Inherited Metabolic Diseases
Dedication

To our patients and their families
The field of inherited metabolic diseases has changed from a limited group of rare, untreatable, often fatal disorders to an important cause of acutely life-threatening but increasingly treatable illness. Unchanged is the orphan nature of these disorders with mostly relatively nonspecific initial clinical manifestations.

The patient does not come to the physician with the diagnosis; the patient comes with a history, symptoms, and signs. This book starts with those and proceeds logically through algorithms from questions to answers. Special emphasis is placed on acutely presenting disorders and emergency situations. The rationale of the approaches presented in this book are based on extensive, collective clinical experience. To utilize as broad an experience as possible, its concept has been extended from a pocket-size book written jointly by five colleagues to a textbook combining the experience of over 20 expert metabolic physicians. It is now imbedded in the environment of Springer Pediatric Metabolic Medicine in addition to the disease-based approach in Inborn Metabolic Diseases edited by John Fernandes and colleagues as well the series edited by Nenad Blau and colleagues on specific biochemical diagnostics, laboratory methods, and treatment.

A system and symptom-based approach to inherited metabolic diseases should help colleagues from different specialties to diagnose their patients and to come to an optimal program of therapy. For metabolic and genetic specialists, this book is designed as a quick reference for what may be (even for the specialist) infrequently encountered presentations.

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Part A

Introduction to Inborn Errors of Metabolism
The classical inborn errors of metabolism are defects in enzymes of the metabolism of amino acids, carbohydrates and fatty acids or in mitochondrial energy metabolism (Fig. A1.1). These disorders are often dynamic; they fluctuate with changes in the metabolic state of the patient and frequently allow successful therapeutic intervention. Most of them are readily diagnosed through basic metabolic investigations which include blood gases, glucose, lactate, ammonia, plasma amino acids, urinary organic acids and an acylcarnitine profile.

Typical aminoacidopathies result from abnormalities in the breakdown of amino acids in the cytosol. In addition, several disorders involving mitochondrial enzymes such as branched-chain ketoacid dehydrogenase (maple syrup urine disease) or ornithine aminotransferase (gyrate atrophy of the choroidea) are classified as aminoacidopathies as they do not involve CoA-activated metabolites. This distinguishes aminoacidopathies from the organic acidurias, which are considered a separate group of disorders affecting mitochondrial enzymes, CoA-activated metabolites, and which have effects on other mitochondrial functions. Clinical symptoms of the aminoacidopathies may be thought of as caused by the accumulation of toxic intermediates that cause specific organ damage. Several defects of amino acid metabolism such as histidinemia are benign because

**Key Facts**

- The classical inborn errors of metabolism are defects in enzymes of the metabolism of amino acids, carbohydrates and fatty acids or in mitochondrial energy metabolism (Fig. A1.1).
- Disorders of intermediary metabolism are often dynamic; they fluctuate with changes in the metabolic state of the patient and frequently allow successful therapeutic intervention.
- Most disorders of intermediary metabolism are readily diagnosed through basic metabolic investigations which include blood gases, glucose, lactate, ammonia, plasma amino acids, urinary organic acids and an acylcarnitine profile.

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**Fig. A1.1** Main pathways of intermediary metabolism

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the metabolites that accumulate are not toxic. The pathogenetic relevance of an inborn error of amino acid metabolism is not always easy to ascertain as clinical symptoms observed in the child may be coincidental or the reason for performing the analysis in the first place. Aminoacidopathies are diagnosed through the analysis of plasma (or urinary) concentrations of amino acids and sometimes of urinary organic acids. A majority is treatable through dietary restriction of protein and of the amino acid involved in the defective pathway and by the avoidance or prompt treatment of catabolic states that lead to the breakdown of large amounts of protein. Another therapeutic strategy that has been successful in hepatorenal tyrosinemia is the inhibition of a biochemical step before the actual genetic deficiency, thereby changing a harmful disease into a more benign amino acid accumulation without the accumulation of the more damaging substances downstream.

A1.2 Organic Acidurias

The classical organic acidurias are deficiencies of enzymes in the mitochondrial metabolism of CoA-activated carboxylic acids, most of which are derived from amino acid breakdown. In this way, they are distinguished from disorders of fatty acid oxidation, which not only involve CoA esters but also present different diagnostic and therapeutic challenges. The term organic acidurias is preferred to the alternative term organic acidemias as they are most often detected by analysis of the urine. Biochemically, some of the reactions impaired in the organic acidurias are parallel to the dehydrogenase, hydratase, or ketothiolase reactions of the mitochondrial $\beta$-oxidation cycle. Clinical features are caused not only by the accumulation of toxic intermediates but also by a disturbance of mitochondrial energy metabolism and carnitine homeostasis; they may include encephalopathy and episodic metabolic acidosis. Organic acidurias are diagnosed through the analysis of organic acids in the urine or acylcarnitines in the blood. Treatment is similar to that of the aminoacidopathies and involves the dietary restriction of the relevant amino acid(s) and the avoidance of protein catabolism. However, as the defective enzymes are distant (more downstream) from the respective amino acids, restriction may not lead to a stoichiometric reduction of pathological metabolites, although it does in methylmalonic aciduria. Unexpected fluctuations occur and complete return to normal intermediary metabolism is usually impossible. Supplementation with carnitine and sometimes other substances such as glycine (e.g., to form isovalerylglycine in isovaleric aciduria) are very useful adjuncts to the treatment.

Disorders of biotin metabolism are included among the organic acidurias. Biotin is a cofactor of the mitochondrial carboxylases and a deficiency of biotinidase or holocarboxylase synthetase leads to multiple carboxylase deficiency. It is also usually diagnosed through urinary organic acid analysis. Biotinidase enzyme analysis of dried blood spots has been included into programs of neonatal screening as it is well treated with biotin supplementation.

A1.3 Disorders of Ammonia Detoxification

The breakdown of protein produces large amounts of nitrogen in the form of ammonia that is highly neurotoxic but is normally converted to urea and excreted in the urine. Defects in enzymes of the urea cycle and other disorders of ammonia detoxification present clinically with encephalopathy and other symptoms of hyperammonemia. Metabolic investigations should include analysis of the amino acids in plasma and urine and urinary orotic acid. Treatment requires the reduction of protein intake in conjunction with the supplementation of essential amino acids, the avoidance of catabolic states and the administration of benzoate or phenylacetate/phenylbutyrate, which remove nitrogen in the form of alternative conjugates of amino acids such as glycine and glutamine.

A1.4 Disorders of Fatty Acid Oxidation and Ketogenesis

Mitochondrial fatty acid oxidation is required for the provision of energy during fasting, either through complete oxidation or through production of ketones in the liver that then serve as an alternative energy source for the brain. Disorders in this pathway typically present as hypoketotic hypoglycemia precipitated by
fasting, leading to coma or convulsions. In addition, some disorders cause severe hepatopathy and (cardio-)myopathy, probably as results of the accumulation of toxic metabolites. The diagnosis is best reached in the acute situation through the analysis of free fatty acids and the ketone bodies 3-hydroxybutyrate and acetoacetate as well as the acylcarnitine profile and urinary organic acids. The diagnosis may be missed if samples are obtained in the normal interval between episodes or after the patient has been treated with intravenous glucose. Treatment consists of avoidance of fasting. Carnitine supplementation is mostly unnecessary and must be carefully balanced in some defects, particularly those that cause cardiomyopathy or hepatopathy.

A1.5 Disorders of Carbohydrate Metabolism and Transport

The disorders in this group display a relatively wide range of clinical features and may cause clinical symptoms because of toxicity, deficiency of energy, hypoglycemia, or storage.

- **Disorders of Galactose and Fructose Metabolism**: Defects in the cytosolic metabolism of galactose and fructose for glycolysis cause disease through accumulation of pathogenic metabolites. Children with galactosemia and fructosemia typically develop evidence of severe damage to the liver and/or kidney after dietary intake of lactose (milk, milk products) or fructose (fruit, sucrose), respectively. Treatment requires the elimination of the intake of galactose or fructose.

- **Disorders of Gluconeogenesis and Glycogen Storage**: Typical metabolic features are hypoglycemia after relatively short periods of fasting and lactic acidemia. There may be variable organ dysfunction, most frequently hepatopathy. Glycogen storage leads to hepatic enlargement, which in infancy may be massive. In some disorders such as glycogenosis type III there are elevations of the transaminases and creatine phosphate kinase, and there may be clinical myopathy. Treatment includes frequent meals, cornstarch supplementation, or continuous overnight tube feeding to avoid hypoglycemia.

- **Disorders of Carbohydrate Transport**: There are a number of different glucose and other carbohydrate carriers, and clinical symptoms differ greatly depending on the tissue localization of the individual defect. Symptoms are frequently gastrointestinal or renal but also include the central nervous system (deficient glucose transport across the blood-brain barrier).

A1.6 Mitochondrial Disorders

Disorders of energy metabolism (usually summarized as mitochondrial disorders although enzymes deficient, e.g., in organic acidurias or fatty acid oxidation defects are also located in the mitochondrion) include genetic defects of the pyruvate dehydrogenase complex, the Krebs cycle and the respiratory electron transport chain, comprising the final pathways of substrate breakdown and the production of ATP. Mitochondrial disorders manifest clinically with symptoms and signs of energy deficiency and a highly variable pattern of organ dysfunctions. In many cases, there are lactic acidemia and progressive neurodegenerative disease. Periods of metabolic stress such as intercurrent infections may trigger a deterioration of the patient’s condition. The diagnostic work-up may be difficult and should include frequent measurements of blood lactate levels, CSF lactate, plasma amino acids and alanine, and often a search for mutations in mitochondrial DNA. Repeated, careful examinations of organ functions as well as imaging are essential. Treatment options are limited but usually include various vitamins and cofactors such as riboflavin, coenzyme Q, or thiamine. Heterozygous mutations in the genes of some Krebs cycle enzymes (e.g., fumarase) cause inherited cancer predisposition syndromes.

A1.7 Disorders of Cobalamin and Folate Metabolism

Genetically determined or nutritional deficiencies of vitamin cofactors may affect various metabolic pathways and cause a wide range of clinical symptoms. They can frequently be satisfactorily treated by supplementation of the deficient substance. Of particular importance in intermediary metabolism are cobalamin (vitamin B₁₂) and folate which are essential for cytosolic methyl group transfer. The cellular methylation reactions require methyl group transfer from serine to S-adenosylmethionine involving the folate cycle,
cobalamin (vitamin B<sub>12</sub>) and the methionine–homocysteine cycle. A disturbance in this pathway may be caused by methylcobalamin deficiency, a disturbance of the folate cycle, or by deficient remethylation of homocysteine to methionine. Most disorders of cobalamin metabolism as well as nutritional deficiency of vitamin B<sub>12</sub> cause methylmalonic aciduria. Clinically, disorders of cytosolic methyl group transfer cause an encephaloneuropathy, often with additional hematological problems such as megaloblastic anemia and thrombembolic complications of hyperhomocysteinemia. The diagnosis involves the analysis of urinary organic acids, plasma amino acids (homocysteine), and levels of folate and cobalamin. Treatment includes supplementation of cobalamin and folate, in some situations with addition of betain and methionine.

A1.8 Disorders of Amino Acid Transport

Deficiencies in the intestinal and/or renal transport of amino acids may be nonsymptomatic or cause symptoms because of deficient absorption of essential amino acids (e.g., tryptophan in Hartnup disease) or because of increased urinary concentration of insoluble amino acids which causes nephrolithiasis (e.g., cystein in cystinuria). These disorders are diagnosed by the quantitative analysis of amino acids in plasma and urine. Treatment depends on the clinical picture. Deficiency of essential amino acids is treated by supplementation with large amounts of these compounds, or in the case of tryptophan deficiency, supply of the cofactor nicotinic acid that is normally synthesized from tryptophan. Renal calculi in cystinuria can be prevented by treatment with a chelating agent such as penicillamine, which forms mixed disulfides with cysteine, and calculi once formed can be resorbed if they have not incorporated too much calcium.

A1.9 Disorders of Peptide Metabolism

- The tripeptide glutathione and the γ-glutamyl cycle have multiple functions in cellular metabolism, ranging from amino acid transport across membranes to detoxification of peroxides. Deficiencies may cause neurological and hematological as well as metabolic problems. Investigations should include the determination of organic acids in the urine and glutathione in various body fluids. Treatment is largely symptomatic; certain drugs should be avoided.

A1.10 Disorders of the Transport or Utilization of Copper, Iron, and Zinc

- Disorders of copper metabolism: Wilson disease causes a chronic hepatopathy and symptoms of central nervous dysfunction, while patients with Menke disease suffer from neurological problems in conjunction with abnormalities of hair, connective tissue, and bones. Diagnosis involves the analysis of copper and coeruloplasmin in serum, urine, and liver tissue. Treatment in Wilson disease is aimed at reducing copper load, while copper should be parenterally substituted in Menke disease.

- Disorders of iron metabolism: Patients affected with such disorders may present with iron-deficient anemia, e.g., due to insufficient intestinal absorption of iron, or with iron overload and liver dysfunction as in hemochromatosis. Secondary iron overload may be observed in some hemolytic anemias. Treatment is directed at substitution or removal of iron.

- Disorders of zinc metabolism: Acrodermatitis enteropathica is characterized by chronic skin problems, alopecia, and central nervous symptoms. It is diagnosed through reduced levels of zinc and alkaline phosphatase and is treated with supplementation of zinc.
Disorders of the Biosynthesis and Breakdown of Complex Molecules

Johannes Zschocke

Key Facts

› Disorders of the biosynthesis and breakdown of complex molecules typically show slowly progressive clinical symptoms and are less likely to cause acute metabolic crises.
› Disorders in this group are not usually recognised by basic metabolic analyses but require specific investigations for their diagnosis.

Disorders in this group typically show slowly progressive clinical symptoms and are less likely to cause acute metabolic crises. They are not usually recognized by basic metabolic analyses but require specific investigations for their diagnosis.

A2.1 Disorders of Purine and Pyrimidine Metabolism

Deficiencies in enzymes required for the biosynthesis or breakdown of purines and pyrimidines cause neuromuscular abnormalities, nephrolithiasis, gouty arthritis, or anemia and immune dysfunction. They may be recognized through increased or reduced urinary urea in relation to creatinine, urine microscopy, or specifically through the analysis of urinary purines and pyrimidines. Some metabolites of pyrimidine breakdown are only recognized by urinary organic acid analysis. Nephrolithiasis may be treated or prevented by allopurinol. A high fluid intake is helpful. Some disorders of pyrimidine metabolism, notably orotic aciduria and overactivity of 5’ nucleotidase (nucleotide depletion syndrome), are treatable with uridine or triacetyluridine. There is no effective treatment for most of the primarily neurological manifestations of disorders of purine metabolism.

A2.2 Lysosomal Storage Disorders

Lysosomes contain a number of hydrolases required for the intracellular breakdown of large lipid and mucopolysaccharide molecules. If one of these enzymes is deficient, its substrate accumulates and causes enlargement and/or functional impairment of the organ system. Clinical features include progressive neurological deterioration, dysmorphic features, and organomegaly. There is usually no metabolic decompensation, although acute symptoms (e.g., severe pain) is a major feature in some conditions. Investigations include careful roentgenographic examination of the skeleton for dysostosis multiplex, analysis of leukocytes and other cells for vacuoles, and assessment of parenchymatous organs. The urine may be investigated for abnormal glycosaminoglycans and oligosaccharides; specific enzyme studies are usually required to make the exact diagnosis. For most disorders there is no specific therapy yet, although enzyme replacement therapy or bone marrow transplantation has been shown beneficial in several disorders.
• **Mucopolysaccharidoses (MPS)**, affected children typically develop progressive dysmorphic features, hepatomegaly and psychomotor retardation or regression. They are usually recognized through the analysis of urine for glycosaminoglycans.

• **Oligosaccharidoses** may resemble the MPS, but many show more severe neurological symptoms and are more frequently symptomatic at birth (nonimmune hydrops fetalis). The diagnosis is made through the demonstration of abnormal oligosaccharide patterns in the urine or enzyme analyses.

• **Sphingolipidoses** and **lipid storage disorders** usually present with progressive neurological deterioration. Hepatomegaly may be present, skeletal deformities and dysmorphic features are rare. Other presentation patterns are found particularly in Fabry disease (pain and paresthesias) and nonneuronopathic Gaucher disease (hematoma, anemia, massive splenomegaly, and abdominal/bone pain). The specific diagnosis usually requires enzyme analysis. The neuronal ceroid lipofuscinoses are usually suspected by electron microscopy and confirmed by mutation analysis. **Mucolipidosis** combine clinical features of the mucopolysaccharidoses and sphingolipidoses and may reflect the deficiency of several lysosomal enzymes as a consequence of defective enzyme processing.

• **Lysosomal transport defects**: Cystinosis causes nephropathy and dysfunction of other organs including the thyroid gland and the eyes; it is diagnosed on the basis of increased cystine content of leucocytes. Sialic acid storage disease causes progressive encephaloneuropathy; it is recognized through elevated free sialic acid in the urine. Both of these disorders result from defective transport out of lysosomes. Cystinosis is treated with oral cysteamine, cysteamine eye drops, and renal transplantation.

**A2.3 Peroxisomal Disorders**

The biochemical roles of peroxisomes are very diverse. Peroxisomal defects usually cause severe, progressive multisystem disorders.

• Defects of **peroxisome biogenesis** or the activation and β-oxidation of long-chain fatty acids cause progressive neurological disease, structural abnormalities as in Zellweger syndrome, and abnormalities in hepatic, intestinal, or adrenal function. They are usually recognized through the analysis of very long-chain fatty acids in blood or cultured fibroblasts. There is no effective treatment.

• Refsum disease is a defect in the metabolism of exogenous **phytanic acid**. It causes slowly progressive neurological, visual, and auditory abnormalities, and often does not present until adulthood. It is diagnosed through the quantification of serum phytanic acid and is treatable by a diet restricted of phytanic acid.

• Defects of **ether-phospholipid biosynthesis** cause rhizomelic chondrodysplasia punctata characterized by proximal shortening of the limbs in addition to neurological and other manifestations. It is diagnosed through quantification of plasmalogens in erythrocytes. There is no effective treatment.

• Catalase deficiency is the only known defect of the **detoxification of oxygen radicals**. It causes chronic ulcers in the oral mucosal membranes.

• Primary hyperoxaluria type I is the only known defect of **glyoxylate metabolism**; it causes nephrolithiasis and nephrocalcinosis. It is recognizable by organic acid or HPLC analysis for oxalate and glyoxylate. It has been treated by transplantation of liver and kidney.

**A2.4 Disorders of the Metabolism of Isoprenoids and Sterols**

Isoprenoids and sterols are essential in many cellular and developmental processes. Most defects of their synthesis are caused by enzyme deficiencies in the postisoprene portion of the pathway. Only mevalonic aciduria and hyperimmunoglobulinemia D syndrome, both due to mevalonate kinase deficiency, are found in the proximal part of the pathway.

• Mevalonate kinase deficiency is the only known defect of **isoprenoid biosynthesis**. It causes dysmorphic features, failure to thrive, mental retardation, and recurrent febrile crises. An attenuated variant causes hyper-IgD syndrome. Treatment is symptomatic.

• Defects of **sterol biosynthesis** cause various structural abnormalities including the dysmorphic features of the Smith–Lemli–Opitz syndrome and mental retardation. Diagnosis involves plasma sterol analysis. In Smith–Lemli–Opitz syndrome, specific treatment by cholesterol supplementation has been of limited success.
A2.5 Disorders of Bile Acid and Bilirubine Metabolism, Inherited Cholestasis and Porphyrias

- Genetic defects of *bile acid biosynthesis* cause symptoms either through bile acid deficiency or through deposition of precursors. The former causes progressive cholestasis and malabsorption, while the precursors can lead to progressive neurological dysfunction and xanthomas. The bile acid biosynthetic pathway is located partly in the peroxisomes and is affected by peroxisomal disorders. Diagnosis involves the analysis of urinary bile acids. Treatment with bile acids is effective in the bile acid deficiency states and to down-regulate bile acid biosynthesis.
- Hem is metabolized to bilirubin and excreted together with bile acids in the urine. Genetic defects may involve specific enzymes or mechanisms of transport into the bile ducts. They cause indirect or direct hyperbilirubinemia. Specific treatment strategies have been developed for some disorders.
- Porphyrias are disorders of hem biosynthesis, frequently inherited as autosomal dominant traits. Neurotoxic metabolites accumulate in deficiencies affecting the first few steps of the pathway and typically cause intermittent acute symptoms such as abdominal pain triggered by various factors, in particular induction of hem-containing enzymes. Porphyrins accumulating in more distal enzyme deficiencies are associated with photosensitivity and dermatological symptoms. The diagnosis involves analysis of porphyrins and porphyrin precursors in urine, feces, or erythrocytes. Management entails the avoidance of precipitating factors.

A2.6 Congenital Disorders of Glycosylation (CDG)

Many proteins including enzymes, transport and membrane proteins, as well as hormones require glycosylation in the Golgi apparatus or endoplasmatic reticulum to render them functional glycoproteins. A deficiency of one of the more than 40 different enzymes involved in glycosylation leads to a wide range of structural abnormalities and disturbances of physiological functions. A disorder from the CDG group should be considered in all patients with unclear multisystem or neurological disorder. The diagnosis in *N*-glycosylation disorders is usually made by isoelectric focussing of transferrin in serum. There is no effective treatment for most disorders of this group.

A2.7 Disorders of Lipoprotein Metabolism

Many disorders of lipoprotein metabolism cause clinical symptoms through the deposition of lipid in tissues and premature atherosclerosis. Others cause gastrointestinal or peripheral neurological problems. They are recognized by quantification of cholesterol and triglycerides and through lipoprotein electrophoresis. Many disorders are open to dietary or pharmacological therapy.

- Elevated blood cholesterol levels in *hypercholesterolemias and mixed hyperlipidemias* cause lipid deposition in the form of xanthomas and xanthelasma. They lead to complications of premature atherosclerosis, especially myocardial infarction and cerebrovascular disease. Therapeutic options include diet, drugs, and lipid apharesis.
- *Hypertriglycerideremia* may be caused by genetic disorders that affect the utilization of chylomicrons and very low-density lipoproteins. They may cause failure to thrive and abdominal symptoms, and sometimes severe pancreatitis. These disorders require stringent restriction of dietary fat.
- Genetic disorders affecting *HDL metabolism* cause a variety of clinical manifestations including premature atherosclerosis, neuropathy, nephropathy, and corneal clouding. Therapy is symptomatic.
- Genetic disorders in which there are *reduced LDL cholesterol and triglycerides* lead to symptoms of fat malabsorption. They are treated by restriction of fat and supplementation with fat soluble vitamins.
Genetic disorders of neurotransmitter metabolism are increasingly recognised as causes of severe metabolic encephalopathy often starting before birth or soon thereafter. Diagnosis usually requires investigations of the CSF. This group should be considered in children with neurological problems when basic metabolic investigations are normal.

A3.1 Disorders of Glycine and Serine Metabolism

Nonketotic hyperglycinemia is one of the best known causes of early-onset epileptic encephalopathy. It is recognised via concomitant amino acid analysis of plasma and CSF. Glycine levels in both are elevated, and the CSF to plasma ratio is increased. Treatment with dextrometorphan, benzoate or folate is of limited success. Disorders of serine biosynthesis cause neurological symptoms. They have been treated with serine and glycine supplementation.

A3.2 Disorders of the Metabolism of Pterins and Biogenic Amines

Affected children suffer from progressive developmental retardation and epileptic encephalopathy. There may be specific symptoms of dopamine and/or serotonin deficiency, such as infantile parkinsonism, dopa-responsive dystonia, oculogyric crises or disturbed temperature regulation. These diseases are sometimes recognised by hyperphenylalaninemia but many exclusively through the analysis of biogenic amines and pterins in CSF.

Disorders of tetrahydrobiopterin biosynthesis and recycling affect the hydroxylation of phenylalanine and have been called atypical or malignant phenylketonuria. The hydroxylations of tyrosine and tryptophan are also affected, leading to deficiency of both, dopamine and serotonin. Investigations should include the analysis of biogenic amines, pterins and amino acids in the CSF as well as amino acids in plasma and pterins in urine. The disorders are treated with L-dopa along with carbidopa and 5-hydroxytryptophan and/or tetrahydrobiopterin and/or tetrahydrobiopterin substitution.

Disorders of the biosynthesis of biogenic amines present similarly with progressive extrapyramidal symptoms and encephalopathy. The deficiency of biogenic amines is treated with of L-dopa along with carbidopa and 5-hydroxytryptophan and/or dopamine agonists.

A3.3 Disorders of Gamma-Aminobutyrate Metabolism

These disorders cause central nervous dysfunction, often including seizures and encephalopathy. They are diagnosed through CSF analysis of amino acids and gamma-aminobutyrate (GABA). Urinary organic acid analysis may reveal 4-hydroxybutyric acid indicative of succinate semialdehyde dehydrogenase deficiency. Vigabatrin has been used in the treatment of SSADH deficiency.
**A3.4 Disorders of Vitamin B<sub>6</sub> Metabolism**

Pyridoxal phosphate (PLP, vitamin B<sub>6</sub>) is a cofactor of all the transamination reactions and some decarboxylation and deamination reactions of amino acids, and as such is also required for the biosynthesis of several neurotransmitters including dopamine and GABA. Intracellular deficiency may be caused by primary or secondary disorders in the biosynthetic pathway and leads to a neonatal epileptic encephalopathy. In the well-known entity of vitamin B<sub>6</sub>-dependent seizures, PLP is inactivated by delta 1-piperideine-6-carboxylate, which accumulates because of an enzyme deficiency in a different pathway. Disorders of vitamin B<sub>6</sub> metabolism are generally treatable with pyridoxine or PLP.

**A3.5 Disorders of Creatine Metabolism**

Creatine is the central compound in cytosolic energy metabolism, and deficiencies in the biosynthesis or transport of creatine manifest as neurometabolic disorders with progressive central nervous dysfunction. They are usually diagnosed through the analysis of creatine and guanidinoacetate in urine and serum; treatment centers on creatine supplementation.

**A3.6 Other Neurometabolic Disorders**

- **Sulphite oxidase deficiency** is a cause of severe infantile seizures and encephalopathy. It is recognised through a sulphite stix test of the urine. Amino acid analysis of plasma and urine may be diagnostic but is less reliable. When it is caused by molybdenum cofactor deficiency there is also xanthine oxidase deficiency, which may be detected by purine analysis of the urine. There is no specific treatment.

- Various cerebral organic acidurias including Canavan disease, L-2- and D-2-hydroxyglutaric aciduria, 2-keto-glutaric aciduria, fumaric aciduria and malonic aciduria present with central nervous dysfunction, which is usually progressive. General metabolic abnormalities are absent, but the specific metabolites are found on organic acid analysis of the urine. The molecular basis of most of the conditions has now been established. There is no specific treatment.
Part B

Approach to the Patient with Metabolic Disease
When to Suspect Metabolic Disease

William L. Nyhan

Key Facts

- Careful clinical and family histories, repeated clinical examinations and a sequential work-up by routine laboratory and organ evaluation remains the best and most often only way to diagnosis.
- While it is imperative to exclude disorders for which effective treatments are available, in cases of slowly progressive, and by experience often incurable disorders, diagnostic procedures should be performed stepwise.
- Unexpected findings in the “routine” laboratory in patients with unusual and unexplained symptoms may be indicative of an inborn error of metabolism.
- Every child who is suspected of suffering from an inborn error of metabolism requires a careful evaluation of organ functions aided by routine laboratory and imaging investigations. The involvement of multiple organ systems is an especially strong indication for an inherited metabolic disease.
- As it can be very difficult to recognize a constellation which was not personally experiences, a second opinion should be sought of in case of unexplained symptoms or disease courses.
- Metabolic investigations are usually not indicated in children with moderate developmental delay, isolated delay in speech development in early childhood, moderate failure to thrive, frequent infections, occasional seizures, e.g. during fever, or defined epileptic syndromes.

B1.1 History

B1.1.1 Family History

A careful family history may reveal important clues that point towards the diagnosis of an inborn error of metabolism. Most metabolic disorders are inherited as autosomal recessive traits, which may be suspected if the parents are consanguineous or the family has a confined ethnic or geographic background. Carriers for particular disorders, and as a consequence affected children, may be more frequent in remote villages, close-knit communities (such as the Amish in Pennsylvania), certain ethnic groups (such as Ashkenazi Jews), or countries that have seen little immigration over many centuries (such as Finland).

Quite often specialist investigations are started only after a second affected child is born into a family. Older siblings may be found to suffer from a similar disorder as the index patient or may have died from an acute unexplained disease classified as “sepsis with unidentified pathogen,” “encephalopathy” or “sudden infant
death syndrome.” The latter is a frequent feature in disorders of intermediary metabolism that may have acute lethal presentations such as disorders of ammonia detoxification, organic acidurias, or fatty acid oxidation disorders.

In assessing medical records of previously affected but undiagnosed family members, it should be taken into account that the written clinical descriptions of complex conditions can be inconsistent and even misleading. Depending on the presumptive diagnosis at that time, important clinical clues may be missing. Parents are sometimes more reliable sources of information. On the other hand, the clinical expression of the same inborn error of metabolism may be variable even within families. Some more common Mendelian disorders are caused by a wide range of different mutations with different degrees of disease severity. Disease manifestations are especially variable in females with X-linked traits because of differences in the lyonization of the X chromosome in carrier females, e.g., ornithine transcarbamylase deficiency. Similarly, dominant disorders with variable penetrance may cause variable clinical problems in different members and generations even of one family, such as Segawa syndrome due to GTP cyclohydrolase deficiency.

As a result of the successful treatment of disorders of intermediary metabolism in which toxic small molecules accumulate, an increasing number of relatively healthy affected women are reaching the reproductive age. If they become pregnant, there is a risk for their fetuses to be harmed by pathological amounts of toxic metabolites from the mother, although the children are themselves not affected but heterozygous. Especially important is maternal phenylketonuria (PKU), which is likely to become a major health problem. Some women at risk may not even know that they are affected with PKU, if they come from countries where newborn screening did not exist or if they have discontinued dietary treatment and medical follow-up in late childhood. The latter will however remember that they had followed a special diet, which should be specifically asked for. Several mothers have been found to suffer from mild PKU only after maternal PKU was diagnosed in one of her children. Other maternal conditions may cause “metabolic” disease in the neonate or infant postnatally, e.g., methylmalonic aciduria and hyperhomocystinemia in fully breastfed children of mothers ingesting a vegan diet, which causes nutritional vitamin B₁₂ deficiency.

**B1.1.2 Prenatal Development and Complications of Pregnancy**

Toxic small molecules that accumulate in many disorders of intermediary metabolism do not harm the fetus because they are removed via the placenta and metabolized by the mother. Children affected with such disorders usually have a completely normal intrauterine development and are born with normal birth measurements at term. In contrast, disorders that interfere with cellular energy metabolism, e.g., mitochondrial disorders, may impair fetal organ development and prenatal growth, causing structural (in particular cerebral) abnormalities, dysmorphic features, and dystrophy. Structural abnormalities and dysmorphic features may be even more pronounced in disorders of the biosynthesis of complex molecules that are necessary for developmental pathways and networks. Notable examples are the defects of sterol biosynthesis that interfere with cholesterol-dependent signaling pathways of development and cause, for example, the Smith–Lemli–Opitz syndrome. Disorders affecting the breakdown of complex molecules such as lysosomal storage disorders cause specific dysmorphic characteristics as in the Hurler disease, and when severe, may already present at birth. An unusual prenatal disease manifestation is found in mothers carrying a fetus affected with long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency or carnitine palmitoyltransferase II deficiency, defects of fatty acid β-oxidation. These mothers have an increased risk of developing acute fatty liver of pregnancy, preeclampsia, or hemolysis, elevated liver enzymes, and low platelets (the HELLP syndrome). Systematic studies in mothers showed that fetal LCHAD deficiency is present in a significant number of women with acute fatty liver of pregnancy, but only in a very small proportion of the far more common HELLP syndrome. The neonates of such mothers should be screened for fatty acid oxidation disorders by acylcarnitine analysis in a dried blood spot.

**B1.1.3 Age of Presentation and Precipitating Factors**

The “typical” ages of manifestation of different groups of metabolic disorders in the first year of life are depicted
When to Suspect Metabolic Disease

Disorders of intermediary metabolism that cause symptoms through the accumulation of toxic molecules (“intoxication”) are usually asymptomatic in the first hours of life. They present after exposure to the respective substrate derived from catabolism or diet. Postnatal protein breakdown requires amino acid catabolism and nitrogen detoxification. Patients with acute aminoacidopathies (e.g., maple syrup urine disease (MSUD)), classical organic acidurias, or urea cycle defects most frequently develop progressive symptoms between days 2 and 5 of life. Subsequent risk periods include the second half of the first year of life (in particular, age 6–8 months) when solid meals with higher protein content are introduced and the children start to fast overnight, and late puberty when hormonal changes and a reduced growth rate change the metabolic state. Important precipitating factors throughout life are catabolic states caused by infections, fever, vaccinations, high-dose steroid therapy, surgery and accidents, as well as prolonged fasting.

Of the disorders of carbohydrate metabolism, galactosemia usually presents after the introduction of milk (which contains the galactose–glucose disaccharide lactose) in the first week of life, while children with hereditary fructose intolerance develop symptoms after the introduction of fruits, vegetables, and particularly table sugar (the fructose–glucose disaccharide sucrose) to the diet, often between 4 and 8 months of age.

Disorders with a reduced fasting tolerance include genetic defects of fatty acid oxidation and ketogenesis, as well as deficiencies in the production and release of glucose. They typically present during periods of reduced food intake and/or increased energy requirement such as prolonged fasting or metabolic stress, and the age of presentation thus overlaps with the “intoxication” disorders. However, the disorders with reduced fasting tolerance are less frequently or less severely symptomatic in the postnatal period and more frequently present in association with infections in the second half of infancy.

Disorders of energy metabolism are frequently symptomatic at birth, but may essentially present at any time of life, depending on the severity of the genetic defect and the organs involved. Acute decompensation in mitochondrial disorders may specifically be triggered by major alterations in carbohydrate intake or the
ingestion of large amounts of rapidly absorbed carbohydrates, while long-chain fatty acids that interfere with energy metabolism in some β-oxidation defects cause clinical features of a mitochondrial disorder during fasting periods. Another characteristic feature of mitochondrial disorders is a marked and frequently irreversible deterioration of the clinical condition with intercurrent illnesses.

Disorders in the metabolism of complex molecules rarely show acute metabolic crises but present with variable and often progressive organ dysfunction throughout childhood. There are usually no precipitating factors. The clinical presentation of neurotransmitter defects and related disorders depends on the ontogenetic expression of neurotransmitter systems and receptors. Affected children are often symptomatic immediately after birth, and there may even be symptoms of intrauterine epilepsy as evidence of prenatal disease manifestations. There are usually no precipitating factors.

**B1.2 Physical Examination**

Every child who is suspected of suffering from an inborn error of metabolism requires a thorough physical examination and a careful evaluation of organ functions aided by routine laboratory and imaging investigations. In addition, hearing and vision should be examined at specialist appointments. Depending on the presenting symptoms and the clinical course, a reevaluation, especially a detailed physical examination, should be repeated every 6 months. The detection of additional manifestations is of great importance even if the patient does not complain of them, particularly if the final diagnosis is still unknown.

The involvement of multiple organ systems is one of the strongest arguments in favor of an inherited metabolic disease. This is especially true for defects of organelle metabolism such as mitochondrial or peroxisomal disorders or the quickly enlargeing group of glycosylation defects or CDG syndromes. Structural abnormalities such as dysmorphic features or malformations may be caused by disorders in the metabolism of complex molecules as well as disorders affecting mitochondrial energy metabolism, but are not usually observed in other disorders of intermediary metabolism.

Generalized organomegaly is often indicative of a (lysosomal) storage disorder, while isolated hepatomegaly is observed in a great variety of enzyme defects. Urine color and body odor can provide diagnostic clues, as discussed later. A list of differential diagnoses of characteristic symptoms and signs is given in the appendix.

**B1.2.1 Unusual Odor**

Unaccustomed odors can serve as alerting signals for several metabolic diseases (Table B1.1). The most commonly encountered is the sweet smell of acetone found in the acute ketoacidosis of diabetes mellitus and the organic acidemias. Other characteristic odors are that of MSUD, the acrid smell of isovaleric acidemia and glutaric aciduria type II, and the odor of phenylacetic acid in PKU. The phenylacetic acid odor is much more prominent in patients with urea cycle defects, treated with sodium phenylacetate, or phenylbutyrate. Very prominent unpleasant odors are found in trimethylaminuria and dimethylglycinuria. Odors can be very useful in suggesting a diagnosis or an appropriate test. It is also important not to discard a potential diagnosis because of the absence of the odor. Some people are simply unable to detect some odors. Many physicians have never really been able to smell the ketotic patient. In other conditions, the acute metabolic crisis leads to a cessation of oral intake and vigorous parental fluid therapy, so that by the time the

<table>
<thead>
<tr>
<th>Odor</th>
<th>Substance</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal like</td>
<td>Phenylacetate</td>
<td>PKU</td>
</tr>
<tr>
<td>Maple syrup</td>
<td>Sotolone</td>
<td>Maple syrup urine disease</td>
</tr>
<tr>
<td>Acrid, short-chain acid</td>
<td>Isovaleric acid</td>
<td>Isovaleric aciduria, glutaric aciduria type II</td>
</tr>
<tr>
<td>Cabbage</td>
<td>2-Hydroxybutyric acid</td>
<td>Tyrosinemia type I, Methionine malabsorption</td>
</tr>
<tr>
<td>Rancid butter</td>
<td>2-Keto-4-methylbutyric acid</td>
<td>Tyrosinemia type I</td>
</tr>
<tr>
<td>Rotten fish</td>
<td>Trimethylamine, dimethylglycine</td>
<td>Trimethaminuria, dimethylglycinuria</td>
</tr>
</tbody>
</table>
When to Suspect Metabolic Disease

A patient reaches the referral hospital the odor has long since disappeared.

**Remember**

Diagnosis by smell is underutilized, but many are not good at it. Too, a characteristic odor maybe absent in a severely ill infant partaking nothing by mouth and receiving parenteral fluids.

The odor of maple syrup led to the recognition and original description of MSUD, before it was known that this was a disorder in the metabolism of the branched-chain amino acids. A keen sense of smell can still be useful in the detection of this disease, but the seriousness of the presentation of metabolic imbalance and a readiness to carry out an analysis of amino acids in plasma are such that most patients diagnosed today do not trigger the smell test. This is also true of acute exacerbation in established patients. Testing for urinary ketones with DNPH and organic acid analysis of the urine are also useful in the diagnosis of this disease. The odor of the patient with isovaleric acidemia has been described as like that of sweaty feet, but it does not smell anything like a locker room. The smell is penetrating, pervasive, and readily recognized. It is the odor of a short-chain volatile acid, and the same smell may be appreciated in patients with multiple acyl-CoA dehydrogenase deficiency (glutaric aciduria type II) during times of acute illness.

Now that screening of newborns for PKU is universal in developed countries, patients with this disease are not likely to be diagnosed because of the characteristic odor, but some of us have made the diagnosis in this way in patients born prior to the development of screening. The odor of the patient with isovaleric acidemia has been described as like that of sweaty feet, but it does not smell anything like a locker room. The smell is penetrating, pervasive, and readily recognized. It is the odor of a short-chain volatile acid, and the same smell may be appreciated in patients with multiple acyl-CoA dehydrogenase deficiency (glutaric aciduria type II) during times of acute illness.

The classic unpleasant odor is that of patients with trimethylaminuria. Trimethylamine is the odor of fish that is not fresh. The compound is a major end product of nitrogen metabolism of teleost fishes, which convert it to the oxide and employ the resulting compound to balance their osmotic pressure with surrounding sea water. In man, trimethylamine is formed from dietary trimethylamine oxide in fish and from choline absorbed from the intestine and transported to the liver, where the trimethylamine oxide is formed and ultimately excreted in the urine. Patients with trimethylaminuria have an inborn error in the metabolism of the oxide, defective activity of hepatic trimethylamine N-oxide synthetase. The metabolic abnormality does not appear to produce a disease as we usually know one; its consequences are nevertheless terrible. An odor so unpleasant leads to social ostracism, poor performance in school, depression, and loss of employment. Suicide is a possibility. Diagnosis is important because a diet low in fish, liver, and egg yolks is usually sufficient to eliminate the odor. The diagnosis is made by identifying the compound by gas chromatography, gas chromatography–mass spectroscopy (GC–MS), FAB-MS, or nuclear magnetic resonance (NMR) spectroscopy. Its excretion is increased by loading with choline, and this may be necessary for the diagnosis in patients who have found dietary ways of minimizing their odor. Following a morning specimen of urine, a 5 g oral supply of choline bitartrate in 3 doses over 24 h led to a 44-fold increase in trimethylamine excretion to $1.098 \, \text{mmol/mg creatinine}$. Normal individuals excreted $0.0042–0.405 \, \text{mmol/mg creatinine}$. The activity of the enzyme has been measured in biopsied liver. It is a flavin-containing monoxygenase, designated FMO₅. Several mutations in the gene have been identified.

Patients have been described in whom the odor of trimethylamine is mild or intermittent. Mutations have been identified in the FMO₅ gene on chromosome 1q23–25. For instance, the P153L mutation has been identified in patients with severe trimethylaminuria and no enzyme activity in vitro. The patients with the mild phenotype have had an allele with two common polymorphisms, E158K in which a 472G→A mutation coded for a lysine instead of a glutamate, and E3086 in which a 923A→G mutation coded for glycine instead of glutamate. Patients have generally been heterozygous for this allele and a disease-producing mutation, but one patient has been homozygous for the variant allele. The

Patients with hepatorenal tyrosinemia and other nonmetabolic patients with hepatic cirrhosis may have a very unpleasant odor that results from the accumulation of methionine.

The image contains text discussing the diagnosis and detection of metabolic diseases, focusing on the smell of patients. The text highlights the importance of smell in diagnosing conditions like MSUD, PKU, and trimethylaminuria, and describes the odors associated with these diseases. The text also notes the challenges and consequences of these odors, as well as the diagnostic methods and potential for treatment through dietary interventions and enzyme deficiencies.
variant allele is common in Caucasian populations; allele frequency was found to be 20% in Germans.

**Dimethylglycinuria** is a newly recognised inborn error of metabolism that causes a fishy odor. The defective enzyme is the dimethylglycine dehydrogenase, which catalyzes the conversion of this compound to sarcosine. A missense mutation in the gene has been identified in an affected patient. Trimethylamine was absent from the patient’s urine. He also complained of muscle fatigue and had elevated levels of creatine kinase in the serum. Dimethylglycine is most readily detected by 1H-NMR spectroscopy. Its presence was confirmed by 13C-NMR spectroscopy and by GC–MS of nonextracted urine, but the compound could not be detected by GC–MS after the usual ethylacetate extraction.

### B1.2.2 Color of the Urine or Diaper

Physicians since at least the time of Hippocrates have recognized that the color of the urine may be the clue that leads to the diagnosis. It was Garrod’s recognition of the significance of the dark urine of patients and families with alkaptonuria that led to the conceptualization of the inborn errors of metabolism.

**Alkaptonuria** is recognized surprisingly infrequently in this way, and many patients reach adulthood and clinical arthritis before the diagnosis is made. This is the result of many factors, among them that the black pigment forms with time and oxygen, and that flushing does away with both. In a patient in whom one seeks to make this visual diagnosis, it is best to alkalinize and shake the urine and look with excellent light for the fine black precipitate. In times past when infants wore cloth diapers, which were laundered with strong alkaline soap, the conditions were perfect, and the diagnosis could be made by the appearance of black pigment in the diaper. Now they wear plastic disposable diapers, many of which turn pink on contact with alkaptonuric urine. So, we can still make the diagnosis early by examining the diaper.

Alkaptonuric urine also gives a positive test for reducing substance and is glucose-negative, and this may be an alerting signal for the diagnosis. Homogentisic acid also reduces the silver in photographic emulsion, and alkaptonuric urine has been used to develop a photograph, an interesting qualitative test for the diagnosis.

The diagnosis is confirmed by quantitative analysis of homogentisic acid in the urine.

#### B1.2.2.1 Examination of the Urine for the Significance of Color

Urine has a normal amber color that is the color of the pigment urochrome. Pale, dilute, or watery urine results from a plentiful fluid intake or diuresis as in diabetes mellitus or diabetes insipidus, or in the recovery phase of a tubular necrosis. Very dark urine or concentrated urine results from dehydration. Pale urine with a high specific gravity suggests diabetes mellitus. Dark urine with a low specific gravity suggests the presence of urobin or bilirubin and is best checked by analysis of the blood for bilirubin. Very bright yellow urine may be seen in infants who ingest large amounts of carotene, but the skin of such infants is usually carotenemic. Urine may, of course, be red because of hematuria, but this is readily recognized by microscopic analysis, and such a specimen is not the subject of differential diagnosis by color. Free hemoglobin in the urine appears brown or black as methemoglobin is formed. The most famous example of this is the black water fever of malaria.

#### B1.2.2.2 Dark Brown or Black Urines

In addition to alkaptonuria, **hemoglobinuria** and **myoglobinuria** both produce brown or dark urine and both are detected by the dipstix for hemoglobin or by the benzidine test. Hemoglobin in the urine is often accompanied by hematuria. Hemoglobinuria in the absence of red cells in the urine is accompanied by evidence of hemolysis, such as anemia, reticulocytosis, or hyperbilirubinemia, while myoglobinuria is often accompanied by muscle pains or cramps and elevation of creatine phosphokinase and uric acid. An
When to Suspect Metabolic Disease

B1 When to Suspect Metabolic Disease

When to suspect metabolic disease

When to suspect metabolic disease, an attack of myoglobinuria should signal a work-up for a disorder of fatty acid oxidation (Chap. C6). It is also seen in enzyme defects localized to muscle, such as myophosphorylase deficiency (McArdle disease) and myodenylate deaminase deficiency. Melaninuria is seen in disseminated melanotic sarcoma.

B1.2.2.3 Red Urine

Porphyrias are the major metabolic cause of red urine. Congenital erythropoietic porphyria is an autosomal recessive disease caused by mutations in the gene for uroporphyrinogen synthase. Uroporphyrina and coproporphyrina are found in the urine. It manifests a variable phenotype from nonimmune hydrops fetalis to a mild adult-onset form with only photosensitive cutaneous lesions. The disease is often first recognized because of a pink, red, or brown stain in the diapers. These patients also develop erythroodontia in which a red fluorescence of the teeth is visible with ultraviolet illumination.

Red urine may also be seen following the ingestion of large quantities of colored foods. The anthrocyaninuria of beet ingestion is quite common. Blackberries have also been associated with red urine. Red dyes, such as rhodamine B, used to color foods and cold drinks have led to red urine of so many children after a weekend party that the condition was termed the Monday morning disorder. Phenolphthalein in laxatives may also cause red urine. In the neonatal period, distinct red spots in the diaper were seen where crystals of ammonium urate dried out. In previous days when cloth diapers were used and accumulated for a while before laundering, a red diaper syndrome was recognized in which the color developed after 24 h of incubation and came from the growth of the chromobacterium, *Serratia marcescens*, which does not produce pigment in the infant’s intestine, but only after aerobic growth at 25–30°C. Red stools may also be seen after the ingestion of red crayons, and in some patients receiving cefdinir, in most but not all of whom receive oral iron.

B1.2.2.4 Green or Blue Urines

Blue pigment in urine containing urochrome usually leads to a green color. Blue color was seen in the blue diapery syndrome. This disorder of the intestinal absorption of tryptophan was described in two siblings who also had hypercalcemia and nephrocalcinosis.
When tryptophan is not efficiently absorbed, intestinal bacteria convert it to indole metabolites that are absorbed and excreted in the urine. The blue color comes from the oxidative conjugation of two molecules of indican to indigotin, or indigo blue, a water insoluble dye. The excretion of indole products is increased by an oral tryptophan load. The condition must be very rare because further patients have not been reported since the initial report in 1964. Indoles including indican are also found in the urine of patients with Hartnup disease, in which there is defective renal tubular reabsorption, as well as intestinal absorption of a number of amino acids including tryptophan, but blue diapers or urine have not been observed.

Biliverdin, the oxidation product of bilirubin, is excreted in the urine, and so green urine may be seen in jaundiced patients, particularly those with chronic obstructive jaundice.

Benign pigments such as methylene blue, found in some tablets, are excreted in urine, and if a sufficient quantity is taken, will color the urine. Indigo-carmine is another blue dye that may find its way into food stuffs.

### B1.3 Routine Laboratory Investigations

Unexpected findings in the “routine” laboratory require critical evaluation. Particularly in patients with unusual and unexplained symptoms they may be indicative of an inborn error of metabolism and can help to direct specific diagnostic investigations. Table B1.3 gives a noncomprehensive collection of such sometimes unexpectedly obtained laboratory abnormalities that may be suggestive of certain metabolic disorders.

### B1.4 When Not to Suspect a Metabolic Disease

Inborn errors of metabolism may be considered in the differential diagnosis of a great variety of clinical problems, and at times it can be difficult to decide that specialist metabolic investigations are not warranted. Whether or not certain specialist investigations are indicated quite obviously also depends on secondary factors such as local or national availability, costs of the test, the likelihood of litigation, and the personal experience of the clinician. It is imperative to exclude disorders for which effective treatments are available, while in cases of slowly progressive, and by experience often incurable disorders diagnostic procedures should be performed stepwise depending on the results of the first
investigations and the appearance and development of signs and symptoms with time. The diagnosis of some metabolic disorders involves procedures that are stressful, such as sedation or lumbar puncture, or potentially dangerous for the child (e.g., fasting or loading studies), and that are often also stressful for the parents. Psychosocial factors should be taken into consideration when the diagnostic work-up is planned. The families need to be guided and supported. In the worst case, a specific diagnosis with a doomed prognosis that shatters the expectations of the parents can even damage the parent–child relationship. On the other hand, in almost all families a specific diagnosis no matter how negative will be one of the most important supports for coping, and of course is critical for timely genetic diagnosis in young families and appropriate counseling.

Specialist metabolic investigations are not usually indicated in children with moderate developmental delay, isolated delay in speech development in early childhood, moderate failure to thrive, frequent infections, occasional seizures, e.g., during fever, or defined epileptic syndromes. An inborn error of metabolism is also unlikely in the healthy sibling of an infant who died of SIDS, provided that this child had been previously asymptomatic. Key factors in the evaluation of symptoms are their isolated appearance vs. the presence of additional pathology, however subtle, i.e., the lack or presence of additional neurological and/or systemic abnormalities, and a static vs. a progressive clinical course. Multisystem or progressive disorders are much more likely to be caused by inborn errors of metabolism.

Key References


