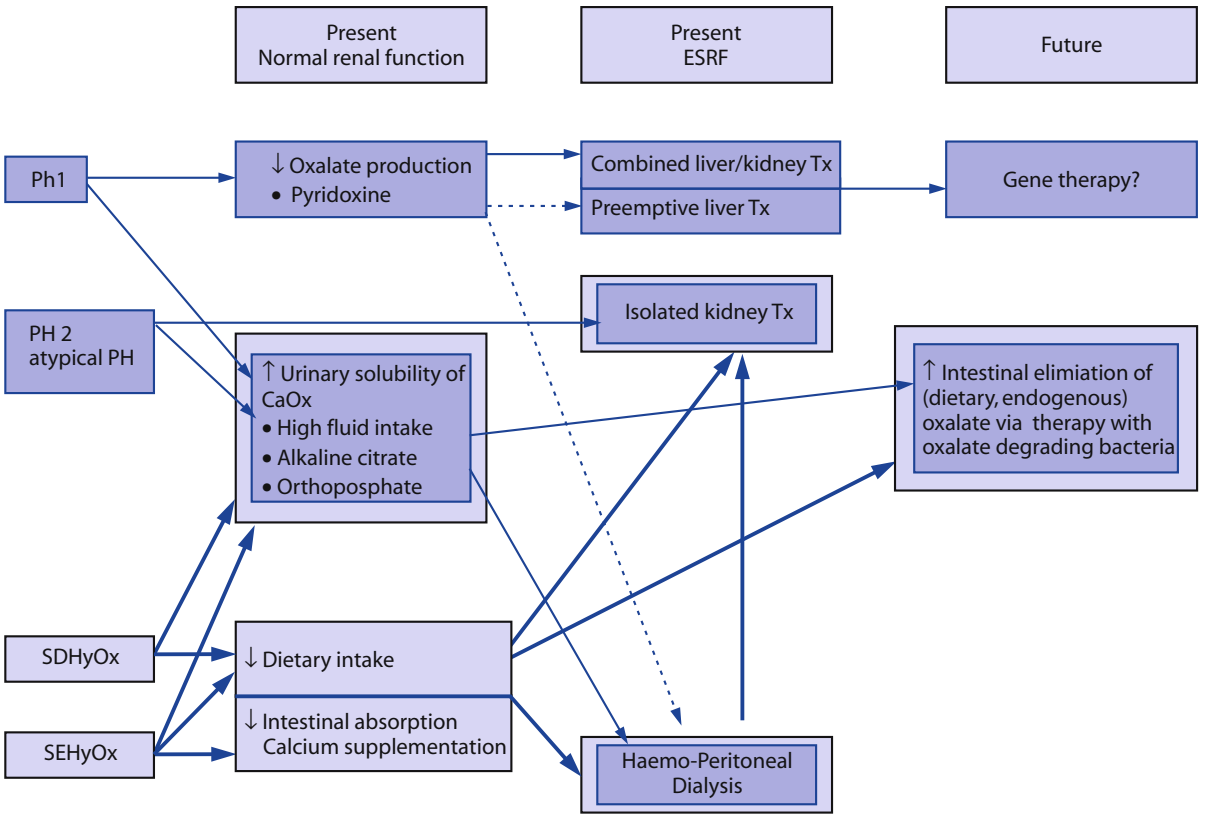

Fig. 26.1. Management of hyperoxalurias

26.2 Nomenclature

No.	Disorder (symbol)	Definitions/comment	Gene symbol	OMIM No.
26	Primary hyperoxaluria (PH)			
26.1	Alanine:glyoxylate aminotransferase (AGT) deficiency (absent, reduced, or mistargeted)	Primary, endogenous overproduction of oxalate (and glycolate), PH type 1, recurrent urolithiasis, nephrocalcinosis, early kidney failure	*PH 1* *AGXT*	259900 604285
26.2	Glyoxylate reductase (GR) deficiency	Primary, endogenous overproduction of oxalate (and L-glyceric acid), PH type 2, milder course of disease compared with PH type 1	*PH 2* *GRHPR*	260000 604296
26.3	Other (atypical PH; no PH-specific enzyme defect detectable)	Unclassified form of primary hyperoxaluria, clinical course and urinary values comparable to PH types 1 and 2		
26.4	Secondary hyperoxaluria			
26.4.1	Dietary hyperoxaluria (SDHyOx, normalized on diet)	Increased dietary intake and absorption of oxalate, microhematuria, (reccurent) urolithiasis, nephrocalcinosis		
26.4.2	Enteric, absorptive hyperoxaluria (SEHyOx)	Increased intestinal absorption of oxalate, often found in malabsorption syndromes, e. g., cystic fibrosis, inflammatory bowel diseases, or after bowel resection, and in absence of intestinal oxalate degrading bacteria such as *Oxalobacter formigenes*		

26.3 Treatment

26.1 AGT deficiency (PH 1)

Trial with *pyridoxine* (vitamin B_6), starting with 5 mg/kg body weight per day, increasing monthly by 5 mg until 20 mg/kg body weight per day. Reliable and repeated baseline values for U_{Ox} are essential. If reduction of U_{Ox} is > 30%, continue with lower dose (5–10 mg/kg per day). If no effect after 6 months, discontinue pyridoxine. Be aware of side-effects (e. g., neuropathy).

Additional measures depending on *clinical subgroup:*

	Clinical category	GFR (% of normal)	P_{Ox} (µmol/l)	Measures
A	Stone former/nephrocalcinosis	> 80%	< 10	Large fluid intake (> 2.5 l/m² BSA/day) plus Alkali (Na/K) citrate 0.3–0.5 mEq (0.1–0.15 mg)/kg body weight per day or Orthophosphate 20–60 mg/kg body weight per day
B	Asymptomatic (no stones, no nephrocalcinosis); U_{ox} < 0.7 mmol/1.73 m² BSA/d on B_6	> 80%	< 10	Large fluid intake (> 2.5 l/m² BSA per day)
C	Reduced renal function: adults	30–80%	> 30	Same as A Medication: reduced dosage may be required
D	Reduced renal function: age 3–18 years	30–80%	> 30	Same as C (Preemptive liver transplantation may be considered – experimental)
E	Renal failure: age 3–50 years	< 30%, ESRF	> 80	Combined liver/kidney transplantation
F	Renal failure: adult, age > 50 years	< 30%, ESRF	> 80	(Isolated kidney transplantation may be an option)
G	Renal failure: adult, *fully* pyridoxine responsive	< 30%, ESRF	< 80	(Isolated kidney transplantation may be considered)
H	Infantile oxalosis	< 30%, ESRF	> 80	Combined transplantation still experimental. No dialysis if transplantation is not considered

26.2 Glyoxylate reductase deficiency (PH 2)

No effect of pyridoxine is to be expected
Benefit of liver transplantation in renal failure has not been established
Other measures as for PH 1

26.3 Atypical PH (enzyme defect not yet defined)

Trial by pyridoxine may be made
Other measures as for PH 1

■ *26.4 Secondary hyperoxaluria*

No.	Symbol	Medication/diet	Dosage
26.4.1	SDHyOx	Diet	Low-oxalate, high-calcium diet[a]
		Fluid intake	> 2 l/m^2 BSA per day
		(calcium supplementation)	250–500 mg/m^2 BSA per day
		(Alkali citrate)	0.3–0.5 mEq (0.1–0.15 mg)/kg body weight per day
26.4.2	SEHyOx	Fluid intake	> 2 l/m^2 BSA per day
		Diet	Low-oxalate, high-calcium diet[a],
		(calcium supplementation)	250–500 mg/m^2 BSA per day
		Alkali citrate	0.3–0.5 mEq (0.1–0.15 mg)/kg body weight per day

[a] Diet: Avoid oxalate-rich food, i. e., spinach, rhubarb, beetroot, cacao, chocolate

Dangers/Pitfalls

1. Urinary oxalate excretion and oxalate/creatinine ratios are falsely low in renal insufficiency because of oxalate retention.
2. Ascorbic acid is a precursor of oxalate and may interfere with oxalate determination.
3. Poor compliance is a serious problem in patients with hyperoxaluria who require long-term therapy.
4. Calcium restriction is contraindicated because it leads to enhanced intestinal oxalate absorption.
5. Renal replacement therapy by (hemo-, peritoneal-) dialysis should be avoided by all means or, at least, not be extended beyond 6 months in patients with primary hyperoxaluria. No form of dialysis is able to eliminate all oxalate generated, thus ongoing systemic deposition of calcium oxalate is inevitable.

26.4 Alternative Therapies/Experimental Trials

No.	Symbol	Medication/diet	Dosage
26.1	PH 1	Oxalate degrading bacteria such as *Oxalobacter formigenes, lactic acid* bacteria, *Eubacterium lentum*, or *Enterococcus faecium*. Hepatocyte transplantation (experimental)	To be determined (studies ongoing)
26.2	PH 2	Oxalate degrading bacteria such as *Oxalobacter formigenes, lactic acid* bacteria, *Eubacterium lentum*, or *Enterococcus faecium*	
26.3	PH ?	Oxalate degrading bacteria such as *Oxalobacter formigenes, lactic acid* bacteria, *Eubacterium lentum*, or *Enterococcus faecium*	
26.4.1	SDHyOx		
26.4.2	SEHyOx	Oxalate degrading bacteria such as *Oxalobacter formigenes, lactic acid* bacteria, *Eubacterium lentum*, or *Enterococcus faecium*	

26.5 Follow-up/Monitoring

26 Primary hyperoxalurias

Age (years)	Clinical monitoring[a]	Biochemical monitoring Basic[b]	U_{Ox}, $U_{citrate}$	P_{Ox}	Renal ultrasonography
< 1	Monthly	Monthly	Monthly	3 monthly	3 monthly
1–10	3–6 monthly	3–6 monthly	6 monthly	Yearly	Yearly
11–18	4–6 monthly	4–6 monthly	6 monthly	2 yearly	2 yearly
> 18	6 monthly	6 monthly	Yearly	2 yearly	2 yearly

[a] Fluid intake, stone passage, general health, growth. More frequent monitoring is required when renal function is reduced

[b] Renal function (serum creatinine), electrolytes, blood gases. Urine: Ca, creatinine; relative density; sediment

Standard Protocol for Intercurrent Illness

Make sure the patient gets a high-fluid intake at all times. Early intravenous fluid administration is indicated in cases of severe diarrhea, vomiting, infection, and high fever. A medical emergency card with appropriate instructions is recommended for patients going abroad.

26.4 Secondary hyperoxalurias

Monitoring depends primarily on the underlying pathology. Dietary hyperoxaluria can easily be treated and cured if the dietary advice (diet low in oxalate, high in calcium) is followed. Such patients thus need no specific long-term intervention if they remain symptom free. All other patients should regularly be monitored.

Age	Clinical monitoring[a]	Biochemical monitoring[b]	Renal ultrasonography
0–12 months	3 monthly	2–3 monthly	6 monthly
1–16 years	6 monthly	6 monthly	6–12 monthly
> 16 years	6–12 monthly	6–12 monthly	Yearly

[a] Fluid intake, stone passage, general health

[b] Renal function (serum creatinine). Urine: oxalate, calcium, citrate, creatinine, relative density, sediment. Plasma oxalate optional

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27 Mitochondrial Energy Metabolism

Carolien Boelen, Jan Smeitink

27.1 Introduction

Although the term "mitochondrial disorder" is very broad, it usually refers to diseases that are caused by disturbances in the mitochondrial oxidative phosphorylation (OXPHOS) system – the final biochemical pathway involved in the production of the principal fuel of the living cell: adenosine triphosphate (ATP). One of the most important substrates for cellular energy production is pyruvate, mainly produced from glucose. Deficiencies in this method of cellular energy production are established in the pyruvate oxidation pathway, including the pyruvate dehydrogenase complex (PDH, disorders 27.1–27.7; see Table 27.1), the citric acid cycle (disorders 27.8–27.12), and the OXPHOS system, composed of the respiratory chain multiprotein enzyme complexes I–V and the two electron carriers coenzyme Q (CoQ) and cytochrome *c* (disorders 27.13–27.17). Furthermore, it has become increasingly clear that several transporting- and protein import systems are necessary for intracellular homeostasis and intergenomic communication (disorders 27.19–27.22).

27.2 Nomenclature

Table 27.1. Nomenclature

No.	Deficiency	Alternative name/comment	Symbol[a]
Pyruvate dehydrogenase complex			
27.1	$E_{1\alpha}$ component of pyruvate DH complex	Pyruvate dehydrogenase complex alpha 1/alpha 2; lipoamide-alpha 1/-alpha 2 (Xp22.1/4q22-q23)	*PDHA1/PDHA2*
27.2	$E_{1\beta}$ component of pyruvate DH complex	Pyruvate dehydrogenase complex beta; lipoamide-beta (3p21.1-p14.2)	*PDHB*
27.3	E_2 component of pyruvate DH complex	Dihydrolipoyl transacetylase; dihydro-lipoamide *S*-acetyltransferase (11q23.1)	*DLAT*
27.4	E_3 component of pyruvate DH complex	Dehydrolipoamide dehydrogenase (7q31-q32)	*DLD*
27.5	E_3-binding protein	Pyruvate dehydrogenase complex, component X (11p13)	*PDHX1*
27.6	Pyruvate DH complex, unspecified		
27.7	Pyruvate DH kinase	Isoenzyme 1, 2, 3, 4	*PDK1/PDK2/ PDK3/PDK4*
Citric acid cycle			
27.8	Aconitase[b]	Aconitase 2, mitochondrial	*ACO2*
27.9	E_3 component of 2-oxoglutarate complex	(7q31-q32)	*DLD*
27.10	2-Oxoglutarate complex, unspecified	α-Ketoglutarate DH complex	*OGDH*
27.11	Succinate dehydrogenase	Complex II	*SDH*
27.12	Fumarase	Fumarate hydratase (1q42.1)	*FH*
OXPHOS system			
27.13	Complex I	NADH dehydrogenase/46 subunits	*NDUF/MTND*
27.11	Complex II	Succinate dehydrogenase/4 subunits	*SDH*
27.14	Coenzyme Q	Ubiquinone	
27.15	Complex III	Cytochrome bc_1 complex/11 subunits	
27.16	Complex IV	Cytochrome *c* oxidase/13 subunits	*COX/MTCO*
27.17	Complex V	ATP synthase/$\sim$ 16 subunits	*ATP5/ATPase*
27.18	Combined defects		
Transporting systems			
27.19	ATP/ADP translocator	Adenine nucleotide translocator	*ANT*
27.20	Malate/aspartate shuttle		
27.21	Protein import		
27.22	Voltage-dependent anion channel		*VDAC*

[a] Approved gene symbols according to the Human Genome Organisation (HUGO) http://www.gene.ucl.ac.uk/cgi-bin/nomenclature/searchgenes.pl
[b] In association with a succinate dehydrogenase deficiency
DH dehydrogenase, *NADH* nicotinamide adenine dinucleotide (reduced form)

27.3 Treatment

General Measurements in Mitochondrial Disorders (DiMauro et al. 2000; Gillis and Kaye 2002; Clay et al. 2001)

27.1–27.7 Pyruvate dehydrogenase complex
27.8–27.12 Citric acid cycle
27.11, 27.13–27.18 OXPHOS system
27.19–27.22 Transporting systems

Despite great progress in the understanding of the metabolic and genetic bases of mitochondrial disorders in the last decade, various therapeutic approaches have had limited success over the years. The clinical management of patients with mitochondrial disease depends on the clinical phenotype, the biochemical and morphological results in muscle and/or fibroblasts, and mutational analysis. There are clear differences in clinical management of young children with encephalomyopathies or multiorgan failure, and older children that often have a more chronic disease course similar to adult patients. Mitochondrial DNA (mtDNA) mutations are uncommon in affected children, whereas most of the adults have pathogenic mtDNA mutations (Smeitink et al. 2001; DiMauro and Schon 2003).
The various treatment strategies can be divided into different categories (DiMauro et al. 2000; Gillis and Kaye 2002):

1. Supportive care
2. Removal of noxious metabolites, i. e., dichloroacetate
3. Administration of artificial electron acceptors, i. e., menadione (vitamin K_3), ascorbate (vitamin C), and ubiquinone (coenzyme Q_{10})
4. Administration metabolites and cofactors, i. e., riboflavin (vitamin B_2), ubiquinone, carnitine, and creatine
5. Administration of oxygen radical scavengers, i. e., tocopherol (vitamin E), ubiquinone, idebenone, selenium, copper, and glutathione peroxidase
6. Dietary interventions
7. Gene therapy

Drugs and Measurements Known to Interfere with Normal Mitochondrial Function

Supportive care is given to any patient suffering a mitochondrial disorder, independent of the primary mitochondrial defect (Table 27.2). The mechanism of action of some anti-epileptic and antibiotic drugs can interfere with normal mitochondrial function. Therefore, these specific drugs are preferably not used (Table 27.3).

Table 27.2. General measurements in mitochondrial disorders

Indication	Measurements
Acute crisis	1. Consider ventilation under sedation 2. Restore normal circulation
Lactic acidosis	1. Sodium bicarbonate 2. Consider (peritoneal) dialysis with sodium acetate
Fever	1. Start aggressive antipyretic treatment 2. Start antibiotic therapy
Epilepsy	Treat with anti-epileptic therapy
Gastrointestinal problems	1. Start tube feeding early, eventually gastrostomy 2. Gastroesophageal reflux therapy with drugs and/or surgery in GER 3. Surgical treatment of pseudo-obstruction can be indicated 4. Replacement of digestive enzymes in exocrine pancreatic dysfunction 5. Liver transplantation in isolated (acute) liver failure
Cardiac abnormalities	1. Prophylactic pacemaker placement in patients with conduction defects 2. Heart transplantation in severe isolated hypertrophic cardiomyopathy
Muscle weakness	1. Carnitine supplement, orally 50–100 mg/kg per day t.i.d., or i.v. 30 mg/kg per day 2. Regular low-impact training
Eye abnormalities	1. Cataract extraction in severe vision impairment 2. Surgery for ptosis and strabismus
Hearing impairment	1. Hearing aids 2. Cochlear implantation
Endocrine system dysfunction	1. Insulin treatment of insulin-dependent diabetes mellitus 2. In Kearns-Sayre syndrome regular control for hypoparathyroidism 3. eventually growth hormone therapy in growth-retarded children; is still under debate
Sideroblastic anemia	Repeated blood transfusions
Sleep apnea	1. Polysomnography 2. Tracheostomy and artificial ventilation during sleep

Table 27.3. Drugs and measurements known to interfere with normal mitochondrial function

Avoid	Indication
Acute crisis	Avoid barbiturates, propofol, nitroprusside, theophylline, and blue dye
Lactic acidosis	Avoid excessive physical exercise; physiological stress, i.e., fasting; alcohol, cocaine, and smoking
Fever	Avoid ascorbic acid, tetracycline, chloramphenicol, and nucleoside analogs
Muscle weakness	Avoid chronic use of corticosteroids
Epilepsy	Avoid high-dose valproate, phenobarbital, and barbiturates

27.4 Alternative Therapies/Experimental Trials

27.1–27.7 Pyruvate dehydrogenase complex
27.13 Complex I
27.11 Complex II
27.14 Coenzyme Q
27.15 Complex III
27.16 Complex IV
27.17 Complex V
Friedreich's Ataxia

Other treatment strategies (2–6, Table 27.4) might be useful in some mitochondrial disorders, although the safety and efficacy of these therapies have not been assessed for certain, due to the small number of patients and study designs. Moreover, the clinical features and molecular defects have been different in most of the patients described. In general, if a specific treatment regimen is not successful within 6 months, it is reasonable to stop.

Table 27.4. Alternative therapies/experimental trials

No.	Medication/Diet	Dosage[a]	Doses[a] per day
27.1–27.7	Dichloroacetate	15–200 mg/kg per day	2–3
	Thiamine (vitamin B_1)	50–500 mg/day	
	α-Lipoic acid	5–50 mg/day	
	Ketogenic diet	60–80% fat energy %	
27.11	Ubiquinone (CoQ_{10})	4–5 mg/kg per day	2
	Tocopherol (vitamin E)	100–300 mg/day	
27.13	Dichloroacetate	15–200 mg/kg per day	2–3
	Menadione (vitamin K_3)	1.1–1.5 mg/kg per day	
	Riboflavin (vitamin B_2)	3–20 mg/kg per day	3–4
	Nicotinamide	50 mg/kg per day	
	Ketogenic diet	60–80% fat energy%	
27.14	Ubiquinone (CoQ_{10})	4–5 mg/kg per day	2
	Idebenone	5–15 mg/kg per day	2
27.15	Menadione (vitamin K_3)	1.1–1.5 mg/kg per day	
	Ascorbate (vitamin C)	50–60 mg/kg per day	
27.16	Dichloroacetate	15–200 mg/kg per day	2–3
	Copper	Unknown	
KSS, NARP, MELAS, CPEO	Creatine monohydrate	4–10 g/day 0.1–0.3 mg/kg perday	2
Friedreich's ataxia	Selenium	100 µg/d	
	Idebenone	5–15 mg/kg per day	2

[a] Therapeutic recommendations differ between metabolic centers in the world, and are evolving continuously. We cannot guarantee for the figures given, and it is recommended to read the manufacturer's drug information carefully or to consult a specialist with respect to the exact modalities of treatment

Gene therapy is not available for therapeutic means in man yet, although several approaches are promising in *in vitro* systems. "Gene shifting" and gene transfer techniques are being developed for mtDNA-related disorders (Taylor et al. 1997; Clark et al. 1997; Taivassalo et al. 1999; Kolesnikova et al. 2000).

Dangers/Pitfalls

1. Dichloroacetate therapy should be adjusted depending on the clinical effect (Fujii et al. 2002); only use for a short period in acute phase or in severe neonatal lactic acidosis.
2. Dichloroacetate may cause peripheral neuropathy (Spruijt et al. 2001), pericardial effusion and renal tubular dysfunction, even when it is administered with thiamine 100 mg/day. Long-term efficacy remains to be established.
3. Long-term tolerance of individuals with PDH deficiency to ketogenic diets has never been assessed (Weber et al. 2001).
4. Complications that may occur from menadione therapy include hemolytic anemia, hyperbilirubinemia, and kernicterus in neonates.
5. Menadione should be administered together with ascorbate. Improvement is not sustained, and success has been limited in other mitochondrial diseases. Furthermore, ascorbate might interfere theoretically with normal mitochondrial function.
6. Riboflavin has been reported to be beneficial in patients with complex I deficiency (Bar-Meir et al. 2001) and MELAS (T3250C mutation).
7. Nicotinamide may decrease lactate and pyruvate concentrations in patients with complex I deficiency and MELAS (A3243G mutation). The clinical condition does not improve.
8. Idebenone, a CoQ10 analogue, may ameliorate cardiac hypertrophy in Friedreich's ataxia. Increasing the dose to 15 mg/kg per day was beneficial in some patients (Rötig et al. 2002). Ataxia did not improve in one study, but was significantly improved in another study.
9. Copper supplementation restores COX activity in cultured cells of SCO2-deficient patients (Jaksch et al. 2001). It has not been used as a therapeutically application in patients.
10. Starting dose of creatine monophosphate 2×5 g/day for 5–14 days, followed by maintenance of 2×2 g/day. Stop every 4^{th} month to avoid cytotoxic effect of formaldehyde, eventually formed by conversion of methylamine, a metabolite of creatine metabolism (Persky and Brazeau 2001).
11. Selenium treatment is only reported in one patient with Friedreich's ataxia (Fryer 2002). Recommended daily allowances, 55–75 µg/day. The therapeutic range is narrow, with a safe upper limit of 400–450 µg/day. In FRDA fibroblasts, selenium increases the glutathione peroxidase (an antioxidant) activity.

Genetic counseling and prenatal diagnosis are improving for diseases due to mutations in the nuclear genome. Molecular defects, e. g., in the genes encoding structural components of PDH, complexes I and II, and proteins involved in mitochondrial assembly, synthesis, and homeostasis are being identified with increasing frequency (Table 27.5) (Shoubridge 2001). Recently, a mutation in one of the structural subunits of complex III has been recognized. Pathogenic mutations in the structural subunits of complexes IV and V are probably lethal.

Table 27.5. Nuclear gene mutations and clinical symptoms of oxidative phosphorylation (OXPHOS) disorders[a]

Gene	Complex	CNS/PNS	Heart	Other
Structural OXPHOS defects				
NDUFS1	Complex I		Hypertrophic cardiomyopathy	
NDUFS2	Complex I	ECM		
NDUFS4	Complex I	LS, Leigh-like syndrome		
NDUFS7	Complex I	LS, Leigh-like syndrome		
NDUFS8	Complex I	LS, Leigh-like syndrome		
NDUFV1	Complex I	ME, macrocephaly, leucodystrophy		
SDHA	Complex II	LS		
SDHB	Complex II	LS		
SDHC	Complex II			Hereditary paraganglioma, pheochromocytomas
SDHD	Complex II			Hereditary paraganglioma, pheochromocytomas
UQCRB	Complex III	Normal		Episodic gastroenteritis, hepatomegaly, and lactic acidosis
Assembly defects				
BCS1L	Complex III	LS		GRACILE
COX10	Complex IV	LS		De Toni-Fanconi-Debre syndrome (tubulopathy)
SCO1	Complex IV	Encephalopathy		Neonatal-onset hepatic failure
SCO2	Complex IV	ECM	cardiomyopathy	
SURF1	Complex IV	LS		
COX15	Complex IV	ECM	cardiomyopathy	
Intergenomic communication defects				
ANT1	ANT	Proximal limb weakness, peripheral neuropathy, sensorineural hearing loss		AD PEO, cataracts, endocrine dysfunction, severe depression
ECGF1	TP	Peripheral neuropathy, leukoencephalopathy		Gastrointestinal dysmotility (MNGIE)
POLG	MtDNA polymerase gamma	PEO, ataxia, dysarthria, MERRF		MNGIE
C10orf2	Twinkle	PEO, depression, proximal limb muscle weakness, MND		

Table 27.5. (continued)

Gene	Complex	CNS/PNS	Heart	Other
Homeostasis and import				
X-25	Frataxin	Friedreich's ataxia (FRDA), muscle weakness, hearing and vision impairment	cardiomyopathy	
SPG7	Paraplegin	Hereditary spastic paraplegia		
TIMM8A	DDP1	Deafness-dystonia syndrome (Mohr-Tranebjaerg syndrome), cortical blindness		Psychiatric symptoms
HSP60	Import chaperonin	AD Hereditary spastic paraplegia		
ATP7B	CTA	Movement disorder		Liver failure (Wilson's disease)
Mitochondrial motility defects				
OPA1	MDRGT	AD Optic atrophy		
Membrane lipid milieu defects				
G4.5	Tafazzins		cardiomyopathy	Myopathy, growth retardation, leucopenia (Barth's syndrome)

[a] See also the Human Genome Organisation (HUGO) http://www.gene.ucl.ac.uk/cgi-bin/nomenclature/searchgenes.pl
AD autosomal dominant, ANT adenine nucleotide translocator, BCS1L cytochrome *b-c* complex assembly protein, COX cytochrome *c* oxidase, CTA copper-transporting ATPase, DDP1 deafness-dystonia protein 1, ECM encephalomyopathy, GRACILE growth retardation aminoaciduria lactic acidosis and early death, LS Leigh's syndrome, MDRGT mitochondrial dynamin-related guanosine triphosphatase, ME myoclonic epilepsy, MND motor neuron disease, NDUFS NADH dehydrogenase (ubiquinone) Fe-S protein, NDUFV SCO synthesis of cytochrome oxidase, PEO progressive external ophthalmoplegia, SDHA-D succinate dehydrogenase subunits A to D, SPG7 spastic paraplegia gene 7, SURF1 surfeit gene 1, TIMM8A mitochondrial-import-machinery in the intermembrane space, TP thymidine phosphorylase

Except perhaps for mutations in the mitochondrial ATP synthase (ATPase) 6 gene, genetic counseling and prenatal diagnosis are still problematic in disorders due to mtDNA mutations (Table 27.6) (Pulkes and Hanna 2001; Anonymous 2003).

Table 27.6. Most frequent mitochondrial DNA (mtDNA) defects and clinical symptoms of OXPHOS disorders[a]

Gene location	CNS/PNS (mtDNA mutation)	Muscle (mtDNA mutation)	Heart (mtDNA mutation)	Other (mtDNA mutation)
mtDNA protein-encoding genes				
ND1	MELAS (T3308C), LHON (T3394C; G3460A; T4160C; T4216C)			
ND2	LHON (A4917G; G5244A)		cardiomyopathy	
ND4L	LHON (G11778A)			
ND4	LHON (G11778A) LHON/dystonia (A11696G)	Myopathy (G11832A)		
ND5	LS, MELAS (G13513A), LHON (G13708A)			
ND6	LHON (T14484C), MELAS, LHON and dystonia (A14459G; T14596A)		cardiomyopathy (G15243A)	
Cyt b	ECM, LHON (G15257A; G15812A), MELAS/Parkinsonism (4-bp deletion 14787)	Myopathy (G15762A), exercise intolerance (G14846A; G15059A; G15048A; G15168A; G15498A; G15723A)		
COXI	ECM (G6930A), MND (5-bp microdeletion), LHON (G7444A)	Myoglobinuria		Sideroblastic anemia (T6721C; T6742C)
COXIII	MELAS (T9957C) LHON (G9438A; G9804A), ECM (G9952A)	Myoglobinuria (15-bp microdeletion)		
ATPase 6	NARP (T8993G), NARP/MILS (T8993C/G; T9176C), MILS (T8993G/C), bilateral striatal necrosis (T8851C; T9176C), LHON (T9101C)			

Table 27.6. (continued)

Gene location	CNS/PNS (mtDNA mutation)	Muscle (mtDNA mutation)	Heart (mtDNA mutation)	Other (mtDNA mutation)
MtDNA protein synthesis genes (total of 2 rRNAs and 22 tRNAs)				
$tRNA^{Phe}$	MELAS (A583G)	Myoglobinuria (A606G)		
rRNA 12S	Parkinsonism, AID (A1555G)		cardiomyopathy (A1555G)	
$tRNA^{Val}$	Ataxia, deafness, seizures, dementia (G1606), MELAS (G1642A), MILS (G1644T)			
$tRNA^{Leu(UUR)}$	MELAS (A3243G; A3243T; A3252G; A3260G; T3271C; T3291C; ΔTnt-3271), deafness (A3243G)	PEO (A3243G; A3251G; C3256T), Myopathy (T3250C; A3288G; A3302G)	cardiomyopathy (C3254G; A3260G; C3303T)	Diabetes (A3243G; T3264C)
$tRNA^{Ile}$	Multiple sclerosis (G4298A)	Myopathy/PEO (T4274C; T4285C; G4298A; G4309A)	cardiomyopathy (A4269G; A4295G A4300G; C4320T)	
$tRNA^{Met}$		Myopathy (T4409C)		
$tRNA^{Trp}$	Dementia/chorea (G5549A), LS (5537T; G5540A)			
$tRNA^{Asn}$		PEO (A5692G; G5703A)		
$tRNA^{Cys}$	MELAS (A5814G)			
$tRNA^{Ser(UCN)}$	Deafness (A7445G; 7472C; T7511C), MERFF/MELAS (T7512C)			
$tRNA^{Asp}$	Infantile encephalopathy (G7543A)			
$tRNA^{Lys}$	MERFF/MELAS (A8344G; T8356C; G8363A), LS (G8328A; A8344G), deafness and ataxia (A8296G), gastrointestinal encephaloneuropathy (G8313A)	PEO (G8342A)	cardiomyopathy (A8296G; 8363A)	Diabetes (A8296G)

Table 27.6. (continued)

Gene location	CNS/PNS (mtDNA mutation)	Muscle (mtDNA mutation)	Heart (mtDNA mutation)	Other (mtDNA mutation)
$tRNA^{Gly}$	SIDS (A10044G)		cardiomyopathy (T9997C)	
$tRNA^{Leu(CUN)}$		PEO (T12311C; G12315A), myopathy (A12320G)		Sideroblastic anemia (G12301A)
$tRNA^{Glu}$	ECM (T14709C)			Diabetes (T14709C)
$tRNA^{Thr}$	Fatal congenital disorder (A15923G), ECM (G15915A)		(A8296G; 8363A) (A15923G)	
$tRNA^{Pro}$		Myopathy (C15990T)		
Rearrangements and giant deletions in mtDNA				
KSS	Single large deletion; large scale tandem duplication		Ptosis, pigmentary retinopathy, conduction disorder	
PS	Single large deletion; deletion-duplication		Sideroblastic anemia, exocrine pancreatic dysfunction	
PEO	Single large deletion		Muscle weakness, exercise intolerance, ophthalmoplegia, ptosis	

[a] See also the Human Genome Organisation (HUGO) http://www.gene.ucl.ac.uk/cgi-bin/nomenclature/searchgenes.pl

ATPase 6 ATP synthase (complex V), CNS central nervous system, Cyt *b* cytochrome *b* subunit of complex III, COX cytochrome *c* oxidase (complex IV), ECM encephalomyopathy, KSS Kearns-Sayre syndrome, LHON Leber's hereditary optic neuropathy, LS Leigh's syndrome, MELAS mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes, MERRF myoclonic epilepsy and ragged red fibers, MILS maternally inherited Leigh's syndrome, MND motor neuron disease, NARP neuropathy, ataxia, and retinitis pigmentosa, ND NADH:ubiquinone oxidoreductase (complex I), OA optic atrophy, PEO progressive external ophthalmoplegia, PME progressive myoclonus and epilepsy, PNS peripheral nervous system, PS Pearson's syndrome, SIDS sudden infant death syndrome. Amino acids symbols: phenylalanine (F); valine (V); leucine (L); isoleucine (I); methionine (M); tryptophan (W); asparagine (N); cysteine (C); aspartic acid (D); lysine (K); glycine (G); glutamic acid (E); threonine (T); proline (P)

27.5 Follow-up/Monitoring

There are no standard protocols for follow-up or monitoring. The follow-up depends on the clinical and biochemical parameters of the patient. In the case of severe lactic acidosis, cardiomyopathy or conduction defects, encephalopathy and epilepsy, eye abnormalities, hearing impairment, anemia, endocrine system dysfunction or apnea, more frequent investigations will be needed (Table 27.7).

Table 27.7. Follow-up/monitoring

Biochemical monitoring[a]	Clinical monitoring[b]	Cardiac monitoring[c]	Ophthalmic monitoring	Neurophysiological monitoring[d]
6–12 monthly	6 monthly	Once a year	Once a year	Once every 2 years

[a] Plasma amino acid, urine organic acid, electrolytes, blood count, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, gamma glutamyl transpeptidase, albumen, urea, creatinine, lactate, blood gas, glucose
[b] Nutrient intake, body growth, general health
[c] Electrocardiogram, X-ray thorax
[d] Electroencephalogram, visual evoked potential (EP), brainstem auditory EP, somatosensory EP, magnetic resonance imaging of cerebrum, and electromyogram, depending on clinical findings

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28 Genetic Dyslipoproteinemias

Serena Tonstad, Brian McCrindle

28.1 Introduction

Familial lipid disorders rarely present with xanthomas in the case of children with homozygous familial hypercholesterolemia (FH) or adolescents with heterozygous FH. Usually lipid disorders are found fortuitously or upon screening children from families with a known lipid disorder or high cardiovascular risk. In the case of homozygous FH, cholesterol lowering is imperative to prevent aortic root disease and sudden death from acute myocardial infarction or acute coronary insufficiency before 30 years of age. In all other cases, treatment should be planned according to the child's risk level for cardiovascular disease (or rarely, pancreatitis). To determine the risk level, the family history, low-density lipoprotein (LDL) cholesterol level, and other risk factors, including diabetes, high-density lipoprotein (HDL) cholesterol level, smoking, hypertension, and obesity should be evaluated. Preferably, the children's treatment should be managed by an experienced outpatient lipid or pediatrics unit that includes a dietician.

The diagnosis of lipid disorders is based on the results of at least two lipid profiles (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, apolipoprotein B, and, optionally, apolipoprotein AI) obtained after an overnight fast. Children with high LDL cholesterol or triglyceride levels should then have a detailed history (including the family history of cardiovascular disease), review of systems, and physical examination, with selected laboratory testing to exclude secondary causes of hyperlipidemia. Lipid profiles from the parents and other family members may be needed to help identify primary hyperlipidemias associated with genetic abnormalities of lipoprotein metabolism.

28.2 Nomenclature

No.	Disorder (symbol)	Definitions/comment	Gene symbol	OMIM No.
28.1	Lipoprotein lipase deficiency	Mutation in lipoprotein lipase	*LPL*	238600
28.2	Apolipoprotein C-II deficiency	Mutation in apolipoprotein C-II	*ApoC-II*	207750
28.3	Familial dysbetalipoproteinemia (FD)	Mutation in apolipoprotein E, including E2/2, E2/3	*ApoE*	107741
28.5.1	Homozygous familial hypercholesterolemia	Mutation in low-density lipoprotein receptor	*LDLR*	143890
28.5.2	Heterozygous familial hypercholesterolemia	Mutation in low density lipoprotein receptor	*LDLR*	143890
28.6	Defective apolipoprotein B-100 (FDB)	Mutation in apolipoprotein B-100	*ApoB-100*	107730
28.7	Familial combined hyperlipidemia	Polygenetic		
28.8	Familial hypertriglyceridemia	Polygenetic		

28.3 Genetic Dyslipidemias

Disorder	Age and risk level	Diet/medication	Dosage/frequency
28.5.2 Heterozygous familial hypercholesterolemia	Prepubertal: low to moderate risk	Saturated fat < 7–10% of energy intake Cholesterol < 200 mg/day	
	Prepubertal: moderate to high risk	Same diet as low risk; and cholestyramine or colestipol	4 g once to twice daily 5 g once to twice daily
	Postpubertal: low to moderate risk	Saturated fat < 7–10% of energy intake Cholesterol < 200 mg/day	
	Postpubertal: moderate to high risk	Same diet as low risk and one of the following: Simvastatin Atorvastatin Pravastatin Lovastatin Fluvastatin	All given once daily 20 mg 10–20 mg 20–40 mg 20–40 mg 20–40 mg
28.5.1 Homozygous familial hypercholesterolemia	Before age 6 years	Same diet as heterozygous	
		FH and atorvastatin	20–40 mg once daily
	From age 6 years	Low-density lipoprotein apheresis and is a statin with or without ezetimibe: Atorvastatin Simvastatin Ezetimibe	Weekly or fortnightly 40–80 mg/day 80 mg/day 10 mg/day

EPA eicosapentanoic acid, *DHA* docosahexanoic

Disorder	Age and risk level	Diet/medication	Dosage/frequency
28.7 Familial combined hyperlipidemia	Overweight	Balance diet and physical activity to maintain body weight in relation to growth. Restrict sugars to < 10% of energy, saturated fat to < 10% of energy	
	Not overweight	Restrict sugars to < 10% of energy and saturated fat to < 10% of energy	
28.8 Familial hypertriglyceridemia (rarely recognized in children)	Overweight	Balance diet and physical activity to maintain body weight in relation to growth. Restrict sugars to < 10% of energy	
		Fish oil capsules (EPA+DHA)	1–2 g once daily
	Not overweight	Restrict sugars to < 10% of energy	
		Fish oil capsules (EPA+DHA)	1–2 g once daily
28.3 Familial dysbetalipoproteinemia	High CHD risk generally	Balanced diet and physical activity for weight control	
		Atorvastatin	10–20 mg
		Bezafibrate (or other fibrate)	200–400 mg once daily
28.1/2 Familial lipoprotein lipase or apolipoprotein C-II deficiency	Main risk is pancreatitis	Fat < 10%–20% of energy. Medium-chain triglycerides	
Familial type V hypertriglyceridemia (severe)		Try fish oil capsules (EPA + DHA)	1–2 g once daily
		Consider a fibrate	
Chylomicronemia syndrome (caused by any form of hypertriglyceridemia)	Sepsis, abdominal pain, pancreatitis	Total parental nutrition (no intralipid). Plasma exchange using heparin	

EPA eicosapentanoic acid, *DHA* docosahexanoic

28.4 Comments

1. Sitosterol/sitostanol margarines may supplement the low saturated fat, low-cholesterol diets.
2. Heterozygous familial defective apolipoprotein B100 can be treated similarly to heterozygous FH; risk may be lower than in FH.

Dangers/Pitfalls

1. Systemic infections and fever lower lipid levels.
2. Iron defiency anemia may be a complication of LDL apheresis.
3. The main complication of untreated homozygous FH is aortic root atherosclerosis.
4. Girls that may be sexually active should have adequate contraception when taking statins.
5. Treatment with bile acid-binding resins cholestyramine and colestipol may lead to low levels of folic acid and increase plasma total homocysteine.
6. Triglyceride levels of $\geq$ 10 mmol/l may lead to pancreatitis and should be lowered.
7. A case of epistaxis with fish oil treatment has been reported.
8. Always look for secondary causes of hypertriglyceridemia.

28.5 Monitoring and Target of Treatment

Treatment	Monitoring	Target of treatment	Comments
Dietary restriction of saturated fat	Height and weight percentiles	Diet may lower LDL cholesterol by 5–15% if untreated previously	No growth problems if unsaturated fat is substituted for most of saturated fat
All statins	Liver transaminases 6–12 weeks after start or increase of dosage then once yearly	LDL cholesterol < 3 mmol/l is ideal, but it is not necessary to attain this level in all children. A 20% or more reduction in LDL cholesterol is good. Measure lipid profile once yearly or 6–12 weeks after change of dose.	If muscle symptoms, do a creatinine phosphokinase level and stop the statin
	Symptoms of myopathy, sleep problems, asthenia		
Fibrates	Liver and kidney function	Reduction in triglycerides about 25–30% or more depending on baseline level	Should only be used very exceptionally.
	Any symptoms		
Fish oil capsules	Not needed, but watch for gastrointestinal symptoms	Reduction in triglycerides by about 25–30% or more depending on baseline level	
Bile acid-binding resins	Folate, plasma total homocysteine, vitamin D	Reduction in LDL cholesterol of about 15–18%, also when combined with statin	Compliance may be very difficult
Ezetimibe	None	Reduction in LDL cholesterol of about 18% seen in adults, also when combined with statin	Very limited experience in children (Gagne et al. 2002)

28.6 Secondary Hyperlipidemias

Secondary causes of hyperlipidemia	Tests to check	Comments
Overweight and obesity	Body mass index (25–29.9 kg/m^2, overweight; ≥30 kg/m^2, obese)	The most common cause of secondary hyperlipidemia
Renal or hepatic dysfunction	Urine for proteinuria	Some children with chronic nephrotic syndrome may benefit from statin therapy to prevent cardiovascular disease or fish oil therapy to prevent pancreatitis
	Serum creatinine Liver function tests	
Hyper- or hypothyroidism	Thyroid function tests	
Diabetes type 1 or 2	Glucose	Insulin in type-1 diabetes corrects lipid abnormalities
Drugs, alcohol, pregnancy, estrogens	As appropriate	

Dangers/Pitfalls
Genetic and secondary causes may coexist, and both may need to be addressed.

28.7 Classification of Risk Category for Children and Adolescents with Heterozygous Familial Hypercholesterolemia

- Low risk
  - Total cholesterol > 5.0–6.9 mmol/l, plus: no early CHD in the family; or the child is female, early CHD only among men in the family
  - Total cholesterol 7.0–8.9 mmol/l, plus: the child is female, no early CHD in the family
- Moderate risk
  - Total cholesterol > 5.0–6.9 mmol/l, plus: the child is male, early CHD in the family; or the child is female, early CHD in the family and also among female relatives
  - Total cholesterol 7.0–8.9 mmol/l, plus: the child is male, no early CHD in the family
  - Total cholesterol ≥ 9.0 mmol/l, plus: the child is female, no early CHD in the family
- High risk
  - Total cholesterol ≥ 9.0 mmol/l, plus: the child is male, no early CHD in the family
  - Total cholesterol ≥ 7.0 mmol/l, plus: early CHD in the family

28.8 Comments to classification of risk

1. Early coronary heart disease (CHD) is defined as CHD in males before the age of 40 and in females before the age of 50 years in a first- or second-degree relative.
2. Consider drug treatment for the high risk and some from the moderate risk categories.
3. Use the presence of other cardiovascular risk factors (diabetes, hypertension, overweight, cigarette smoking, low HDL cholesterol level) to further determine risk level. The presence of these factors may move a child to a higher risk category.
4. For children aged 10 years or older, the National Cholesterol Education Program (NCEP) guidelines suggest that drug therapy be considered when LDL cholesterol levels are ≥ 4.9 mmol/l after a trial of lifestyle change or ≥ 4.1 mmol/l in the presence of a positive family history or with two other risk factors after a trial of lifestyle change. A positive family history is defined

as CHD in males before 55 years or females before 65 years. The NCEP guidelines suggest that a minimal target of treatment is LDL cholesterol < 3.4 mmol/l and the ideal target is LDL cholesterol < 2.9 mmol/l.

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29 Disorders of Steroid Synthesis and Metabolism

Anna Biason-Lauber

29.1 Introduction

The present chapter deals with patients who either cannot produce steroid hormones because of genetic defects of the enzymes involved in their synthesis (steroid synthesis defects) or are unable to respond to steroids because of genetic defects of the corresponding receptors (steroid hormone resistances). In patients with steroid biosynthetic defects, the goal of the medical intervention is twofold: (Joint LWPES/ESPE CAH Working Group 2002) replacement of the absent hormones; and (Rink and Adams 1998) suppression of the reactive overproduction of hormones that do require the defective enzymatic step for their synthesis. To reach this goal, all patients with the most common form of steroid synthesis defect, congenital adrenal hyperplasia (CAH) need substitutive therapy with glucocorticoids and mineralocorticoids. This therapy inhibits also the excessive "reactive" production of sex hormones. In some cases, however, the supplementation of sex hormones is necessary at the time of expected puberty.

Patients suffering from steroid hormone resistance cannot profit from any specific therapy. Patients with an abnormal *in utero* sex hormones production have ambiguous external genitalia and usually need surgical correction.

29.2 Nomenclature

No.	Disorder (symbol)	Definitions/comment	Gene symbol	OMIM No.
29.1	STAR deficiency	Lipoid adrenal hyperplasia	*STAR*	201710
29.2	17α-Hydroxylase deficiency	Congenital adrenal hyperplasia	*CYP17A1*	202110
29.3	3β-Hydroxysteroid dehydrogenase deficiency	Congenital adrenal hyperplasia	*HSD3B2*	201810
29.4	21-Hydroxylase deficiency	Congenital adrenal hyperplasia	*CYP21*	201910
29.5	11β-Hydroxylase deficiency	Congenital adrenal hyperplasia	*CYP11B1*	202010
29.6	Corticosterone methyloxidase deficiency	Salt loss	*CYP11B2*	124080
29.7	Glucocorticoid-suppressible hyperaldosteronism (GRA)	Glucocorticoid-sensitive hypertension	*CYP11B1/ CYP11B2*	103900
29.8	11β-Hydroxysteroid dehydrogenase type 2 deficiency	Apparent mineralocorticoid excess	*HSD11B2*	218030
29.9	11β-Hydroxysteroid dehydrogenase type 2 deficiency	Apparent cortisone reductase deficiency	*HSD11B1*	600713
29.10	17,20-Lyase deficiency	Male pseudohermaphroditism	*CYP17A1*	202110
29.11	17β-Hydroxysteroid dehydrogenase type III deficiency	Male pseudohermaphroditism	*HSD17B3*	264300
29.12	5α-Reductase type II deficiency	Pseudovaginal perineoscrotal hypospadia	*SRD5A2*	264600
29.13	Aromatase deficiency	Female pseudohermaphroditism	*CYP19*	107910
29.14	Androgen-insensitivity syndrome (AIS)	Testicular feminization Reifenstein syndrome	*AR*	300068
29.15	Estrogen receptor defect	Estrogen resistance	*ESR1*	133430
29.16	Progesterone resistance	Pseudocorpus luteum deficiency	*PGR*	264080
29.17	Glucocorticoid receptor defect	Glucocorticoid resistance	*GCCR (NR3C1)*	138040
29.18	Mineralocorticoid defect	Pseudohypoaldosteronism (salt loss)	*NR3C2*	264350

No.	Disease	Age	Medication	Dosages
29.1.1	Lipoid adrenal hyperplasia	Infancy/childhood	Hydrocortisone (HC)	10–15 mg/m^2 per day (divided into three doses)
		Adolescence/adulthood	Fludrocortisone	0.05–0.30 mg/m^2 per day
			All of the above + estrogen/progestin	
29.1.2	17α-Hydroxylase deficiency	All ages	HC	10–15 mg/m^2 per day (divided 3 times daily)
			Antihypertensive drugs	
		Adolescence/adulthood	Estrogen/progestin	
29.1.3	3β-Hydroxysteroid dehydrogenase deficiency	Infancy/childhood	HC	10–15 mg/m^2 per day
			Fludrocortisone	0.05–0.3 mg/m^2 per day
		Adolescence/adulthood	Add sex hormones:	
			Male: testosterone depot	100 mg i.m. every 4 weeks for 1–2 years
			Female: ethinyl estradiol	0.01–0.05 mg per day
29.1.4	21-Hydroxylase deficiency			
	Classic forms	Infancy	HC	10–15 mg/m^2 per day (some patients might require up to 25 mg/m^2 per day)
			Fludrocortisone	0.05–0.30 mg/m^2 per day
			NaCl supplement	1–3 g/day (17–51 mEq/day
		Childhood	HC	10–15 mg/m^2 per day (some patients might require up to 25 mg/m^2 per day)
			Fludrocortisone	0.05–0.20 mg/m^2 per day
		Adolescence/adulthood	Prednisolone or:	2–4 mg/m^2 per day (one-fifth the HC doses)
			Dexamethasone	0.25–0.375 mg/m^2 per day
			Fludrocortisone	0.05–0.20 mg/m^2 per day
		Stress[a]	HC	Oral: 3 times the maintenance doses i.v.:
		0–3 years		25 mg, followed by 25 mg per day
		3–12 years		50 mg, followed by 50–60 mg per day
		Adolescence/adulthood		100 mg, followed by 100 mg per day
	NCCAH	Childhood	HC	10–15 mg/m^2 per day
		Adolescence/adulthood	Prednisolone or	2–4 mg/m^2 per day (one-fifth the HC doses)
			Dexamethasone	0.25–0.375 mg/m^2 per day
29.1.5	11β-Hydroxylase type I deficiency	Infancy	HC	10–15 mg/m^2 per day
			Fludrocortisone	Only for the first 2 weeks after initiation of the HC therapy (to prevent the transient salt loss due to suppression of the mineralocorticoid precursors)
		Childhood/adolescence/adulthood	Add antihypertensive drugs	0.05–0.3 mg/m^2 per day
29.1.6	Corticosterone methyloxidase deficiency	All ages	Mineralcorticoid antagonists (e. g., spironolactone)	

No.	Disease	Age	Medication	Dosages
29.1.7	Glucocorticoid-suppressible hyperaldosteronism	All ages	HC	15–25 mg/m^2 per day
29.1.8	Apparent mineralocorticoid excess	All ages	Mineralocorticoid antagonists	
29.1.9	Apparent cortisone reductase deficiency	All ages	No specific therapy Antiandrogens	
29.1.10	17,20-Lyase deficiency	Adolescence/adulthood	Sex hormones: Male: testosterone depot Female: ethinyl estradiol	 100 mg i.m. every 4 weeks for 1–2 years 0.01–0.05 mg per day
29.1.11	17β-Hydroxysteroid dehydrogenase type III deficiency	Adolescence/adulthood	Sex hormones: Male: testosterone depot Female: ethinyl estradiol	 100 mg i.m. every 4 weeks for 1–2 years 0.01–0.05 mg per day
29.1.12	5α-Reductase type II deficiency	Adolescence/adulthood	Dihydrotestosterone	
29.1.13	Aromatase deficiency	Adolescence/adulthood	Ethinyl estradiol	0.01–0.05 mg per day
29.2.	Steroid hormone resistances AIS Estrogen resistance Progesterone resistance Pseudohypoaldosteronism Glucocorticoid resistance	All ages	None Mineralocorticoid antagonists	

[a] Fever, vomiting, trauma, surgery, participation in endurance sports. Mental and emotional stress, such as school examinations, *does not* require increased doses

Special Issues

Prenatal Treatment of 21-Hydroxylase Deficiency

Inclusion criteria for prenatal treatment include:

1. A previously affected sibling or first-degree relative with known mutations causing classic CAH, proven by DNA analysis
2. Reasonable expectation that the father is the same as the proband's
3. Availability of rapid, high-quality genetic analysis for confirmation of the mutation
4. Therapy started less than 9 weeks after the last menstrual period
5. No plans for therapeutic abortion
6. Reasonable expectation of patient compliance

Procedure

***Dose*:** dexamethasone 20 μg/kg maternal body weight, divided into three doses

***Timing*:** as soon as pregnancy is confirmed or no later than 9 weeks after the last menstrual period

***Duration*:** treatment is continued to term in affected female fetuses and discontinued in all other fetuses

***Monitoring*:** maternal blood pressure, weight, glycosuria, HbA1C, plasma cortisol, DHEA, androstenedione every 2 months (Joint LWPES/ESPE CAH Working Group 2002)

Disease	Age	Biochemical follow-up[a]	Frequency	Clinical follow-up	Frequency
Lipoid adrenal hyperplasia	Infancy	Electrolytes	Monthly	General status	Monthly
	Adulthood	Electrolytes	Yearly	Growth	Yearly
17α-Hydroxylase deficiency	Infancy	Electrolytes	Every 3–6 months	Blood pressure	Every 3–6 months
	Childhood/ adolescence/ adulthood	Electrolytes		General status Growth	
		Urinary THB	Yearly	Sexual development	Yearly
3β-Hydroxysteroid dehydrogenase deficiency	Infancy/ childhood	Electrolytes		General status Growth	Every 3 months
	Adolescence/ adulthood	Electrolytes		Sexual development	Yearly
21-Hydroxylase deficiency					
Classic forms	Infancy	Electrolytes Androstenedione Testosterone Urinary metabolites (pregnanetriolone)	Every 3 months	General status Growth	Every 3 months
	Childhood	Androstenedione	Every 6–12 months	Growth	Every 6–12 months
	Adolescence/ adulthood	Androstenedione	Yearly	Sexual development	Yearly
NCCAH	All ages	Androstenedione	Yearly	Growth Sexual development	Yearly
11β-Hydroxylase type I deficiency	Infancy	Electrolytes Urinary THS	Every 3 months	Blood pressure Growth	Every 3 months
	Childhood/ adolescence/ adulthood	Androstenedione Testosterone Urinary THS	Every 6–12 months	Sexual development	Every 6–12 months

[a] All parameters are meant to be measured in plasma or serum, unless otherwise specified

Disease	Age	Biochemical follow-up[a]	Frequency	Clinical follow-up	Frequency
Corticosterone methyloxidase deficiency	All ages	Electrolytes	Every 1–2 years	Blood pressure	Every 1–2 years
Glucocorticoid-suppressible hyperaldosteronism	All ages	Electrolytes	Every 1–2 years	Blood pressure	Every 1–2 years
Apparent mineralocorticoid excess	All ages	Electrolytes	Every 1–2 years	Blood pressure	Every 1–2 years
Apparent cortisone reductase deficiency	All ages		Every 1–2 years		Every 1–2 years
17,20-lyase deficiency	Adolescence/ adulthood	Testosterone Estradiol	Every 1–2 years	Sexual development	Every 1–2 years
17β-Hydroxysteroid dehydrogenase type III deficiency	Adolescence/ adulthood	Testosterone Estradiol	Every 1–2 years	Sexual development	Every 1–2 years
5α-reductase type II deficiency	Adolescence/ adulthood	Dihydrotestosterone (if DHT is used)	Every 1–2 years	Sexual development	Every 1–2 years
Aromatase deficiency	Adolescence/ adulthood	Testosterone Estradiol	Every 1–2 years	Sexual development	Every 1–2 years
Steroid hormone resistances	All ages				
AIS			Every 1–2 years	Sexual development	Every 1–2 years
Estrogen resistance					
Progesterone resistance					
Pseudohypoaldosteronism		Electrolytes	Every 1–2 years		Every 1–2 years
Glucocorticoid resistance	All ages	Electrolytes	Every 1–2 years	Blood pressure	Every 1–2 years

[a] All parameters are meant to be measured in plasma or serum, unless otherwise specified

Dangers/Pitfalls

Physical and genital examination for ambiguous genitalia over the lifespan. The prior practice of frequent genital examinations should be abandoned. Therefore, unless there is clinical or laboratory evidence of poor control or one seeks to asses the pubertal progress and size of the clitoris, genital examination should not be performed.

29.5 Surgical Management

The decision about surgery should be made by the parents, together with the clinical team, after complete disclosure of all relevant clinical information and all available options have been discussed and after informed consent has been obtained. The goals of surgery are: (1) genital appearance compatible with gender; (2) unobstructed urinary emptying without incontinence or infections; and (3) good adult sexual and reproductive function.

Once a decision has been made to raise a newborn as female, surgery for those with virilized genitalia caused by CAH is recommended when the patient has a high proximal junction between the vagina and urethra (Rink and Adams 1998; Schnitzer and Donahoe 2001). Surgery on infants with ambiguous genitalia requires a high degree of expertise and should only be performed in centers with significant experience. Based on recent clinical experience, the recommended time for surgery is at age 2–6 months; although, at present, this is not universal practice. It is important to note that surgery at this stage is technically easier than at later stages.

When the degree of virilization is less (minimal clitoromegaly and the junction between the vagina and urethra near the perineum), surgery may not be necessary. In such cases, the decision to operate should be based on appropriate contrast studies of the urinary tract and examination under anesthesia, with cystoscopy. Surgery to reduce clitoral size requires careful consideration. Total removal of the clitoris should never be performed. If clitoral reduction is elected, it is crucial to preserve the neurovascular bundle, the glans, and the preputial skin related to the glans (Hutson et al. 1991; Baskin et al. 1999). The early operation should be a one-stage complete repair using the newest techniques of vaginoplasty, clitoral, and labial surgery (Rink and Adams 1998; Schnitzer and Donahoe 2001; Hutson et al. 1991) and should be carried out at a center with experience of at least 3–4 cases/year. Revision vaginoplasty is often required at adolescence, and the timing should be decided with the patient and family. Patients who wish to consider further procedures should be treated by a surgeon experienced in the current techniques.

Surgery between the age of 12 months and adolescence is not recommended in the absence of complications causing medical problems. Vaginal dilatations

are contraindicated at this stage, although this procedure is often useful in adolescence and in adulthood. Repeated genital examinations should be minimized. Genital photography should be discouraged and only be done with parental consent and, except in infancy, performed only under anesthesia.

At each designated center, one surgical team should be responsible for all surgery involving ambiguous genitalia. There should be close cooperation between centers to broaden experience, to audit results, and to allow adequate evaluation of outcomes. We acknowledge that there are concerns about early surgery. However, surgical techniques have improved. We urge caution in judging outcome from outdated procedures. Systematic studies are needed to evaluate ultimate function for all girls undergoing surgery.

It is recognized that 46,XX children with significant virilization may present at a later age. Consideration for sex reassignment must be undertaken only after thorough psychological evaluation of patient and family. Surgery appropriate to gender assignment should be undertaken after a period of endocrine treatment.

29.6 Experimental Therapies and Future Developments

■ 21-Hydroxylase Deficiency

● *Adrenalectomy in CAH*

Bilateral adrenalectomy by laparoscopy is effective in decreasing adrenal androgens and the likelihood of iatrogenic hypercortisolism (Van Wyk et al. 1996; Meyers and Grua 2000). It should be considered only in cases where conventional therapy is failing. Vigilance in maintaining regular substitution of HC and fludrocortisone is mandatory, with prompt institution of stress dosages at the onset of illness. The patient must be monitored, throughout life, for activation of ectopic adrenal rest tissue. The procedure should only be carried out where long-term follow-up is secured, and in the form of ethically approved clinical studies.

● *Corticotropin-Releasing Hormone Antagonists for Adrenal Suppression in CAH*

The use of corticotropin-releasing hormone (CRH) antagonists in CAH is promising on theoretical grounds but awaits future developments of drugs with improved pharmacological properties.

- *Treatment with Antiandrogens and Aromatase Inhibitors in Addition to HC and Fludrocortisone*

Based on the success of an earlier approach in familial male sexual precocity, it has been hypothesized that the deleterious effects of elevated androgens on adult height could be prevented by using an antiandrogen to block androgen action and/or an aromatase inhibitor to block conversion of androgen to estrogen. Limited short-term (2 year) studies in CAH show improved control of height velocity and bone maturation at reduced glucocorticoid dosage (Merke et al. 2000a). Long-term safety data are not available and reproductive effects are not known. Liver function has to be carefully monitored.

- *Epinephrine Deficiency in CAH*

Patients with CAH suffer from varying degrees of dysplasia and dysfunction of the adrenal medulla, expressed primarily as epinephrine deficiency (Merke et al. 2000b). This may play a role in response to stress. Possible therapeutic implications are under study.

- *Innovative genetic approaches*

Preimplantation genetic diagnosis for CAH is possible, but further research is required to determine its utility. Gene therapy is currently not possible in humans with this disorder.

- *Dehydroepiandrosterone Replacement in CAH*

CAH patients on glucocorticoid treatment have low dehydroepiandrosterone (DHEA) levels. Studies in adult patients with Addison's disease have shown beneficial effects of DHEA replacement (Arlt et al. 1999), but the relevance in CAH is unknown.

11β-Hydroxysteroid Dehydrogenase Inhibitors in CAH

11β-Hydroxysteroid dehydrogenase (11β-HSD) inhibitors have the potential for modulating tissue-specific activity of glucocorticoids (Walker and Stewart 2000). At present, there are no specific compounds that are selective inhibitors of 11β-HSD type I or type II, and clinical experience with nonspecific 11β-HSD inhibitors is limited. Therefore, the use of these inhibitors cannot be recommended, at present.

- *GH Treatment with or Without Administration of Gonadotrophin-Releasing Hormone (GnRH) Agonists*

A meta-analysis of 561 patients with CAH (the majority with 21OH deficiency) has revealed an overall mean final height SD score of –1.4 (Eugster et al. 2001). Thus, an acceptable height is achieved by many patients with CAH, and the mean adult height deficit is substantially less than frequently thought. However, some CAH patients fail to reach normal adult height. A small group of short CAH patients have been treated with GH for 2 years, either alone or in combination with a GnRH agonist. This significantly improved growth rate and predicted final height (Quintos et al. 2001), but adult height data are not yet available.

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30 Inborn Errors of Cholesterol Biosynthesis

Dorothea Haas, Richard I. Kelley

30.1 Introduction

Defects of cholesterol biosynthesis comprise a heterogeneous group of disorders, most of which have only recently been described. With the exception of cholesterol supplementation in Smith-Lemli-Opitz syndrome, no therapeutic regimens have yet been proven effective.

Mevalonic aciduria (MVA) and hyperimmunoglobulinemia D syndrome (HIDS) are due to defects in mevalonate kinase, an enzyme located proximally in the pathway of cholesterol biosynthesis. Patients affected with these disorders present with recurrent febrile attacks and, in the case of classic MVA, often have malformations, neurological symptoms, and psychomotor retardation (Hoffmann et al. 1993). Long-term administration of coenzyme Q10 together with vitamin C and E to treat an intrinsic deficiency in the synthesis of coenzyme Q10 and to treat a possible increased sensitivity to reactive oxygen species seems to stabilize the clinical course and improve somatic and psychomotor development (Haas et al. 2001; Prietsch et al. 2003). Dietary supplementation of cholesterol may reduce frequency and severity of febrile attacks in some mildly affected patients, but has further compromised more severely affected patients, similar to the apparent adverse effect of lovastatin in some patients (Hoffmann et al. 1993). In two patients (siblings) followed closely, intervention with corticosteroids was highly beneficial during clinical crises, with resolution of the crises within 24 h. The severity of attacks can also be reduced with the leukotriene receptor inhibitors montelukast and zafirlukast (R. I. Kelley, unpublished observations). Despite the apparent adverse effect of lovastatin in classic MVA, a recently completed study has shown a beneficial effect of simvastatin in HIDS (Simon et al. 2004).

The main characteristics of CHILD (congenital hemidysplasia, ichthyosiform erythroderma, and limb deficiency) syndrome (König et al. 2000) and Conradi-Hünermann syndrome (Kelley et al. 1999) are skeletal defects, including, notably, chondrodysplasia punctata and ichthyosiform skin lesions. All reported cases of Greenberg dysplasia (also called hydrops-ectopic calcification-"moth-eaten" skeletal dysplasia, HEM) have had nonimmune hydrops fetalis, short limbs, abnormal severe chondro-osseous calcifications and have been lethal prenatally. This autosomal recessive disorder is caused by a deficiency

of sterol-Δ^{14} reductase encoded by the LBR gene (Waterham et al. 2003). *LBR* was first known to encode for the lamin B receptor. Missense mutations in this gene recently have been reported also to cause Pelger-Huët anomaly, a disorder characterized by abnormally shaped blood granulocytes (Hoffmann et al. 2002) with heterozygous *LBR* mutations and developmental delay, epilepsy, and skeletal abnormalities in some patients homozygous for specific *LBR* mutations. Antley-Bixler syndrome is a rare, multiple anomaly syndrome with limb anomalies, craniofacial dysmorphisms and, in some, ambiguous genitalia. In patients with ambiguous genitalia, Kelley et al. (2002) have found increased levels of lanosterol and dihydrolanosterol, suggesting a functional deficiency of lanosterol-14α demethylase, a cytochrome P450 enzyme, encoded by *CYP51*. Mutation analysis of *CYP51*, however, discloses no obvious pathogenic mutation. Instead, mutations in the POR gene encoding P450 oxidoreductase, the obligate electron donor for all cytochrome P450 enzymes, have been identified in patients with Antley-Bixler syndrome (Flück et al. 2004).

As a general rule, patients with defects in the more proximal steps in cholesterol biosynthesis have normal cholesterol serum levels. Furthermore, the pathology appears to be mostly if not exclusively embryonic, without evidence for most precursor sterols that their usually trivial levels are harmful beyond the embryonic period. Therefore, there are few indications for treatment of most of these conditions with cholesterol, unless the level of cholesterol is abnormally low and the level of the precursor sterols is elevated substantially more than usual. The principal exceptions among these disorders are the very rare male hemizygote for CDPX2, the occasional unfavorably lyonized CDPX2 heterozygote with hypocholesterolemia and severe skin disease, and patients with CHILD syndrome who have severe, persistent psoriasiform skin lesions.

Desmosterolosis and lathosterolosis are malformation syndromes involving many different organ systems (FitzPatrick et al. 1998; Brunetti-Pierri et al. 2002). The total of four patients (two for each disorder) so far reported have clinical characteristics that overlap with SLOS, but serum cholesterol is normal or only marginally diminished in the two patients for whom serum data are available. There currently is no experience with treatment of lathosterolosis. Theoretically, patients with lathosterolosis should require the same cholesterol therapy used for SLOS if the cholesterol level is low and the level of lathosterol is increased. However, unlike SLOS, lathosterolosis is characterized by clinically significant lipid storage, possibly storage of cholesterol esters, which might be aggravated by supplemental cholesterol. Only one patient with desmosterolosis and a borderline low cholesterol level has been treated with cholesterol supplementation (50 mg/kg per day. There was no clinical effect, but a mild reduction in the plasma level of desmosterol was observed. Theoretically, the same criteria for treatment of SLOS should apply to desmosterolosis, with a goal of achieving a normal blood cholesterol level and a concomitant reduction in the level of desmosterol.

Smith-Lemli-Opitz syndrome, caused by a deficiency of 7-dehydrocholesterol reductase (DHCR7), is characterized by an accumulation of 7- and 8-dehydrocholesterol (7-DHC and 8-DHC), and, in 90% of patients, a lower-than-normal level of cholesterol in blood and all body tissues (Irons et al. 1993). SLOS has a highly variable phenotype, ranging from lethally affected infants with multiple organ and skeletal malformations to mildly affected patients with moderate mental retardation, mild dysmorphism, and a normal life expectancy. A large proportion of patients may require nasogastric tube feeding or gastrostomy to provide adequate caloric intake. However, it is important not to overfeed the children to archive a better growth. SLOS patients have a genetically determined short stature and, additionally, as a result of their muscle hypoplasia, their normal, well-nourished weight during infancy typically is 1–2 standard deviations less than their length. Trying to achieve arbitrary and inappropriately high weight goals based on age or length alone only increases adipose tissue and thereby limits the availability of cholesterol to the organs.

Cholesterol supplementation results in improved growth and behavior in most patients (Irons et al. 1997; Kelley and Hennekam 2000). Treatment with supplements of bile acids has not been effective (Elias et al. 1997) except in severely affected patients with cholestasis or when there is a clinically evident deficiency of bile acids. Unfortunately, an effect of cholesterol supplementation on intrinsic cognitive abilities has been absent or minimal, most likely because cholesterol cannot be transported across the blood-brain barrier and because prenatal developmental insults cannot be reversed. Plasma sterol levels often improve slowly over many months or years after initiation of cholesterol supplementation. However, effects on behavior often are evident after only several days of cholesterol treatment, possibly because of changes in levels of adrenal steroids, many of which, unlike cholesterol, can cross the blood-brain barrier. Treatment of mildly affected SLOS patients with simvastatin, an inhibitor of HMG-CoA reductase, causes a rapid fall of 7- and 8-DHC and a rise of cholesterol (Jira et al. 2000), probably via augmentation of residual DHCR7 activity, allowing more complete conversion of the abnormal sterols to cholesterol (Wevers et al. 2003). Mental, motor, and social development as well as weight, length, and head circumference reportedly improved in two patients who were not pretreated with cholesterol. However, in several patients with satisfactory improvement on cholesterol treatment, the addition of simvastatin had no measurable clinical benefit at the same time that potentially serious side-effects of simvastatin developed in some (Starck et al. 2002a; D. Haas, unpublished observations). Studies in a larger group of patients are needed to evaluate the use of simvastatin. Simvastatin should not be used in severely affected patients (ratio of (7-DHC + 8-DHC) to cholesterol is greater than 0.5) expected to have no or minimal residual DHCR7 activity, because it might further lower cholesterol levels, with severe side-effects (Starck et al. 2002b).

30.2 Nomenclature

No.	Disorder/ deficiency	Definition/comment	Gene	Gene symbol	OMIM No.
30.1a	Mevalonic aciduria	Mevalonate kinase deficiency, urinary mevalonate typically >500 mmol/mol creat.	Mevalonate kinase	*MVK*	251170
30.1b	Hyper-IgD syndrome	Mevalonate kinase deficiency, urinary mevalonate typically <100 mmol/mol creat.	Mevalonate kinase	*MVK*	260920
30.2	Desmosterolosis	3β-Hydroxysteroid-Δ^{24} reductase deficiency	24-Dehydro-cholesterol reductase	*DHCR24*	602398
30.3	Antley-Bixler syndrome (lanosterolosis)	Lanosterol-14α demethylase deficiency (secondary), skeletal dysplasia	Cytochrome P450 oxidoreductase	*POR*	207410
30.4a	Greenberg dysplasia	Sterol-Δ^{14} reductase deficiency, severe chondrodysplasia punctata	Lamin B receptor	*LBR*	215140
30.4b	Pelger-Huët anomaly	Sterol-Δ^{14} reductase deficiency, mild skeletal anomalies, cognitive deficits (homozygous)	Lamin B receptor	*LBR*	169400
30.5	CHILD syndrome	3β-Hydroxysteroid dehydrogenase deficiency	NAD[P]H steroid dehydrogenase-like enzyme	*NSDHL*	308050
30.6	Conradi-Hünermann syndrome (X-linked dominant chondrodysplasia punctata)	Sterol-Δ^{8} isomerase deficiency	Emopamil-binding protein	*EBP*	302960
30.7	Lathosterolosis	3β-Hydroxysteroid-Δ^{5} desaturase deficiency	Sterol C5 desaturase	*SC5D*	607330
30.8	Smith-Lemli-Opitz syndrome	3β-Hydroxysteroid-Δ^{7} reductase deficiency	7-Dehydro-cholesterol reductase	*DHCR7*	270400

30.3 Treatment/Alternative Therapies/Experimental Trials

■ *Disorders 30.2, 30.3, 30.4, 30.7*

No treatment.

■ *30.1 Mevalonate kinase deficiency*

30.1a Mevalonic aciduria (MVA)
30.1b Hyper-IgD syndrome (HIDS)

No.	Symbol	Medication	Dosage (mg/kg per day[a]	Doses per day
30.1a	MVA	Coenzyme Q10	5–10	3
		Tocopherol	25	3
		Ascorbic acid	50–60	2
		Cholesterol	50–100	3
		Alpha-lipoic acid	15	3
30.1b	HIDS	Coenzyme Q10	5–10	3
		Simvastatin	0.5–1.0	2

[a] Adult dosages based on body weight of 40–50 kg

Dangers/Pitfalls

1. Treatment with cholesterol may reduce the frequency and severity of febrile attacks in mildly affected patients but has further compromised severely affected patients, possibly by excessive downregulation of HMG-CoA reductase activity.
2. Intervention with HMG-CoA reductase inhibitors should not be attempted in MVA. An experimental trial in two patients resulted in clinical decompensation manifesting as elevated body temperature, acute myopathic changes, highly elevated creatine kinase, and worsened ataxia, diarrhea, and vomiting (Hoffmann et al. 1993).

Emergency Treatment

No.	Symbol	Age	Medication	Dosage (mg/d)	Duration
30.1a	MVA	All ages	Prednisone[a]	2 mg/kg per day	Daily during crises
		2–5 years	Montelukast	4 mg	Daily during crises
			Zafirlukast	10 mg	
		6–14 years	Montelukast	5 mg	
			Zafirlukast	10 mg	
		> 14 years	Montelukast	10 mg	
			Zafirlukast	20 mg	
30.1b	HIDS	All ages	Prednisone[a]	2 mg/kg per day	Daily during crises
		2–5 years	Montelukast	4 mg	Daily during crises
			Zafirlukast	10 mg	
		6–14 years	Montelukast	5 mg	
			Zafirlukast	10 mg	
		> 14 years	Montelukast	10 mg	
			Zafirlukast	20 mg	

[a] Because of the efficacy of leukotriene inhibitors, the use of steroids for treament of some inflammatory crises can be avoided

30.5 CHILD syndrome

Age	Indication	Medication	Dosage (mg/d)	Doses per day[b]
0–10 years[a]	Cholesterol < 120 mg/dl	Cholesterol	50–150 mg/kg per day	3
Adults			500–1000 mg	3
All ages	Active skin disease	Cholesterol	500 mg	3

[a] Normal serum cholesterol is 60 ± 15 mg/dl in the newborn period and rises to near adult level over the first 6–12 months
[b] With feedings/meals

30.6 Conradi-Hünermann syndrome

Age	Indication	Medication	Dosage (mg/d)	Doses per day[b]
0–10 years[a]	Cholesterol < 120 mg/dl	Cholesterol	50–150 mg/kg per day	3
Adults			500–1000 mg	3
All ages	Active skin disease	Cholesterol	500 mg	3

[a] Normal serum cholesterol is 60 ± 15 mg/dl in the newborn period and rises to near adult level over the first 6–12 months.
[b] With feedings/meals

30.8 Smith-Lemli-Opitz syndrome (SLOS)

(7-DHC+8-DHC) to cholesterol ratio	Age/indication	Medication	Dosage (mg/day)	Doses per day
≤ 0.5	0–10 years	Cholesterol	50–100 mg/kg per day[a]	3
	Adults		500–1000 mg[a]	3
	All ages	Simvastatin	0.5–1 mg/kg per day[b]	2
> 0.5	0–2 years	Cholesterol	100–200 mg/kg per day	3
	> 2 years		100–150 mg/kg per day[a]	3
	Cholestasis	Ursodeoxycholate	15–25 mg/kg per day	2–3

[a] Dosage for purified cholesterol powder. Cholesterol is more efficiently absorbed when given as egg yolk (cooked or, preferable in pasteurized, liquid form), in which form a dosage of 40 mg/kg per day, or 500 mg/day in adults, usually is sufficient

[b] Therapy should be started with 0.5 mg/kg per day and increased to 1 mg/kg per day after 4 weeks when there is no increase in CK or transaminases

Dangers/Pitfalls

1. Hepatotoxic side-effects were reported in one patient with a ratio of (7+8-DHC) to cholesterol of > 1 under simvastatin treatment (Starck et al. 2002a, b).
2. A moderate and reversible increase in creatine kinase was reported in a patient with a (7+8-DHC) to cholesterol ratio of < 0.5 under simvastatin-treatment (Starck et al. 2002a, b).

Emergency Treatment

For acute illness, when enteral cholesterol supplementation cannot be continued, or under conditions of severe stress likely to deplete LDL cholesterol, frozen plasma can be given as an emergency source of LDL cholesterol. Acute respiratory distress syndrome (ARDS) appears to be a common if unpredictable complication in severe SLOS, typically associated with lower respiratory-tract infections and after anesthesia, and may be treated with frozen plasma and/or surfactant.

No.	Symbol	Indication	Medication	Dosage
30.8a, 30.8b	SLOS	Surgical interventions, acute illnesses when enteral cholesterol supplementation not possible	Frozen plasma	10 ml/kg 1 ×/d or 2 ×/d
		ARDS	Surfactant	50–100 mg/kg[a]
			Frozen plasma	10 ml/kg × 1/day or ×2/day
		Adrenal insufficiency	Hydrocortisone	30 mg/m^2 per day depending on age
			NaCl 0.9%, glucose 10% 1:1 (v/v)	

[a] Depending on preparation

30.4 Follow-up/Monitoring

- *30.1a Mevalonic aciduria*

Age	Biochemical monitoring[a]	Clinical monitoring[b]	Opthalmological monitoring[c]	Cranial MRI
Children	6 monthly	6 monthly	Yearly	Every 2 years[d]
Adults	Yearly	Yearly	Yearly	

[a] CK, cholesterol, coenzyme Q10, vitamin E, hepatic function, renal function

[b] Body growth, general health. Detailed psychomotor and neurobehavioral examination and testing every 2 years until the age of 6, starting from the age of 24 months, e. g., with the Bayley Scales of Infant Development.

[c] Cataracts as well as retinal dystrophy have been described in several patients (Prietsch et al. 2003). The diagnostic work-up should comprise a slit-lamp examination, funduscopy, and, in individual patients, ocular electrophysiology (ERG)

[d] Until the age of 6 years

30.8 Smith-Lemli-Opitz syndrome

Age	Biochemical monitoring[a]	Clinical and developmental monitoring[b]
Infants	3 monthly	Every 8 weeks
Children < 6 years	3 monthly	6 monthly
Children > 6 years	6 monthly	6 monthly
Adolescents/adults	Yearly	Yearly

[a] Serum sterols, transaminases, albumin, total protein, Fe, ferritin, folate, vitamin B_{12}. For severely affected children: coagulation studies, assessment of adrenal function. Patients on simvastatin: CK, transaminases, and sterols 4 and 12 weeks after start of the treatment

[b] Body growth, general health. Detailed psychomotor and neurobehavioral examination and testing every 2 years until the age of 6, starting from the age of 24 months, e. g., with the Bayley Scales of Infant Development. Autism assessment in patients with a developmental quotient (DQ) > 18 months

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31 The Porphyrias

Elisabeth Minder, Xiaoye Schneider-Yin

31.1 Introduction

Patients with one of the porphyrias present either with acute abdominal pain, due to autonomous nervous system dysfunction and eventually further neurological damage, or with photosensitivity (Minder and Schneider 2003). Dependent on the type of porphyria, only nervous dysfunction, or only photosensitivity, or both symptoms may be present. Nervous system dysfunction develops episodically, but photosensitivity is usually continuously present. Therapeutic interventions are mainly aimed at reducing or eliminating clinical symptoms, whereas long-time disease monitoring is less prominent in the porphyrias, with the important exception of liver affection in erythropoietic protoporphyria (EPP).

The symptom of acute abdominal pain is presumably caused by toxicity of porphyrin intermediates, most likely of 5-aminolevulinic acid. Alternatively or in addition, heme deficiency in the nervous system eventually triggers clinical disease. The episodic outbreak of symptoms is due to endogenous or exogenous factors inducing an increase in hepatic heme synthesis by stimulation of the rate-limiting enzyme delta-aminolevulinic acid (ALA) synthase. Enhanced hepatic heme synthesis together with a block in the biosynthesis pathway leads to accumulation of intermediates.

Photosensitivity is caused by accumulation of porphyrins in the skin. With the exception of protoporphyrin, all other porphyrins are oxidized derivatives of the physiological intermediates, the porphyrinogens. Porphyrins are fluorescent substances with an excitation wavelength in the visible region at about 404 nm. Therefore, sun blockers absorbing in the UV region do not improve porphyrin-induced photosensitivity. Only those skin ointments that reflect sunlight by titanium oxide reduce the irradiation at the wavelength harmful to porphyria patients.

The therapeutic strategy varies between the so-called acute (hepatic) porphyrias with acute abdominal pain and excessive urinary aminolevulinic acid (and eventually porphobilinogen) and the nonacute porphyrias. The four acute porphyrias are ALA dehydratase deficiency (ALA-D; disorder 31.2), acute intermittent porphyria (AIP; disorder 31.2), hereditary coproporphyria (HC; disorder 31.5), and porphyria variegata (PV; disorder 31.6). The variant porphyrias

(disorder 31.9) usually are subsumed under the acute ones, dependent on whether any acute form is involved.

Management of Acute Attacks

The first measure in a patient symptomatic from an acute attack of porphyria is to eliminate any precipitating factor. The main precipitating factors for acute porphyric attacks are certain drugs (see below), excessive alcohol consumption, sexual hormones, starvation, and stress. Before the application of any drug to a porphyria patient, it must be confirmed that the drug is safe in acute porphyria. The only exception from this rule is an acutely life-threatening situation where any life-saving drug shall be given and an eventual exacerbation of porphyria will be managed by heme application (see below). Drug descriptions such as package inserts are not a reliable information source, as they frequently do not indicate whether a substance is unsafe in acute porphyria. Instead, the most reliable and up-to-date sources on drug safety in acute porphyrias are the web pages from recommended porphyria centers (e. g., with information in different European languages, http://www.porphyria-europe.com; and, in French, http://perso.wanadoo.fr/porphyries-france/medicaeti.htm).

The severe colicky abdominal pain of an acute attack necessitates adequate analgesia, specifically opiates. These types of narcotics should not be withheld because of fear of dependency induction. A combination of analgesia with chlorpromazine up to 75 mg/day in an infusion has been beneficial to some of our patients. Next, the frequently present hyponatremia that eventually is a symptom of syndrome of inappropriate antidiuretic hormone secretion (SIADH) and an eventual hypomagnesemia should be corrected parenterally. Hypertension is best treated by beta-blocking agents. A close supervision of the patients is required, as severe hypotension as well as life-threatening cardiac arrhythmias have been observed.

Lastly, the causal treatment by glucose and heme (Normosang or Panhematin) is effective to reduce exaggerated heme synthesis by repression of the induced hepatic ALA synthase (Herrick et al. 1989). If a patient suffers from early or mild symptoms of an acute attack, they should be advised to consume increased amounts of carbohydrates (200–500 g/day). If inappetite or nausea prevents consumption of food, patients may change to fluids enriched with glucose. In the case of recurrent attacks, the number of carbohydrate-enriched meals may be increased to five per day in periods of increased vulnerability such as the premenstruum in certain women.

If an attack progresses, including repeated vomiting and severe abdominal pain necessitating hospitalization, a 24-h trial with intravenous glucose (200–500 g/24 h) has been recommended. In our experience, glucose is ineffective in hospitalized patients. Therefore, we quickly institute heme administration 3–5 mg/kg in a short infusion once a day for 3–5 days with additional intravenous glucose. Heme administration should immediately be instituted in any patient

who develops motor pareses. Heme infusion may cause severe phlebitis. Mixing the heme solution into a 4% albumin for the infusion and extensively rinsing the vein with physiological sodium chloride solution afterward reduces the risk of phlebitis. The levels of urinary porphyrin precursors significantly drop within 24 h after heme institution, and the abdominal symptoms disappear within 2–3 days.

A few patients suffer from repeated attacks. They are mainly young adult women, and their attacks are often during the premenstrual period. We recommend that such patients should be referred as soon as possible to a clinically experienced porphyria specialist. A number of porphyria centers within Europe are listed on the web pages mentioned above.

Management During Latency Period

Any newly diagnosed individual with acute porphyria should be extensively informed to avoid any precipitating factors. Counseling the patient is very effective as secondary prevention of further attacks. As the three frequent acute porphyrias (AIP, PV, and HC) are autosomal dominant diseases, 50% of direct relatives also carry the mutated gene. Family screening and counseling of affected family members to avoid precipitating factors is recommended. Information support in several languages for both patients and affected family members can be downloaded from http://www.porphyria-europe.com.

A minority of patients with acute porphyrias, especially with PV (disorder 31.6), present with skin symptoms exclusively rather than with the classic symptom of acute abdominal pain. These patients should be counseled on precipitating factors. The therapy for their skin symptoms is given below.

Treatment of Photosensitivity

Both acute as well as nonacute porphyrias may manifest themselves in an individual patient with photosensitivity as the only symptom. As treatment modalities differ between the different porphyria disorders, an unambiguous diagnosis has to be established first by adequate biochemical testing and eventually molecular testing (Minder and Schneider 2003).

Generally, sunlight should be avoided in all photosensitizing porphyrias. Physical barriers such as hats, gloves, long shirts and trousers or staying indoors are most effective. As stated above, skin ointments must be protective at 404-nm (visible) light to be efficacious. Artificial lightening does not cause harm to porphyria patients, with two exceptions: (1) intense theatre lighting during liver transplantation in EPP, and (2) phototherapy of the newborn with congenital erythropoietic porphyria (CEP) or hereditary coproporphyria (HEP).

In addition to these general measures, patients with skin blisters due to one of the two acute porphyrias PV (disorder 31.6) and HC (31.5), should eliminate eventual precipitating factors (as outlined above).

PCT (disorder 31.4) is the only porphyria with a highly effective treatment option. Iron overload (hemosiderosis of the liver) is inhibitory to the hepatic enzyme uroporphyrinogen decarboxylase. Iron removal by phlebotomies reactivates this enzyme and photosensitivity disappears. Phlebotomies (400 ml once or twice a week) should be performed until the photosensitivity dissolves or the patient develops iron-deficient anemia. Patients should be informed that porphyria symptoms may reappear, necessitating a new phlebotomy course after some years. If no signs of increased body iron load is present or in patients with iron-deficient anemia, lowdose chloroquine or hydroxychloroquine is effective. High-dose chloroquine in PCT patients may cause acute liver failure! PCT may develop in women during oral hormone replacement therapy (HRT). A percutaneous hormone application avoids the first liver passage and apparently is better tolerated. If chronic hemodialysis provokes PCT, it can effectively be treated by application of recombinant erythropoietin or an increase in its dose to improve erythropoiesis. If hemodialysis is complicated by severe iron overload, erythropoietin may be combined with phlebotomies to remove excessive body iron stores.

In EPP (disorder 31.7), a minority of patients profit from beta-carotene treatment. The dosage should be adjusted according to blood levels. A small percentage of EPP patients develop acute or subacute liver failure due to intrahepatic protoporphyrin accumulation. The liver function, protoporphyrin blood level, and urinary porphyrin excretion should therefore be monitored once or twice a year in every EPP patient. In the case of impaired liver function, a trial with ursodesoxy cholic acid, to improve protoporphyrin excretion into the bile, may be made. If a terminal liver failure develops, liver transplantation can save the life of the patient. To prevent harm by the intense theatre lighting during transplantation, preoperative blood exchange reducing protoporphyrin blood level and light filters absorbing at 404 nm have been recommended. Liver transplantation does not cure EPP. Further, recurrence of protoporphyrin-induced damage in the transplanted liver has been described.

The most severe porphyrin-induced photosensitivity is seen in patients with CEP (disorder 31.3) or HEP (disorder 31.8), with mutilating scarring in light-exposed skin areas such as face and hands. Photosensitivity starts in the neonatal period. Thus, phototherapy to reduce neonatal hyperbilirubinemia may cause lethal skin burning. Patients with CEP or HEP diagnosed early in life should be evaluated for bone marrow transplantation. It is the only curative therapy option, and the severity of the disease urges for any effective treatment even with a risk of mortality. CEP and HEP patients not selected for bone marrow transplantation must protect themselves from sunlight carefully as outlined above. Beta-carotene in a dosage as for EPP may slightly ameliorate the symptoms. Late-onset cases with milder disease not distinguishable clinically from PCT have been described. They also will profit from any means to reduce sunlight exposure.

Nomenclature

No	Disorder	Abdominal pain, neurological damage	Photosensitivity (only in light-exposed skin areas)	Gene symbol	OMIM No.
31.1	ALA-dehydratase deficiency (ALAD-D)	Yes	No	*ALAD*	125270
31.2	Acute intermittent porphyria (AIP)	Yes	No	*HMBS* *PBGD* *UPS*	176000
31.3	Congenital erythropoietic porphyria (CEP)	No	Skin blisters, scarring and severe mutilations, acute and chronic skin pain	*UROS*	263700
31.4	Porphyria cutanea tarda (PCT)	No	Skin blisters	*UROD*	176100
31.5	Hereditary coproporphyria (HC)	Yes	Skin blisters	*CPO*	121300
31.6	Porphyria variegata (PV)	Yes	Skin blisters	*PPOX*	176200
31.7	Erythropoietic protoporphyria (EPP)	No	Acute, severely painful photodermatosis, edema	*FECH* *FCE*	177000
31.8	Hepatoerythropoietic porphyria (HEP)	No	Skin blisters, scarring and severe mutilations, acute and chronic skin pain	*UROD*	176100
31.9	Variant porphyria(s) unclassified	Variable	Variable		

31.2 Treatment

■ Acute Porphyrias

31.1 ALAD-D
31.2 AIP
31.5 HC
31.6 PV

Table 31.1. Principles of treatment of an acute attack of porphyria

No	Disorder	Preventive measure	Treatment modalities (dependent on severity of symptoms)
31.1	ALA-dehydratase deficiency	Avoid: precipitating drugs, alcohol excess, hormones, starvation, (stress)	Eliminate precipitating factors, use only drugs approved to be safe (see below); oral carbohydrates (200–500 g/day); adequate pain therapy (opiates, eventually combined with chlorpromazine); intravenous carbohydrates (200 or 500 g/day); heme arginate or panhematin 3–5 mg/kg per day 3–5 days intravenously; correction of electrolyte imbalance (especially sodium, magnesia); treat hypertension
31.2	Acute intermittent porphyria		
31.5	Hereditary copro-porphyria		
31.6	Porphyria variegata		
31.9	Variant porphyria(s) unclassified		

■ Photosensitivity in Nonacute Porphyrias

31.3 CEP
31.4 PCT
31.5 HC
31.6 PV
31.7 EPP
31.8 HEP

Table 31.2. Treatment principles of skin symptoms

No	Disorder	Preventive measure[a]	Treatment modalities (dependent on severity of symptoms)
31.3	Congenital erythropoietic porphyria	Strict avoidance of sun light Sun-blocking ointments	Bone marrow transplantation in early childhood; blood transfusion to correct severe anemia; removal of excessive iron by chelation therapy, if present
31.4	Porphyria cutanea tarda	Prevent/treat iron overload Eliminate alcohol overconsumption Stop oral hormone replacement therapy (hrt) or replace it by percutanous application	Weekly phlebotomies and/or low-dose chloroquine or hydroxychloroquine (125 mg twice a week)
31.5	Hereditary coproporphyria	Eliminate precipitating factors as outlined under Treatment of Acute Attacks	No specific treatment available
31.6	Porphyria variegata	Same as 31.5	Same as 31.5
31.7	Erythropoietic protoporphyria	Avoid liver-damaging factors Monitor liver function 1–2 times a year	Beta-carotene (blood level of 600–800 µg/100 ml or 11–15 µmol/l)
31.8	Hepatoerythropoietic porphyria	Strict avoidance of sunlight Sun-blocking ointments	Bone marrow transplantation in early childhood; blood transfusion to correct severe anemia; removal of excessive iron by chelation therapy, if present
31.9	Variant porphyria(s) unclassified	Dependent on the type of porphyria present	Dependent on the type of porphyria present

[a] General measures for all photosensitizing porphyrias: avoidance of exposure to sunlight; it may be detrimental even behind window glass! Only ointments blocking light at 404 nm are effective

31.3 Alternative Therapies/Experimental Trials

- Photosensitivity

In a case report on HEP (disorder 31.8) (Horina and Wolf 2000) and one on CEP (disorder 31.3), recombinant human (rh) erythropoietin has been found to improve not only the severe anemia but also the skin symptoms.

- *EPP (disorder 31.7)*

Mathews-Roth et al. (2002) published recently a study on oral cysteine being effective in some EPP patients.

- Acute Porphyrias (ALAD-D, AIP, HC, and PV)

Tin protoporphyrin and zinc mesoporphyrin has been shown in animal studies to inhibit heme oxygenase (Schuurmans et al. 2001; Dover et al. 1993). It is hypothesized that a reduced heme degradation would increase the so-called regulatory heme pool and by this repress the induced activity of ALA synthase in the acute porphyrias. Tin protoporphyrin is toxic and should not be used in patients. The available preliminary clinical data of zinc mesoporphyrin do not support the efficacy of this new approach to treat acute porphyrias (Fig. 31.1). In otherwise not-manageable cases of acute porphyrias Liver transplantation should be considered, as this treatment has been efficacious in a few cases.

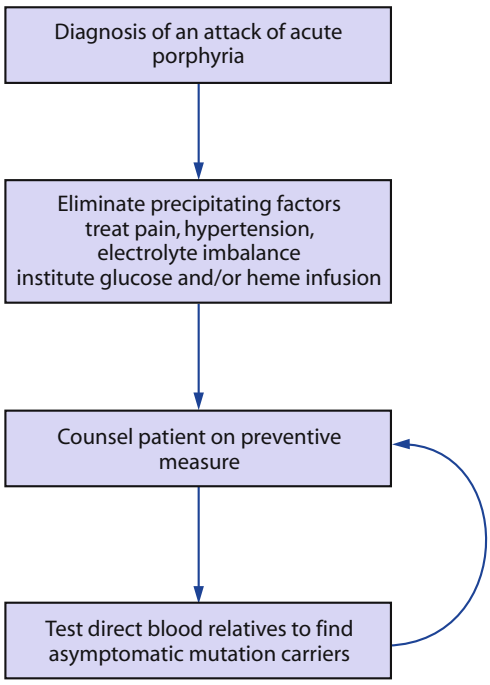

Fig. 31.1. Acute porphyrias

31.4 Follow-up/Monitoring

All porphyrias but EPP are only treated if patients are symptomatic. In the disorder EPP, liver function requires a follow-up as outlined above once to twice a year to detect its detoriation as early as possible. Further, EPP patients are prone to gallstones.

The acute porphyrias increase the risk of primary liver cancer, but there are no general recommendations yet to regularly monitor such patients (Antant et al. 1998).

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32 Disorders of Bile Acid Synthesis

Peter T. Clayton

32.1 Introduction

This chapter summarises the treatment of inborn errors of bile acid synthesis in patients that present in infancy or childhood with cholestatic liver disease and malabsorption of fat and fat-soluble vitamins. Synthesis of chenodeoxycholic acid and cholic acid is essential for activating bile solute pumps (via nuclear receptors such as the farnesoid X receptor) and for fuelling bile flow. Transport of bile acids leads to the flow of water. Abnormal bile acids may actually inhibit the canalicular bile salt pump; thus impaired bile flow (cholestasis) and an increased plasma concentration of conjugated bilirubin commonly occur in bile acid synthesis defects. The cholestasis, in infants at least, is usually associated with signs of hepatocyte damage (raised transaminases, a giant cell hepatitis on biopsy). In most bile acid synthesis defects, the liver function tests and biopsy appearances can be normalised by treatment with chenodeoxycholic acid and/or cholic acid. In some, liver damage progresses, requiring liver transplantation.

Reduced secretion of chenodeoxycholic acid and cholic acid into the intestine impairs the digestion and absorption of fats and fat-soluble vitamins. Thus inborn errors of bile acid synthesis can present dramatically in infancy with bleeding due to vitamin K deficiency, or fits due to hypocalcaemia caused by severe rickets. More insidious presentations in infancy include failure to thrive, with steatorrhoea and rickets or progressive intrahepatic cholestasis. Fat-soluble vitamins are usually only required in the early stages of treatment; once the bile acid deficiency is corrected, a supplement is not required. Indeed care should be taken not to give high doses of vitamin D for a prolonged period after bile acid replacement therapy has been started or hypercalcaemia will ensue.

In several of the peroxisomal disorders, there is impaired bile acid synthesis and some impairment of liver function. However, other pathways are often impaired and neurological disease usually predominates. These disorders are considered elsewhere, with one exception: α-methyl-acyl-CoA racemase deficiency can present with neonatal cholestasis and is considered in this chapter.

After infancy the major route for catabolism of cholesterol occurs via a bile acid synthesis pathway that starts with the conversion of cholesterol to 7α-

hydroxycholesterol. This rate-limiting step for the pathway is subject to feedback inhibition by bile acids. Defects in cholesterol 7α-hydroxylase have recently been shown to lead to hypercholesterolaemia.

Cholesterol and its saturated analogue cholestanol accumulate in tissues in cerebrotendinous xanthomatosis (CTX), giving rise to tendon xanthomata, atheroma and dementia. The defect is in cholesterol 27-hydroxylase, which is important both in the "neutral" pathway for bile acid synthesis, which starts with conversion of cholesterol to 7α-hydroxycholesterol, and in the "acidic" pathway, which starts with conversion of cholesterol to 27-hydroxycholesterol. The reasons for accumulation of cholesterol and cholestanol in the tissues are complex. Conversion of cholesterol to oxysterols and C27 bile acids may represent a significant route for elimination of cholesterol from extrahepatic tissues. However, there is also evidence of conversion of 7α-hydroxycholesterol to cholestanol. Other intermediates along the cholesterol 7α-hydroxylase pathway are converted to bile alcohol glucuronides and excreted in the urine in CTX. Treatment with chenodeoxycholic acid reduces the rate of synthesis of cholestanol and the urinary excretion of bile alcohols. One mechanism is likely to be inhibition of cholesterol 7α-hydroxylase. Certainly ursodeoxycholic acid, which does not inhibit cholesterol 7α-hydroxylase, is ineffective in reducing bile alcohol excretion. Chenodeoxycholic acid also reduces cholesterol synthesis in CTX. This may be due to its ability to inhibit HMG-CoA reductase. Whatever the exact mechanisms of action of chenodeoxycholic acid are, what is observed clinically is a reversal of the patient's neurological disability, with clearing of the dementia, improved orientation, a rise in intelligence quotient and enhanced strength and independence. The magnetic resonance (MR) images of the brain may not show any improvement, and osteoporosis, another feature of CTX, also appears to be resistant to chenodeoxycholic acid treatment.

32.2 Nomenclature

No.	Disorder (symbol)	Definitions/comment	Gene symbol	OMIM No.
32.1	3β-Hydroxy-Δ^5-C_{27}-steroid dehydrogenase (3β-HSD) deficiency	See Clayton et al. 1987; Ichimiya et al. 1990, 1991; Horslen et al. 1992; Clayton 1991; Akobeng et al. 1999; Schwarz et al. 2000	*C27-3BETA-HSD* *HSD3B7*	607764
32.2	Δ^4-3-Oxosteroid 5β-reductase deficiency (5β-reductase deficiency)[a]	See Clayton et al. 1996; Lemonde et al. 2004	*SRD5B1* *AKR1D1*	235555 604741
32.3	Sterol 27-hydroxylase deficiency (Cerebrotendinous xanthomatosis, CTX)	See Clayton et al. 1995, 2002; Berginer et al. 1984, 1994	*CYP27A1*	213700 606530
32.4	Oxysterol 7α-hydroxylase deficiency	Reference Setchell et al. 1998	*CYP7B1*	603711
32.5	α-Methyl-acyl-CoA racemase deficiency	See Ferdinandusse et al. 2000; Van Veldhoven et al. 2001; Setchell et al. 2003	*AMACR*	604489
32.6	Cholesterol 7α-hydroxylase deficiency	See Pullinger et al. 2002	*CYP7A1*	118455

[a] Only patients proven to have mutations in the Δ^4-3-oxosteroid 5β-reductase gene have been included.

Disorders of peroxisome biogenesis and defects of peroxisomal β-oxidation (such as D-bifunctional protein deficiency) affect bile acid synthesis but are considered elsewhere. α-Methyl-acyl-CoA racemase is located both in peroxisomes and mitochondria; the deficiency disorder is considered here because, like disorders 32.1–32.4, it can present with neonatal cholestatic jaundice without neurological abnormalities.

32.3 Treatment

■ Treatment of the Consequences of Fat-Soluble Vitamin Malabsorption

For treatment strategies, See Fig. 32.1.

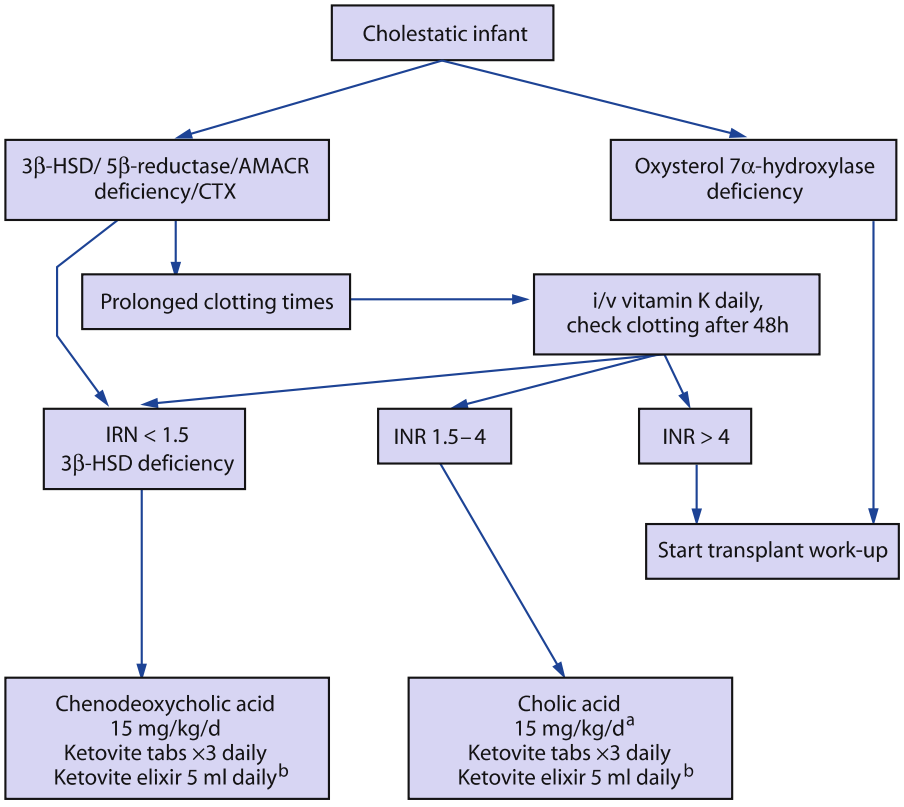

Fig. 32.1. Initial treatment of bile acid synthesis defects accompanied by choleastasis. *a*, or cholic acid 7.5 mg/kg per day plus chenodeoxycholic acid 7.5 mg/kg per day. *b*, rapid healing of rickets may require more vitamin D (as 1,25-dihydroxycholecalciferol) and a calcium supplement

32.1 3β-Hydroxysteroid-Δ^5 – C_{27}-steroid dehydrogenase deficiency (3β-HSD deficiency)
32.2 Δ^4-3-Oxosteroid 5β-reductase deficiency (5β-reductase deficiency)
32.3 Sterol 27-hydroxylase deficiency (cerbrotendinous xanthomatosis, CTX)
32.5 α-Methyl-acyl-CoA racemase deficiency

Treatment for	Medication	Dose	Route	Target
Vitamin K-deficient bleeding	Vitamin K (phytomenadione)	1 mg daily	i.v. slowly[a]	Normal clotting times
Hypocalcaemia (fits, tetany)	10% Calcium gluconate (plus 1,25-dihydroxycholecacliferol; see below)	0.1–0.3 ml/kg per dose	i.v. slowly	Normal ionised calcium
Rickets	1,25-Dihydroxycholecalciferol	0.25–1.00 µg/day	Oral	Normal calcium, healing of rickets. Avoidance of hypercalcaemia
Basic defect	Chenodeoxycholic acid and/or Cholic acid	See individual disorders	Oral	Normal liver function tests etc.
Vitamin E deficiency	Alpha-tocopherol acetate	50 mg	Oral	Normal plasma vitamin E
Vitamin A deficiency	Vitamin A	2500 U, e. g., Ketovite elixir 5 ml daily	Oral	Normal plasma vitamin A

[a] Immediate treatment of a coagulopathy caused by vitamin K deficiency may be life-saving, but intravenous phytomenadione can cause anaphylaxis

Once coagulopathy has been corrected and rickets healed, bile acid replacement therapy should be adequate to prevent any manifestations of fat-soluble vitamin malabsorption; however, it is wise to continue for approximately 3 months after starting treatment with a vitamin supplement containing all four fat-soluble vitamins, e. g., Ketovite tabs, iii daily (provides 15 mg α-tocopheryl acetate and 1.5 mg acetomenaphthone), plus ketovite elixir 5 ml daily (provides 2500 U of vitamin A and 400 U ergocalciferol).

32.1 3β-Hydroxysteroid-Δ^5 – C_{27}-steroid dehydrogenase deficiency (3β-HSD deficiency)

Condition	Medication	Dose	Route	Target
Basic defect	Chenodeoxycholic acid			Normalisation of liver function tests, prevention of fat-soluble vitamin malabsorption
	Initial dose	12–18 mg/kg per day	Oral	
	After 2 months	9–12 mg/kg per day	Oral	
	Or			
	Chenodeoxycholic acid plus	7 mg/kg per day	Oral	
	Cholic acid	7 mg/kg per day	Oral	
Consequences of fat-soluble vitamin malabsorption	See above	See above	See above	See above

32.2 Δ^4-3-Oxosteroid 5β-reductase deficiency (5β-reductase deficiency)

Condition	Medication	Dose	Route	Targets
Basic defect	Chenodeoxycholic acid plus	8 mg/kg per day	Oral	Normal liver function tests
	Cholic acid or	8 mg/kg per day	Oral	
	Cholic acid alone	15 mg/kg per day	Oral	
Consequences of fat-soluble vitamin malabsorption	See above	See above	See above	See above
Failure to respond to bile acid replacement	Liver transplant			

Patients with 5β-reductase deficiency usually present with cholestatic liver disease in infancy. It is important to distinguish patients with mutations in the 5β-reductase gene from patients in whom excretion of 3-oxo-Δ^4 bile acids is secondary to severe liver damage caused by another genetic disorder (e. g., tyrosinaemia) or an acquired disorder (e. g., hepatitis B).

32.3 Sterol 27-hydroxylase deficiency (cerbrotendinous xanthomatosis, CTX)

Condition	Medication	Dose	Route	Targets
Cholestasis in infancy	Cholic acid	7–15 mg/kg per day	Oral	Normal liver function tests
Fat-soluble vitamin deficiencies	See above	See above	See above	See above
Dementia, neurological disease, xanthomata	Chenodeoxycholic acid	750 mg daily (adult dose)	Oral	Reduced bile alcohol excretion, plasma cholestanol, improved neurology

32.4 Oxysterol 7a-hydroxylase deficiency

Condition	Medication	Dose	Route	Targets
Basic defect	Liver transplant			
Coagulopathy due to vit K deficiency	Vitamin K (phytomenadione)	1 mg daily	i.v. slowly	Normal clotting times
Rickets	1,25-Dihydroxy-cholecalciferol	0.25–1.00 μg/day	Oral	Normal calcium, healing of rickets[a]. Avoidance of hypercalcaemia
Vitamin E deficiency	α-Tocopheryl polyethyleneglycol 1000 succinate	25 U/kg twice daily	Oral	Normal plasma vitamin E[a]
Vitamin A deficiency	Water-miscible vitamin A, e. g., Aquasol A	0.1 ml (5000 U) daily	Oral	Normal plasma vitamin A

The liver disease does not respond to bile acid treatment. Cholestasis will persist until liver transplantation can be undertaken. Therefore these children require forms of the fat-soluble vitamins that are water soluble or can be given by injection

[a] Intramuscular preparation may be required

32.5 α-Methyl-acyl-CoA racemase deficiency

Condition	Medication	Dose	Route	Targets
Cholestasis in infancy	Cholic acid	15 mg/kg per day	Oral	Normalisation of liver function tests
Fat-soluble vitamin deficiencies	See above	See above	See above	See above
High plasma pristanate and phytanante	Low phytanic acid diet			Pristanate < 5 mM Prevention of neuropathy, retinopathy

32.6 Cholesterol 7α-hydroxylase deficiency

Condition	Medication	Dose	Route	Targets
Hyperlipidaemia	Atorvastatin plus	40–80 mg/day (adult dose)	Oral	Normal cholesterol
	Niacin	4–7 g/day (adult dose)	Oral	

32.4 Alternative Therapies/Experimental Trials

■ *32.3 Cerebrotendinous xanthomatosis*

Mode of treatment	Dose	Route	Comment	Reference
Lovastatin (mevinolin; HMG-CoA-reductase inhibitor)	6.25 mg twice daily (adult dose)	Oral	Insufficient data to assess efficacy	Lewis et al. 1983
Low-density lipoprotein apheresis			Insufficient data to assess efficacy	Mimura et al. 1993

32.5 Follow-up/Monitoring

Cholestatic liver disease due to:-

32.1 3β-Hydroxysteroid-Δ^5 – C_{27}-steroid dehydrogenase deficiency (3β-HSD deficiency)
32.2 Δ^4-3-Oxosteroid 5β-reductase deficiency (5β-reductase deficiency)
32.3 Sterol 27-hydroxylase deficiency (cerbrotendinous xanthomatosis, CTX)
32.5 α-Methyl-acyl-CoA racemase deficiency

Time after diagnosis	Outcome measure	Target
1 month	Weight gain	Catch-up
> 1 month	Weight gain	Normal
> 1 month	Steatorrhoea	Cured
> 1–6 month	Liver function tests	Normal
> 1–6 month	Fat-soluble vitamins	No deficiency, rickets healed
> 1 month	Plasma concentration of chenodeoxycholic acid (if used for treatment)	1–20 μM[a]
> 1 month	Plasma concentration of cholic acid (if used for treatment)	1–15 μM
> 6 month	Plasma concentration of chenodeoxycholic acid (if used for treatment)	0.5–15 μM
> 6 month	Plasma concentration of cholic acid (if used for treatment)	0.2–5 μM

[a] High concentrations of chenodeoxycholic acid with LFT's that are not improving or are deteriorating suggests the need to use a reduced dose and/or substitute with cholic acid.

Specific Targets

32.1 3β-Hydroxysteroid-Δ^5 – C_{27}-steroid dehydrogenase deficiency (3β-HSD deficiency)

Time after diagnosis	Outcome measure	Target
> 2 month	Plasma concentration of Δ^5-C_{24} bile acids	< 1.0 µM
> 2 month	Urinary excretion of Δ^5-C_{24} bile acids	Less than excretion of conjugates of dihydroxy- and tri-hydroxy-cholanoic acids

32.2 Δ^4-3-Oxosteroid 5β-reductase deficiency (5β-reductase deficiency)

Time after diagnosis	Outcome measure	Target
> 2 mo	Plasma concentration of 3-oxo Δ^4 bile acids	< 0.5 µM
> 2 mo	Urinary excretion of 3-oxo Δ^4 bile acids	< 50% pre-treatment value

32.3 Sterol 27-hydroxylase deficiency (cerbrotendinous xanthomatosis, CTX)

Time after diagnosis	Outcome measure	Target
> 2 month	Urinary excretion of bile alcohol glucuronides	< 25% pretreatment value
> 6 month	Urinary excretion of bile alcohol glucuronides	< 5% pretreatment value
> 2 month	Plasma 5β-cholestane-3α,7α,12α,25-tetrol	< 2 µM
> 6 month	Plasma 5β-cholestane-3α,7α,12α,25-tetrol	< 0.5 µM
> 6 month	Plasma cholestanol	Lower than pretreatment value
> 1 year	IQ, neurological signs	No deterioration/improvement

32.5 α-Methyl-acyl-CoA racemase deficiency

Time after diagnosis	Outcome measure	Target
Depends on age at diagnosis	Neurological examination Nerve conduction Electroretinogram	Avoidance of neuropathy, retinopathy

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33 Disorders of Copper, Zinc, and Iron Metabolism

Eve A. Roberts

33.1 Introduction

Metabolic diseases associated with abnormal disposition of metals are generally rare, with the exception of hereditary hemochromatosis (HFE1) in northern European populations. They are highly disparate disorders.

33.1 Wilson disease

Wilson disease (hepatolenticular degeneration) is an autosomal recessive disorder of copper disposition in the liver and certain other organs, notably the brain, kidneys, mammary glands, and placenta. It is associated with copper overload in the liver and secondary accumulation of copper in certain parts of the brain, cornea (Kaiser-Fleischer ring), and in the kidneys, heart, and synovia. Wilson disease can present as liver disease, progressive neurological disease, or psychiatric illness (Roberts and Schilsky 2003). The hepatic presentation usually occurs at younger ages. Wilson disease is fatal if not treated, but with effective treatment, especially if commenced early (ideally in the presymptomatic stage), the outlook for a normal healthy life is excellent. If a specific treatment must be discontinued because of adverse side-effects, alternate treatment must be substituted. Treatment should be continued through pregnancy. Dietary management by itself is inadequate, but foods containing very high concentrations of copper (shellfish, nuts, chocolate, mushrooms, and organ meats) should be avoided, especially in the 1st year of treatment. Liver transplantation is indicated for patients unresponsive to medical treatment and for those with fulminant hepatic failure.

33.2 Menkes disease

Menkes disease is a rare (1:250,000) complex disorder of copper disposition leading to systemic copper insufficiency. The major features of Menkes disease involve neurodegeneration, vascular (usually arterial) abnormalities, and abnormal hair structure (pili torti: occasioning the disease's alternative name of "kinky hair" syndrome). Detailed examination of the hair shaft reveals typical changes. Treatment with copper supplementation provided as subcutaneous in-

jections of copper-histidine (Sarkar et al. 1993; Christodoulou et al. 1998) must be started before 3 weeks of age if severe neurological disease is to be avoided. Preemptive treatment of male sibs subsequent to the proband in a family may produce the best clinical outcome. Life expectancy in Menkes disease is reduced, usually to less than 10 years.

A mild variant of Menkes disease has been reported with later onset of symptoms and relative sparing of the central nervous system. Although these children may have the same facies, typical skin and hair abnormalities, their neurological disease is often limited to ataxia and dysarthria. The biological basis for this milder form of Menkes disease is not known.

33.3 Occipital Horn syndrome

This is a mild allelic form of Menkes disease, whose phenotypic mechanism is unknown.

33.4 Acrodermatitis enteropathica

This rare autosomal recessive disorder presents clinically with a constellation of findings: typical rash involving the perineum and perianal region, hands, and feet; diarrhea, alopecia, and visual disorders (photophobia). Poor growth and recurrent infections, associated with immunodeficiency, may occur. Most patients do not have all the possible clinical features. The disorder typically becomes evident at the time of weaning. The diagnosis is usually confirmed by finding very low concentrations of serum zinc; urinary zinc excretion is also very low. Classic acrodermatitis enteropathica is due to mutations in the *ZIP4* gene implicated in zinc uptake (Dufner-Beattie et al. 2003). Treatment is with zinc replacement and is life-long and may need to be increased in times of increased growth demands, such as during adolescence or pregnancy.

A skin disorder resembling acrodermatitis enteropathica has been associated with the urea cycle defect involving ornithine transcarbamylase (Lee et al. 2002).

33.5 Congenital cholestasis with hepatic zinc accumulation

An infantile cholestatic liver disease with hepatic zinc accumulation has been described in North American Indians mainly from Ontario, Canada, most of whom belonged to a single extended kindred. Two unrelated North American Indian children appeared to have extrahepatic biliary atresia clinically and at laparotomy (Phillips et al. 1996). The pathogenesis of this zinc-overload liver disease is not known. Treatment is general management of chronic cholestatic liver disease and orthotopic liver transplantation if indicated.

33.6 Hemochromatosis

The term "hemochromatosis" refers to iron accumulation in parenchmyal cells of the liver and other tissues. Approximately 90% of primary hemochromatosis is due to mutations in the *HFE* gene. Other types of primary hemochromatosis are rare. Secondary hemochromatosis is usually related to congenital hemolytic anemia requiring chronic transfusion or to dietary excess in a genetically susceptible individual (Bantu siderosis).

33.6.1 Hereditary hemochromatosis, classic form

Classic hereditary hemochromatosis with abnormal iron uptake from the intestinal tract is due to mutations in the gene HFE on chromosome 6 near the HLA-A region (Feder et al. 1996). Classic hereditary hemochromatosis usually becomes symptomatic in men at 40–50 years of age, somewhat later in women. Arthropathy, cardiac disease, and pituitary dysfunction (with loss of libido) are important early extrahepatic manifestations; skin pigmentation and diabetes mellitus tend to be later features. Liver disease is common and may lead to cirrhosis and hepatocellular carcinoma. Early diagnosis (based on elevated fasting transferrin saturation and serum ferritin, abnormal serum aminotransferases, and positive genetic testing) permits reduction of total body iron load by phlebotomy (Tavill 2001). Treatment is indicated even if cirrhosis has developed, and symptoms relating to extrahepatic disease may improve on treatment. Vitamin C supplements should be avoided.

33.6.2 Juvenile hemochromatosis

This iron-accumulation disease usually becomes symptomatic in adolescence (Camaschella et al. 2002). Although the liver is involved as in classic hereditary hemochromatosis, affected individuals usually have severe cardiac disease which dominates the clinical presentation. Arthropathy and hypogonadism may also be present. The typical biochemical profile includes extremely high serum ferritin and transferrin saturation. The genetic basis *HFE2* is on chromosome 1q21 (Papnikolaou et al. 2004). Its gene product, hemojuvelin, may affect hepcidin expression. A clinically indistinguishable disease has recently been described in two kindred with mutations in hepcidin, a protein that plays a role in regulating intestinal iron absorption (Roetto et al. 2002). Treatment with phlebotomy is indicated.

33.6.3 TFR2 deficiency

This rare form of hemochromatosis is due to mutations in the transferrin receptor-2 gene (on 7q22). Clinical features are similar to those found with mutations in *HFE* (Roetto et al. 2002).

33.6.4 Ferroportin deficiency

This is an important cause of hereditary hemochromatosis not related to the *HFE* locus. The disorder is inherited in an autosomal dominant pattern (Montosi et al. 2001; Njajou et al. 2001). Patients present with anemia, diabetes, and arthritis. The serum ferritin is elevated but transferrin saturation is normal. Diagnosis depends on genetic sequencing. Treatment is by phlebotomy is difficult because of anemia.

33.6.5 Perinatal hemochromatosis

Perinatal hemochromatosis (also known as neonatal hemochromatosis or neonatal iron-storage disorder) comprises a group of disorders with similar clinical appearance: neonatal liver failure accompanied by iron overload in the liver, pancreas, heart, and other organs except the reticuloendothelial system (Goldfischer et al. 1981; Knisely et al. 2003). The extent of organ damage indicates prenatal injury. The disease mechanism is not known. In some cases congenital infection with parvovirus B19 may be the etiology; nevertheless, when possible etiologies have been excluded, a group of cases remains with an apparent genetic, or at least familial, basis. Mutations in *HFE* are not implicated.

Most affected infants present shortly after birth, although a few have been diagnosed later in the neonatal period (Kelly et al. 2001), with classic chronic-pattern neonatal liver failure. The liver and certain other organs (pancreas, kidneys, adrenal glands, and heart – not the reticuloendothelial system) show marked iron accumulation. Histologically apparent iron deposition in salivary glands on buccal biopsy or evidence of iron overload by magnetic resonance imaging of the liver and pancreas supports the diagnosis.

Supportive treatment in a neonatal intensive care unit is essential; liver transplantation is usually required. A multiple-drug regimen, called the "antioxidant cocktail" (Shamieh et al. 1993), has been used extensively with some success. Not all infants respond to this regimen (Sigurdsson et al. 1998), but early institution of treatment may favor success. Monitoring subsequent pregnancies closely appears critically important. Surviving infants appear to stabilize clinically; they may develop cirrhosis or have no residual liver disease. Incidental hepatocellular carcinoma has been reported in three infants. Recurrent iron accumulation in the liver graft occurred in one infant after transplantation.

33.6.6 Perinatal hemochromatosis with renal tubular dysgenesis

This condition is not necessarily a separate disorder from perinatal hemochromatosis. In addition to neonatal liver failure with characteristics of perinatal hemochromatosis, proximal convoluted tubules are abnormal (Bale et al. 1994). The prognosis is even more guarded than for perinatal hemochromatosis.

33.6.7 Trichohepatic-enteric syndrome

This constellation of hair abnormalities, hepatic dysfunction with iron overload, and intractable diarrhea has been reported in one or two families (Verloes et al. 1997). This syndrome may be related to perinatal hemochromatosis, but its basis has not been determined.

33.6.8 GRACILE syndrome (Fellman syndrome)

GRACILE syndrome was first reported in Finnish kindreds but has since been identified in Turkish and British patients. The classic clinical features include growth retardation, cholestatic liver disease, hepatic iron overload, severe lactic acidosis, and early death (Fellman et al. 1998). This rare disorder is due to mutations in the *BCS1L* gene, which encodes a protein in the mitochondrial inner membrane essential for assembly of complex III in the mitochondrial respiratory chain (Visapaa et al. 2002). Treatments used thus far have proven ineffective.

33.7 Aceruloplasminemia

Defective ceruloplasmin production is inherited as an autosomal recessive disorder; the ceruloplasmin gene is on 3q25. Ceruloplasmin is a ferroxidase; in its absence copper disposition remains normal, but iron accumulation occurs in the liver and in other organs. Patients with aceruloplasminemia develop anemia, retinal degeneration, diabetes mellitus, and neurodegeneration involving the cortex and basal ganglia, manifested as ataxia (most common), involuntary movement disorders, parkinsonism, and dementia (Miyajima et al. 2003). Symptoms typically begin in the third and fourth decades. Treatment of the iron overload is difficult, in part because ceruloplasmin is involved in the mechanism by which iron exits tissues, and aceruloplasminemia may be refractory to chelating agents such as desferroxamine.

33.2 Nomenclature

	Disease	Defect	Gene	OMIM No.
33.1	Wilson disease (hepatolenticular degeneration)	Hepatic Cu overload; defective synthesis of holoceruloplasmin and inefficient biliary excretion of Cu	*ATP7B*	277900
33.2	Menkes disease	Systemic Cu deficiency; defective intestinal uptake of Cu; decreased synthesis of Cu-containing enzymes	*ATP7A*	309400
	1. "Classic" form	–		
	2. "Mild" form (atypical)	–		
33.3	Occipital Horn syndrome	Defective extrahepatic Cu disposition as for Menkes disease	*ATP7A*	304150
33.4	Acrodermatitis enteropathica	Systemic Zn deficiency due to abnormal intestinal absorption of Zn	*ZIP4*	201100
33.5	Congenital cholestasis with hepatic zinc accumulation	Unknown	–	–
33.6	Hemochromatosis			
33.6.1	1. Classic form, HFE-deficient (HFE1)	Systemic Fe overload due to excess intestinal absorption of Fe	*HFE*	235200
33.6.2	2. Juvenile form (HFE2)	Systemic Fe overload, mechanism uncertain	*HFE2*	602390
33.6.3	Transferrin receptor-2 deficiency (HFE3)	Systemic Fe overload due to transferrin receptor dysfunction	*TFR2*	604250
33.6.4	Ferroportin deficiency (HFE4)	Systemic Fe overload with defective cellular export	*SLC11A3*	606069
33.6.5	Perinatal hemochromatosis	Hepatic/extrahepatic Fe overload sparing reticuloendothelial system, mechanism unknown	–	–
33.6.6	Perinatal hemochromatosis with renal tubular dysgenesis	Unknown	–	–
33.6.7	Trichohepato-enteric syndrome	Unknown	–	222470
33.6.8	GRACILE syndrome	Hepatic Fe overload with mitochondrial dysfunction	*BSC1L*	603358
33.7	Aceruloplasminemia	Greatly decreased production of ceruloplasmin	*Cp*	604290

33.3 Treatment

33.1	Wilson disease	D-Penicillamine: 1000–1500 mg per day in two or three divided doses initially, with 750 or 1000 mg used for maintenance therapy. Tolerability may be enhanced by beginning with incremental doses, 250–500 mg per day, increased by 250 mg increments every 4–7 days to a maximum of 1000–1500 mg per day in 2–4 divided dosages. Dosing in children is 20 mg/kg per day rounded off to the nearest 250 mg and given in two or three divided doses. Food interferes with efficacy.[a] Neurological disease may deteriorate, usually transiently, when treatment is commenced. Adverse effects occur in 20–30% of patients necessitating discontinuing penicillamine and substituting trientine or zinc: early sensitivity reaction with fever/rash/proteinuria; leukopenia, thrombocytopenia, aplastic anemia; late nephrotoxicity with proteinuria; lupus-like syndrome; various dermatological abnormalities (Roberts and Schilsky 2003) Trientine: 750–1500 mg per day in two or three divided doses initially, with 750 or 1000 mg used for maintenance therapy. Dosing in children is 20 mg/kg per day rounded off to the nearest 250 mg and given in two or three divided doses. Food interferes with efficacy.[a] Neurological disease occasionally deteriorates transiently when treatment is commenced. Adverse reactions are rare: anemia, extremely rare aplastic anemia, gastritis, loss of taste, rashes. Zinc salts (sulphate; gluconate; acetate) to provide 50 mg elemental Zn tid. Children's dose is 25 mg elemental Zn tid. Minimal dosing frequency is bid. Food interferes with efficacy.[a] Adverse reactions are uncommon, mainly gastritis with nausea.
33.2	Menkes disease	
	1. "Classic" form	Copper-histidine subcutaneous injection: 50–150 µg/kg per day. Typical dosage is 100 µg/kg per day in newborns and 1 mg/day in older children.
	2. "Mild" form (atypical)	Copper-histidine subcutaneous injection as above
33.3	Occipital Horn syndrome	Copper-histidine subcutaneous injection as above
33.4	Acrodermatitis enteropathica	Zinc salts (sulphate; gluconate; acetate) to provide initially 5–10 mg elemental Zn/kg per day. Response is usually rapid, with improvement in skin lesions beginning within 24–48 h of starting treatment. Complete resolution and restoration of normal hair growth may take 2–4 weeks. Thereafter maintenance does is 1–2 mg elemental Zn/kg per day by mouth.
33.5	Congenital cholestasis with hepatic zinc accumulation	Standard treatment for chronic cholestatic liver disease, then orthotopic liver transplantation if indicated
33.6	Hemochromatosis	
33.6.1	1. Classic form, HFE-deficient (HFE1)	Phlebotomy to remove 500 mL of blood weekly or biweekly until serum ferritin < 50 µg/l, then decrease frequency to once every 2–4 months to maintain serum ferritin in 25–50 µg/l range
33.6.2	2. Juvenile form (HFE2)	Same as for HFE1
33.6.3	Transferrin receptor-2 deficiency (HFE3)	Same as for HFE1
33.6.4	Ferroportin deficiency (HFE4)	Phlebotomy as for HFE1 except that interval should be extended to every 3–4 weeks or as tolerated

33.6.5	Perinatal hemochromatosis	"Antioxidant cocktail": *N*-acetylcysteine (140 mg/kg by mouth or nasogastric tube as a loading dose then 70 mg/kg every 4 h to a total of 17–21 doses); selenium 2–3 μg/kg per day intravenously over 24 h for ∼ 4 weeks; α-tocopheryl polyethylene glycol succinate 20–30 IU/kg per day given by mouth in two equally divided doses for ∼ 4 weeks or longer; prostaglandin E_1 as a continuous intravenous infusion (0.4–0.6 μg/kg per hour) for 2–4 weeks; desferroxamine (30 mg/kg per day) by continuous intravenous infusion over 8 h daily until the serum ferritin is < 500 μg/l. Note that prostaglandin E_1 cannot be administered if the ductus arteriosus is patent. Orthotopic liver transplantation, if indicated
33.6.7	Perinatal hemochromatosis with renal tubular dysgenesis	No specific treatment
33.6.7	Trichohepato-enteric syndrome	No specific treatment
33.6.8	GRACILE syndrome	No specific treatment
33.7	Aceruloplasminemia	Phlebotomy as for HFE1 or as tolerated; hematocrit should be checked before each phlebotomy and it should be no lower than 20% below its starting value; desferroxamine

[a] Best if taken 1 h before or 2 h after meals but closer proximity to meals (with possible dose adjustment) is acceptable if required for adequate compliance.

33.4 Alternative Therapies/Experimental Trials

33.1	Wilson disease	Tetrathiomolybdate, alone or in combination with zinc (Brewer et al. 2003) – note significant risk of bone marrow, hepatotoxicity and brain toxicity Vitamin E (α-tocopherol)
33.2	Menkes disease	
	1. "Classic" form	None
	2. "Mild" form (atypical)	None
33.3	Occipital Horn syndrome	None
33.4	Acrodermatitis enteropathica	None
33.5	Congenital cholestasis with hepatic zinc accumulation	None; liver transplantation may be necessary
33.6	Hemochromatosis	
33.6.1	1. Classic form, HFE-deficient (HFE1)	None
33.6.2	2. Juvenile form (HFE2)	None
33.6.3	Transferrin receptor-2 deficiency (HFE3)	None
33.6.4	Ferroportin deficiency	None
33.6.5	Perinatal hemochromatosis	Gamma-globulin infusions to mother during latter half of pregnancy
33.6.6	Perinatal hemochromatosis with renal tubular dysgenesis	Antioxidant cocktail; combined liver + kidney transplantation
33.6.7	Trichohepato-enteric syndrome	Antioxidant cocktail; combined liver + intestinal transplantation
33.6.8	GRACILE syndrome	Intravenous administration of apotransferrin followed by exchange transfusion; antioxidant cocktail
33.7	Aceruloplasminemia	Vitamin E (α-tocopherol)

33.5 Follow-up/Monitoring

33.1	Wilson disease	Clinical review and physical examination every 6–12 months; serum AST, ALT, ALP, GGT, conjugated bilirubin, albumin, International Normalized Ratio (INR), serum Cu and ceruloplasmin, complete blood count, urinalysis every 6–12 months Twenty-four-hour urinary copper excretion every 12–18 months if on stable dose of medication: for patients taking D-pencillamine or trientine, it should be 3–8 µmol (200–500 µg) per day, and for patients on any zinc salt it should be no more than 1.2 µmol (75 µg) per day For patients taking zinc serum zinc or 24-h urinary zinc excretion every 12 months
33.2	Menkes disease	
	1. "Classic" form	Clinical follow-up relates to major features of the disease: seizures, neurodegeneration, arterial abnormalities, bone and joint disorders. Efficacy of treatment is determined by normalization of serum copper and ceruloplasmin and 24-h urinary copper excretion. Exceptionally: measurement of hepatic parenchymal copper concentration may be required to assess efficacy of treatment
	2. "Mild" form (atypical)	As for classic Menkes disease

33.3	Occipital Horn syndrome	As for classic Menkes disease
33.4	Acrodermatitis enteropathica	Clinical examination to ensure normal skin and hair. Serum Zn concentrations should be measured every 6–12 months; 24-h urinary excretion of Zn should be measured every 1–2 years. Serum Cu should be measured every 6–12 months, and the complete blood count should be monitored regularly to check for development of a Cu-deficiency anemia. Zn supplementation expected to be life-long; pregnancy or use of oral contraceptive pill may increase Zn demands
33.5	Congenital cholestasis with hepatic zinc accumulation	Routine surveillance for progressive liver disease
33.6	Hemochromatosis	
33.6.1	1. Classic form, HFE-deficient (HFE1)	Clinical examination to monitor hepatic and extrahepatic disease; serum ferritin, fasting transferrin saturation, and complete blood count every 3–4 months or more often depending on maintenance phlebotomy requirements; screening for hepatocellular carcinoma mandatory in any patient with cirrhosis
33.6.2	2. Juvenile form (HFE2)	Same as HFE1
33.6.3	Transferrin receptor-2 deficiency (HFE3)	Same as HFE1
33.6.4	Ferroportin deficiency (HFE4)	Same as HFE1
33.6.5	Perinatal hemochromatosis	Clinical review and physical examination every 3–12 months; serum AST, ALT, ALP, GGT, conjugated bilirubin, albumin, INR, complete blood count, urinalysis, serum iron, transferrin saturation and ferritin at each visit. Liver sonogram every 2–4 years
33.6.6	Perinatal hemochromatosis with renal tubular dysgenesis	As for perinatal hemochromatosis, if infant survives
33.6.7	Trichohepato-enteric syndrome	As for perinatal hemochromatosis, if infant survives
33.6.8	GRACILE syndrome	As for perinatal hemochromatosis, if infant survives
33.7	Aceruloplasminemia	Regular clinical review and physical examination for neurological disease; regular ophthalmologic examination of retina; serum ferritin and transferrin saturation; complete blood count to monitor anemia; serum AST, ALT, ALP, GGT, albumin

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34 Leukotrienes

Ertan Mayatepek

34.1 Introduction

Leukotrienes comprise a group of biologically highly active lipid mediators derived from 20-polyunsaturated fatty acids, predominantly arachidonic acid via the 5-lipoxygenase pathway. They include the cysteinyl leukotrienes (LTC_4, LTD_4, and LTE_4) as well as LTB_4. Synthesis of the primary cysteinyl leukotriene LTC_4 results from conjugation of the unstable LTA_4 with glutathione and is mediated by LTC_4 synthase. Stepwise cleavage of glutamate and glycine from $LTC_4$by γ-glutamyl transpeptidase and membrane-bound dipeptidase yield LTD_4 and LTE_4, respectively. During the last decade, leukotrienes have been mainly investigated because of their role as inflammatory mediators, especially in asthma bronchiale. Their role in the CNS is yet poorly understood, but there is increasing evidence that they are messengers or modulators of CNS activity.

A few disorders have been identified causing secondary disturbances in leukotriene elimination and degradation, e. g. defective hepatobiliary elimination of cysteinyl leukotrienes as seen in Dubin-Johnson syndrome, impaired ω-oxidation of LTB_4 in Sjögren-Larsson syndrome, or altered β-oxidation in disorders of peroxisome biogenesis such as the Zellweger syndrome. However, in these conditions leukotriene synthesis itself is not affected. Patients with Sjögren-Larsson syndrome, an inborn error of lipid metabolism, are characterized clinically by congenital ichthyosis, mental retardation, and spasticity. However, they also suffer from severe pruritus. In this disorder degradation of LTB_4 is defective, resulting in increased levels of LTB_4 which might be involved in the pathogenesis of pruritus. With respect to the agonising pruritus, at least some patients with Sjögren-Larsson syndrome might benefit from treatment with Zileuton (in a dosage of up to 600 mg four times a day), which is capable to inhibit an increased synthesis of LTB_4.

In the synthesis of the leukotrienes, hereditary primary defects have been detected in three of the enzymatic steps: LTC_4-synthase, γ-glutamyl transpeptidase, and membrane-bound dipeptidase. Deficiency of these enzymes results in abnormal levels and profiles of cysteinyl leukotrienes in CSF, urine, and/or plasma. In general, the known defects seem to be rare. At present there have been reported a total number of eight patients with a primary defect in the synthesis of cysteinyl leukotrienes.

In LTC_4 synthase deficiency ($n = 2$), patients seem to be most severely affected by, for example, muscular hypotonia, psychomotor retardation, microcephaly, and failure to thrive. The clinical picture in γ-glutamyl transpeptidase deficiency ($n = 5$) is heterogeneous, varying from mental retardation and psychosis to a nearly normal phenotype. There has been only one patient described with membrane-bound dipeptidase (cysteinyl-glycinase) deficiency, presenting with mental retardation, motor impairment, and peripheral neuropathy.

Because of the very limited number of patients identified so far and because of the lack of profound understanding of the role of leukotrienes in the brain and their pathophysiological significance in deficiency states, there exists at present no treatment or experimental therapeutic approaches. It is possible that such disoders are still underdiagnosed, suggesting that leukotriene analysis should be included in the routine metabolic work-up in patients with neurological symptoms who have no other apparently obvious metabolic cause.

34.2 Nomenclature

No.	Disorder (symbol)	Definitions/comment	Gene symbol	OMIM No.
34.1	LTC_4-synthase deficiency (LTC)		*LTC4S*	246530
34.2	γ-Glutamyl transpeptidase deficiency (GGT)		*GGT1*	231950
34.3	Membrane-bound dipeptidase (cysteinyl-glycinase) deficiency (MBD)		*DPEP1*	179780

34.3 Treatment

■ *34.1 LTC_4-synthase deficiency (LTC)*

No specific treatment available.

■ *34.2 γ-Glutamyl transpeptidase deficiency (GGT)*

No specific treatment available.

■ *34.3 Membrane-bound dipeptidase (cysteinyl-glycinase) deficiency (MBD)*

No specific treatment available.

34.4 Alternative Therapies/Experimental Trials

Except of symptomatic treatment there exist currently no alternative therapies or experimental trials.

34.5 Follow-up/Monitoring

Besides a general clinical follow-up, there exists no specific follow-up or monitoring recommendation.

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35 Hyperinsulinism of Infancy

Khalid Hussain

35.1 Introduction

Hyperinsulinism of infancy (HI) is the commonest cause of recurrent and severe hypoglycaemia in the neonatal and infancy period (Hussain and Aynsley-Green 2003). It is characterized by the excessive and inappropriate secretion of insulin in relation to the prevailing blood glucose concentration. HI can be either persistent or transient.

35.2 Transient Hyperinsulinism

The transient form of HI is associated with maternal diabetes mellitus, intrauterine growth retardation, perinatal asphyxia (Collins and Leonard 1984), erythroblastosis fetalis (Barrett and Oliver 1968), Beckwith-Wiedemann syndrome, after the maternal administration of some drugs such as sulphonylureas, and after intravenous maternal glucose infusions during labour. The transient form may also be "idiopathic" (Mehta and Hussain 2003). A connection between hyperlactataemia and severe transient neonatal hyperinsulinism has also been recognised in non-asphyxiated infants (Hussain et al. 2004). The mechanism(s) causing transient HI in these conditions is not clear. In these cases the HI tends to resolve spontaneously.

35.3 Congenital HI

Persistent HI is the most common cause of severe persistent hypoglycaemia in neonates and infants during their 1st year of life (Aynsley-Green et al. 2000). It has previously masqueraded under a variety of different descriptive names, including "idiopathic hypoglycaemia of infancy", leucine-sensitive hypoglycaemia, neonatal insulinoma, microadenomatosis, focal hyperplasia, nesidioblastosis, and persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI).

The organic hyperinsulinism causes hypoglycaemia primarily as a result of increased utilisation of glucose together with a decreased rate of endogenous

glucose production. These effects are entirely due to inappropriate secretion of insulin.

Both sporadic and familial variants of congenital hyperinsulinism of infancy are recognised, with sporadic forms being relatively uncommon (incidence 1 per 40,000 live births; Bruining 1990) and familial forms being common in communities with high rates of consanguinity; in these communities the incidence may be as high as 1 in 2,500 live births (Mathew et al. 1988).

35.4 Clinical Presentation

The condition presents primarily in the newborn period and during the first 2–6 months after birth in full-term and preterm neonates (Hussain and Aynsley-Green 2004). Many neonates have a characteristic appearance resembling strikingly that of an infant of a diabetic mother. This appearance suggests that the hyperinsulinism in these infants has been present for some time before birth. Very rarely HI may present in an older child when it is likely to be due to an insulinoma (Hussain et al. 2002).

35.5 Diagnosis

The characteristic metabolic and endocrine profile in a blood sample drawn at the time of hypoglycaemia is one of hyperinsulinaemic, hypoketotic, hypo-fatty acidaemic hypoglycaemia with inappropriately raised insulin and accompanied by high concentrations of C-peptide levels. High intravenous infusion rates of glucose may be required to maintain a blood glucose concentration above 3 mmol/l. Because of the anabolic effects of insulin, the hypoglycaemia occurs despite a liver engorged with glycogen that can be mobilised by administration of glucagon. The glycaemia can usually be improved by an infusion of somatostatin that will switch off insulin secretion (Aynsley-Green et al. 2000).

It is important to emphasise that the level of insulin in the blood may not necessarily be particularly high. However, what is an appropriate insulin concentration for normoglycaemia becomes inappropriate in the presence of hypoglycaemia (Aynsley-Green et al. 2000). The demonstration of any measurable insulin in a hypoglycaemic sample is strong evidence for a failure of basal insulin control (Figure 35.1 outlines the diagnostic and management approch to HI).

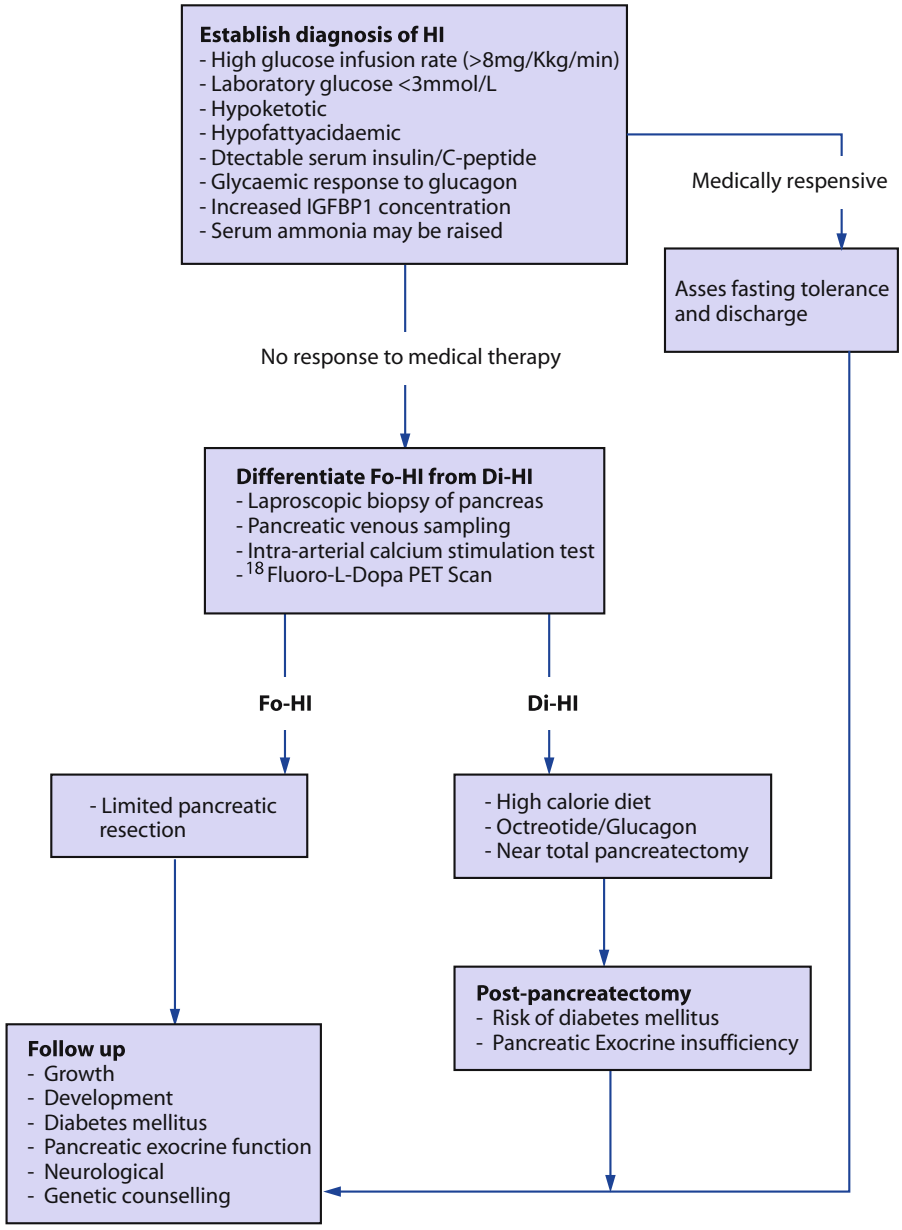

Fig. 35.1. Diagnosis and management of hyperinsulinism of infancy

35.6 Pathophysiology

Recent advances in understanding the defect in the molecular physiology of congenital hyperinsulinism have given unique insights into understanding how glucose metabolism is coupled to regulated insulin secretion (Dunne et al. 2004). The stimulus "response coupling" event is controlled by potassium channels in the pancreatic β-cell membrane which are sensitive to intracellular nucleotides, in particular the ratio between adenosine triphosphate (ATP) and adenosine diphosphate (ADP). As the intracellular glucose concentration increases, β-cell glycolysis increases the ratio of ATP to ADP. This closes the potassium ATP-sensitive channel, resulting in depolarisation of the β-cell membrane. This phenomenon leads to the influx of calcium through voltage-gated calcium channels which triggers exocytosis (Kane et al. 1996). Thus, the potassium channel functions as an "on-off" switch for triggering insulin secretion.

Potassium ATP channels consist of a heteromultimeric complex of at least two proteins designated SUR1 and Kir6.2 (Clement et al. 1997). The functional integrity of both of these proteins is necessary for potassium channel movement and the genes responsible for them have been localised very closely to each other on the short arm of chromosome 11 (11p14–15.1).

A number of mutations in the SUR1 and Kir6.2 genes have been defined, particularly in children with the familial forms of HI (HI-K_{ATP}) (Glaser et al. 2000). Histologically two forms of the disease have been described (Rahier et al. 2000). The diffuse form (Di-HI) affects all the β-cells and is most commonly due to recessive mutations in the two components of the K_{ATP} channel (Glaser et al. 2000). The focal (Fo-HI) form of the disease appears to e associated with a different genetic background, namely, genetic imprinting with loss of heterozygosity and paternal imprinting (De Lonlay et al. 1997).

Two other recent discoveries have emphasised further the complexity of hyperinsulinism. Thus, abnormal activation of glucokinase (HI-GCK) (Glaser et al. 1998) and of glutamate dehydrogenase (HI-GDH) (Stanley et al. 1998) both lead to increased intracellular concentrations of ATP, which triggers insulin secretion in the absence of any defect in membrane polarisation. It has been proposed that the glutamate dehydrogenase syndrome, which leads to hyperammonaemia with hypoglycaemia, may be the cause of the so-called leucine-sensitive hypoglycaemia described in previous years. HI has also been reported in association with exercise (Meissner et al. 2001) and with defects of fatty acid metabolism (HI-SCHAD) (Clayton et al. 2001). Table 35.2 summarises the nomenclature for the different forms of HI. Table 35.1 outlines the location and nomenclature of the genes described so far that cause HI.

Table 35.1. Location of genes causing HI

No	Title	Gene symbol	OMIM No.
35.1	ATP-binding cassette, subfamily C, (member 8 sulfonylurea receptor)	*ABCC8*	600509
35.2	Potassium inwardly rectifying channel	*KCNJ11*	600937
35.3	Glutamate dehydrogenase-1	*GLUD1*	138130
35.4	Glucokinase (hexokinase-4)	*GCK*	138079
35.5	Short-chain L-3-hydroxyacyl-CoA dehydrogenase	*SCHAD*	601609

Table 35.2. Nomenclature

Disorder	Description
Di-HI	Diffuse hyperinsulinism of infancy due to recessive mutations in the components of the K_{ATP} channel
Fo-HI	Focal hyperinsulinism of infancy due to somatic event (loss of heterozygosity and mutation in components of the K_{ATP} channel)
HI-GDH	Hyperinsulinism of infancy due to gain of function mutations in the *GLUD 1* gene
HI- GCK	Hyperinsulinism of infancy due to gain of function mutations in the glucokinase gene
HI-SCHAD	Hyperinsulinism of infancy due to defects in short-chain L-3-hydroxyacyl-CoA dehydrogenase
HI-E	Hyperinsulinism related to exercise

35.7 Management

The immediate imperative is to give sufficient glucose to maintain blood glucose concentrations above 3 mmol/l. This can be in the form of intravenous glucose and or high calorie feeds. Infusion rates in excess of 4–6 mg/kg per min may be necessary; rarely, infusion rates > 20 mg/kg per min may be needed. Having stabilised the blood glucose concentration, it is then imperative to determine whether the patient will respond to the conventional medical therapy. If there is no response to medical therapy the only other option is surgical. Table 35.3 summarises the dietary, medical, and surgical management of different forms of HI, and Table 35.4 summarises the doses and side-effects of the medical therapies used in the management of HI.

Table 35.3. The dietary, medical and surgical management of different forms of HI

Type of HI	Diet	Medical	Surgical
Di-HI	High calorie	D/C/N/G/O	Near-total pancreatectomy
Fo-HI	High calorie	D/C/N/G/O	Limited pancreatectomy
HI-GDH	Protein restriction/ high calorie	D	No surgery
HI-CGK	High calorie	D	No surgery
HI-SCHAD	High calorie	D	No surgery
HI-E	N/A	D or avoidance of exercise	No surgery

D diazoxide, *C* chlorothiazide, *N* nifedipine, *G* glucagon, *O* octreotide

Table 35.4. Medical therapy for HI

Medication	Route of administration	Dose	Mechanism of action	Side-effects
Diazoxide	Oral	5–20 mg/kg per day divided into 2 or 3 doses	Agonist of the K_{ATP} channel	Fluid retention, hypertrichosis, hyperuricaemia, eosinophilia, leukopaenia, rarely hypotension
Chlorothaiazide (used in conjunction with diazoxide)	Oral	7–10 mg/kg per day divided into 2 doses	Activation of K_{ATP} channels	Hyponatraemia, hypokalaemia
Nifedipine	Oral	0.25–2.5 mg/kg per day divided into 3 doses	Calcium channel blocker	Hypotension
Glucagon	SC/IV infusion/ IM injection	1–20 μg/kg per h	Increases glycogenolysis and gluconeogenesis	Nausea, vomiting, paradoxical insulin secretion Skin rashes
Octreotide	SC/IV continuous infusion 6–8 hourly SC injections	5–25 μg/kg per day	Multiple actions in the β-cell (see text)	Suppression of GH, TSH, ACTH, glucagon, diarrhoea, steatorrhoea, cholelithiasis, abdominal distension, growth suppression, tolerance

GH growth hormone, *TSH* thyroid stimulating hormone, *ACTH* adrenocorticotrophic hormone

Medical Therapy

Medication: diazoxide (oral):

- Mechanism of action: Diazoxide is a ligand of K_{ATP} which will activate intact K_{ATP} channels, reversing glucose-induced channel closure. Diazoxide also increases gluconeogenesis and increases adrenaline secretion.
- Pharmacodynamics/kinetics: Diazoxide is structurally related to the thiazide diuretics but has an antidiuretic action producing fluid retention. It is readily absorbed from the gastrointestinal tract and more than 95% of the drug is bound to albumin. Diazoxide is partially metabolised by oxidation and sulphate conjugation and is excreted by glomerular filtration as unchanged drug and metabolites. In adults the plasma half-life of diazoxide is estimated to be about 20–45 h, whereas in children the half-life is thought to be considerably shorter, 9.5–20 h (Pruitt et al. 1973), but there is no data on neonates. The concentration of diazoxide required in the blood for the hyperglycaemic action in neonates and children is not known, although in adults a peak blood level of 16 μg/ml can cause hyperglycaemia within 4 h after oral administration of a single dose of 10 mg/kg per day.
- Dosage: 5–20 mg/kg per day orally in two to three divided doses.

- Adverse effects: Fluid retention and hypertrichosis are common side-effects. The fluid retention is mostly observed in the neonatal period and may cause cardiac failure; hence the concurrent use of a thiazide diuretic to prevent fluid retention. Hypertrichosis (excess hair growth, which may involve vellus hair and/or pigmented terminal hair especially on the eyebrows, eyelashes, back, and arms) is a major cosmetic side-effect. This is reversible and disappears when the diazoxide is stopped. Other side-effects include increased uric acid levels, ketoacidosis and hyperosmolar coma, neutropenia, eosinophilia, thrombocytopenia, and allergic reaction.
- Interactions with other drugs: Significant interactions of diazoxide have been reported with diuretics (Aynsley-Green and Alberti 1973), phenytoin (Petro et al. 1976), warfarin (Sellers and Koch-Weser 1970), chlorpromazine (Aynsley-Green and Illig 1975) and aspirin (Newman and Brodows 1983). The interactions with phenytoin, warfarin and chloropromazine involve either displacement from albumin-binding sites or increased/decreased metabolism by induction of liver enzymes. The mechanism of hyperglycaemia due to thiazide diuretics such as chlorothiazide involves activation of potassium channels in the β-cell membrane (Barnes et al. 2000), but the mechanism is unclear in the case of loop diuretics such as frusemide.

Medication: nifedipine (oral):

- Mechanism of action: calcium channel antagonist
- Dose: 0.25–2.5 mg/kg per day divided into 3 doses
- Side-effects: No major side-effects have been reported when nifedipine has been used in patients with hyperinsulinaemic hypoglycaemia. Overall the response to nifedipine has been disappointing. Children who have hyperinsulinism as a result of an abnormality in the two components in the K_{ATP} channel usually fail to respond to nifedipine. Despite this there have several recent reports of nifedipine-responsive forms of HI (Bas et al. 1999; Ranganath et al. 1999).

Medication: glucagon (subcutaneous infusion)

- Mechanism of action: Glucagon activates adenylate cyclase via the G-protein coupled receptor (G_s). Activated adenylate cyclase phosphorylates cAMP-dependent protein kinase PKA that triggers a cascade of events. These include activation of phosphorylase kinase (release of glucose from stored glycogen), deactivation of pyruvate kinase effectively creating an excess of phosphoenol-pyruvate (gluconeogenesis) and the transcription of phosphoenolpyruvate carboxykinase (PEPCK), which catalyses the reaction from oxaloacetate to phosphoenolpyruvate (gluconeogenesis). In summary glucagon stimulates glycogenolysis, gluconeogenesis, lipolysis, protein degradation, amino acid catabolism and ketogenesis. Onset of action of glucagon is within 10–15 min.

- Dose: 1–20 µg/kg per h (subcutaneous or intravenous continuous infusion)
- Interactions: Glucagon stimulates the synthesis and release of growth hormone, insulin and pancreatic somatostatin. Amino acids, cortisol, infections, stress, adrenergic stimulators and acetylcholine all stimulate glucagon secretion.
- Side-effects: A common side-effect of glucagon is a brief period of nausea and vomiting. The nausea is not mediated by effects on the brain but due to the delay in gastric emptying caused by glucagon as shown in adults (Ranganath et al. 1999). There has been one case report of a 35-week-gestation infant who developed severe hyponatraemia and thrombocytopenia after continuous infusion of glucagon for the treatment of intractable hypoglycaemia (Belik et al. 2001). Another possible side-effect of glucagon therapy may be erythema necrolyticum migrans, which was reported in two neonates with persistent hyperinsulinaemic hypoglycaemia (Wald et al. 2002).

Intramuscular glucagon injection is the treatment of choice in situations where intravenous access is not accessible in patients with hyperinsulinaemic hypoglycaemia (1-mg dose). It is important to remember that glucagon will not be effective in correcting hypoglycaemia in patients with glycogen storage disease. Higher doses of glucagon (> 20 µg/kg per hour) can cause insulin secretion, which leads to worsening of the hypoglycaemia in patients with hyperinsulinism.

Medication: octreotide:

- Background: Octreotide is the acetate salt of a cyclic octapeptide. It is a long-acting octapeptide with pharmacologic properties mimicking those of the natural hormone somatostatin.
- Indication: the short- and long-term management of hyperinsulinaemic hypoglycaemia
- Mechanism of action: Octreotide is one of the many octapeptide and hexapeptide somatostatin analogs that, unlike somatostatin, show a high degree of affinity for somatostatin receptors (sstr) 2 and 3 and little or no binding to sstr1 (Patel 1999). Somatostatin and its analogs can inhibit insulin secretion by activation of sstr 5, which is mediated by stimulation of the G_i/G_o protein (Patel 1999). Subcutaneous or intravenous octreotide inhibits first-phase insulin secretion and attenuates insulin responses to activated G_s-protein-coupled receptors (such as the glugagon-like peptide-1R). In pancreatic β-cells, activation of sstr 5 inhibits calcium mobilisation and acetylcholine activity and decreases insulin gene promoter activity, resulting in reduced insulin biosynthesis (Benali et al. 2000). Somatostatin also exhibits an effect on insulin secretion distal from the inhibition of Ca^{2+} mobilisation and adenylate cyclase inhibition (Renstrom et al. 1996). It has been suggested that the β-cell sstr is coupled to the K_{ATP} channel (Ribalet and Eddlestone 1995), but the effect of this is not considered to be relevant physiologically, as somatostatin is still capable of reducing insulin secretion in the presence of sulfonylureas (Abel et al. 1996).

- Pharmacodynamics/kinetics: The activity of octreotide is similar to that of somatostatin. Octreotide, however, has a longer half-life, greater selectivity for inhibiting glucagon, growth hormone and insulin release, and a lower incidence of rebound hypersecretion following discontinuation.

Octreotide is administered by subcutaneous injection and is rapidly absorbed, with peak concentrations of 5.2 ng/ml occurring around 25 min after a 100-µg dose. Distribution occurs rapidly, with approximately 65% of a dose bound to lipoprotein and albumin in a concentration-dependent manner. The apparent half-life of octreotide is approximately 1.7 h, which is significantly greater than the somatostatin half-life of 1–3 min. The effects of octreotide are variable but can last for up to 12 h.

- Dose: 5–25 µg/kg per day
- Side-effects: Local reactions at the site of injection include pain, sensation of stinging, tingling and burning, as well as redness and swelling. Gastrointestinal side-effects include anorexia, nausea, abdominal pain, bloating, flatulence, loose stools and diarrhoea. Octreotide causes the inhibition of the release of several hormones, including growth hormone, serotonin, gastrin, vasoactive intestinal polypeptide (VIP), secretin, motilin, pancreatic polypeptide, ACTH and thyroid-stimulating hormone (TSH). The suppression of GH (including insulin-like growth factors) and thyroid hormones may lead to stunting of growth. Octreotide can decrease gallbladder contractility and bile secretion, leading to steatorrhoea, cholestasis, hepatic dysfunction and cholelithiasis. Blood flow to the splanchic circulation is decreased by octreotide, hence it must be used cautiously in babies at risk of necrotising entercolitis. Resistance to octreotide therapy can occur even at high doses.

Surgical Management

It is now imperative to identify those children with the Fo-HI, as their management will be radically different compared with those with Di-HI. Those with Fo-HI will require a limited pancreatectomy with the aim of resecting only the focal lesion and preserving as much normal pancreatic tissue as possible. On the other hand, those with diffuse disease will usually require a 95% pancreatectomy. Pancreatectomy is not without risk and is not a procedure to be undertaken lightly. Some children remain hypoglycaemic despite this when a further attempt can be made to control the procedure by diazoxide therapy. In a minority of cases, a total pancreatectomy may be necessary to control the severe hyperinsulinism which may be exacerbated by regeneration of the pancreatic remnant.

The diffuse form of the disease can now be identified by performing a laparoscopic biopsy of the pancreas (K. Hussain et al., unpublished work). Current methods of localising focal lesion include intrahepatic pancreatic portal ve-

nous sampling (Dubois et al. 1995), and the intra-arterial calcium stimulation test (Abernethy et al. 1998). Both of these methods are highly invasive. Even more recently ^{18}F-fluoro-L-dopa PET positron emission tomography has been successfully used to localise the focal domain (Otonkoski et al. 2003). This has many advantages over the highly invasive pancreatic venous sampling and intra-arterial calcium stimulation tests.

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36 Other Metabolic Disorders

Georg F. Hoffmann, Nenad Blau

36.1 Introduction

Trimethylaminuria, also called fish-odor syndrome, is an autosomal recessive disorder characterized by a distinctive smell of rotten fish emanating from the urine, breath, and skin. It is caused by a deficient trimethylamine-oxidizing system resulting in accumulation of trimethylamine, a tertiary amine, which is volatile and responsive for the offensive smell (Mitchell 1996; Rehman 1999).

Dimethylglycinuria was described in 1999 in an adult with "fish-odor syndrome," muscular fatigue, and raised serum creatine kinase (Molenaar et al. 1999).

Sjögren-Larsson syndrome is a neurocutaneous disorder caused by a deficiency of the microsomal enzyme fatty aldehyde dehydrogenase catalyzing the oxidation of medium- and long-chain fatty aldehydes to their corresponding acids. Clinically it is characterized by the triad congenital ichthyosis, spastic di- or quadriplegia, and mental retardation (Willemsen et al. 2001a). Retinal changes ("glistening white dots"), pruritus, and severe speech disturbance with pseudobulbar dysarthria are also part of the clinical spectrum.

Hypophosphatasia is a metabolic bone disease causing defective mineralization of the skeleton and teeth. The clinical spectrum is very wide, ranging from perinatally lethal forms ("the boneless fetus"), rickets-like disease in infants and children, to an exclusively dental form in adults (Whyte 2001).

36.2 Nomenclature

No.	Disorder (symbol)	Definitions/comment	Gene symbol	OMIM No.
36.1	Trimethylaminuria	Fish-odor syndrome	*FMO3*	602079
36.2	Dimethylglycinuria	Fish-odor syndrome	*DMGDHD*	605849
36.3	Hypophosphatasia	Phosphoethanolaminuria	*TNSALP*	146300
				241500
				241510
36.4	Sjögren-Larsson syndrome		*ALDH*	270200

36.3 Treatment

36.1 Trimethylaminuria

Management of trimethylaminuria is not always easily accomplished. Treatment involves counseling and dietary adjustments. The latter include avoidance of choline-rich products (egg yolk, liver, kidney, legumes, soybeans, peas as well as fish, including shellfish). The reduced intake may reduce the excretion of trimethylamine and consequently the odor. The additional restriction of milk has proved useful in some cases. Some individuals have trimethylaminuria that is not responsive to dietary management. Occasionally, a short course of metronidazole, neomycin and lactulose can suppress production of trimethylamine by reducing the activity of gut microflora. In some patients, soaps with a pH value 5.5–6.5 have been reported to reduce the odor dramatically. They act by retaining secreted trimethylamine (a strong base) in a less-volatile salt form (Mitchell 1996; Rehman 1999).

36.2 Dimethylglycinuria

The intensity of the odor in dimethylglcine dehydrogenase deficiency increases with physiological stress, such as illness, as well as during times of increased physical activity. No treatment strategy has as yet been established.

36.3 Hypophosphatasia

A variety of medical treatments to improve osteomalacia in hypophosphatasia have been tried. In general results have not been beneficial or long-lasting (Whyte 2001). Assessment of therapy is hampered by the low numbers of patients and the uncertain natural course of disease, which includes spontaneous improvements.

Supplementation of vitamin D and/or mineral should be avoided, unless obvious deficiencies have been documented. In hypophosphatasia circulating levels of Ca, P, and vitamin D are generally not low, and hypercalcemia and hy-

percalciuria will be worsened by supplementation. In contrast, dietary intake of calcium often needs to be restricted in generalized infantile disease. Chlorothiazide has successfully improved hypercalcemia, hypercalciuria, and chronic bone demineralization in infantile hypophosphatasia (Girschick et al. 1999). Treatment with synthetic calcitonin may be needed to control hypercalcemia (Barcia et al. 1997).

■ *36.4 Sjögren-Larsson Syndrome*

Therapy for Sjögren-Larsson syndrome rests in an interdisciplinary approach between dermatology, neurology, and orthopedics. Ichthyosis and pruritus can be treated with topical lubrications as well as with oral retinoids (Willemsen et al. 2001a).

Epilepsy is usually responsive to conventional antiepileptics. Spasticity is often troublesome and early, and consequent physical therapy is a cornerstone of therapy. If necessary different neuropharmacological drugs can be used to ameliorate severe spasticity, such as baclofen and benzodiazepines. Injections of botulinum toxin and intrathecal baclofen administration have also been tried with anecdotal success, but no data are available in the literature.

Dangers/Pitfalls

In children the benefit of administration of retinoids has to be weighted against potential side-effects on the developing skeleton. Growth has to be carefully and regularly monitored clinically as well as radiologically.

Teratogenic actions of retinoids are a major concern in women of childbearing age.

36.4 Alternative Therapies/Experimental Trials

■ *36.3 Hypophosphatasia*

Enzyme replacement has been repeatedly attempted by infusions of different alkaline phosphatases, e. g., from patients with Paget bone disease, with disappointing physiological as well as clinical responses. There is a single report of clinical and radiological improvement following haploidentical bone marrow transplantation (Whyte 2001).

36.4 Sjögren-Larsson Syndrome

A fat-modified diet enriched with medium-chain fatty acids has been tried without convincing clinical success (Maaswinkel-Mooij et al. 1994; Auada et al. 2002). Conceptionally, it could only exert a positive effect, if started in early childhood.

Recently, promising results could be obtained in an experimental trial using Zileuton, an inhibitor of the synthesis of leukotriene B_4 (Willemsen et al. 2001b).

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