1 A Clinical Approach to Inherited Metabolic Diseases

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Introduction

Inborn errors of metabolism (IEM) are individually rare, but collectively numerous. The recent application of tandem mass spectrometry (tandem MS) to newborn screening and prenatal diagnosis has enabled pre-symptomatic diagnosis for some IEM. However, for most, neonatal screening tests are either too slow, expensive or unreliable and, as a consequence, a simple method of clinical screening is mandatory before initiating sophisticated biochemical investigations. The clinical diagnosis of IEM relies upon a limited number of principles:

- To consider IEM in parallel with other more common conditions; for example, sepsis or anoxic-ischemic encephalopathy in neonates, and intoxication, encephalitis and brain tumors in older patients.
- To be aware of symptoms that persist and remain unexplained after the initial treatment and the usual investigations have been performed.
- To suspect that any neonatal death may possibly be due to an IEM, particularly those that have been attributed to sepsis.
- To carefully review all autopsy findings.
- Not to confuse a symptom (such as peripheral neuropathy, retinitis pigmentosa, cardiomyopathy, etc.) or a syndrome (such as Reye syndrome, Leigh syndrome, sudden infant death, etc.) with etiology.
- To remember that an IEM can present at any age, from fetal life to old age.
- To know that although most genetic metabolic errors are hereditary and transmitted as recessive disorders, the majority of individual cases appear sporadic because of the small size of sibships in developed countries.
- To initially consider inborn errors which are amenable to treatment (mainly those that cause intoxication).
- In the acute, emergency situation, to undertake only those few investigations that are able to diagnose treatable IEM.
- To obtain help from specialized centers.

Based mainly upon personal experience over 40 years, this chapter gives an overview of clinical clues to the diagnosis of inborn errors of metabolism in pediatrics and adulthood. In the following pages, inborn errors amenable to treatment are printed in bold.

Do not miss a treatable disorder
First take care of the patient (emergency treatment) and then the family (genetic counselling)

1.1 Classification of Inborn Errors of Metabolism

1.1.1 Pathophysiology

From a pathophysiological perspective, metabolic disorders can be divided into the following three diagnostically useful groups.

Group 1: Disorders which give rise to intoxication. This group includes inborn errors of intermediary metabolism that lead to an acute or progressive intoxication from the accumulation of toxic compounds proximal to the metabolic block. In this group are the inborn errors of amino acid catabolism (phenylketonuria, maple syrup urine disease, homocystinuria, tyrosinemia etc.), most organic acidurias (methylmalonic, propionic, isovaleric etc.), congenital urea cycle defects, sugar intolerances (galactosemia, hereditary fructose intolerance), metal intoxication (Wilson, Menkes, hemochromatosis), and porphyrias. All the conditions in this group share clinical similarities: they do not interfere with the embryo-fetal development and they present with a symptom-free interval and clinical signs of »intoxication«, which may be acute (vomiting, coma, liver failure, thromboembolic complications etc.) or chronic (failure to thrive, developmental delay, ectopia lentis, cardiomyopathy etc.). Circumstances that can provoke acute metabolic attacks include catabolism, fever, intercurrent illness and food intake. Clinical expression is often both late in onset and intermittent. The diagnosis is straightforward and most commonly relies on plasma and urine amino acid, organic acid and acylcarnitine chromatography. Most of these disorders are treatable and require the emergency removal of the toxin by special diets, extra-corporeal procedures, or »cleansing« drugs (carnitine, sodium benzoate, penicillamine, etc.).

Although the pathophysiology is somewhat different the inborn errors of neurotransmitter synthesis and catabolism (monoamines, GABA and glycine) and the inborn errors of amino acid synthesis (serine, glutamine, and proline/ornithine) can also be included in this group since they share many characteristics: they are inborn errors of intermediary metabolism, their diagnosis relies on plasma, urine, and CSF investigations (amino acid, organic acid analyses etc.), and some are amenable to treatment even when the disorder starts in utero, for example 3-phosphoglycerate dehydrogenase deficiency [1].

Group 2: Disorders involving energy metabolism. These consists of inborn errors of intermediary metabolism with symptoms due at least partly to a deficiency in energy production or utilization within liver, myocardium, muscle, brain or other tissues. This group can be divided into mitochondrial and cytoplasmic energy defects. Mitochondrial defects are the most severe and are generally untreatable.

They encompass the congenital lactic acidemias (defects of pyruvate transporter, pyruvate carboxylase, pyruvate dehydrogenase, and the Krebs cycle), mitochondrial respiratory chain disorders and the fatty acid oxidation and ketone body defects. Only the latter are partly treatable. Cytoplasmic energy defects are generally less severe. They include disorders of glycolysis, glycogen metabolism and gluconeogenesis, hyperinsulinism (all treatable disorders), the more recently described disorders of creatine metabolism (partly treatable), and the new inborn errors of the pentose phosphate pathway (untreatable). Common symptoms in this group include hypoglycemia, hyperlactatemia, hepatomegaly, severe generalized hypotonia, myopathy, cardiomyopathy, failure to thrive, cardiac failure, circulatory collapse, sudden unexpected death in infancy, and brain involvement. Some of the mitochondrial disorders and pentose phosphate pathway defects can interfere with the embryo-fetal development and give rise to dysmorphism, dysplasia and malformations [2]. Diagnosis is difficult and relies on function tests, enzymatic analyses requiring biopsies or cell culture, and on molecular analyses.

Group 3: Disorders involving complex molecules. This group involves cellular organelles and includes diseases that disturb the synthesis or the catabolism of complex molecules. Symptoms are permanent, progressive, independent of intercurrent events and unrelated to food intake. All lysosomal storage disorders, peroxisomal disorders, disorders of intracellular trafficking and processing such as alpha-1-antitrypsin, congenital disorders of glycosylation (CDG), and inborn errors of cholesterol synthesis belong to this group. Almost none are treatable acutely; however enzyme replacement therapy is now available for several lysosomal disorders.

1.1.2 Clinical Presentation

Besides newborn screening in the general population (as for phenylketonuria) or in at-risk families, there are four groups of clinical circumstances in which physicians are faced with the possibility of a metabolic disorder:

- Early symptoms in the antenatal and neonatal period
- Later-onset acute and recurrent attacks of symptoms such as coma, ataxia, vomiting, and acidosis
- Chronic and progressive generalised symptoms which can be mainly gastrointestinal (chronic vomiting, failure to thrive), muscular or neurological (developmental delay, neurological deterioration)
- Specific and permanent organ presentations suggestive of an inborn error of metabolism, such as cardiomyopathy, hepatomegaly, lens dislocation etc.

These four categories of clinical conditions are presented in the following sections. For the first two categories, which often present as emergencies and are treatable, the clinical presentations, the metabolic abnormalities and the laboratory tests required for a tentative diagnosis, are described in detail. Chronic progressive generalised symptoms and signs which raise suspicion of an IEM are listed in tables that take into account system and organ involvement, leading symptoms and other signs, and age of onset. Specific organ presentations are listed in alphabetical order. For each presentation, the diagnostic possibilities listed encompass not only inborn errors of metabolism, but also diverse inherited syndromes which mimic and are possibly related to inborn errors, and a number of non-inherited disorders which should be considered in the differential diagnosis. All treatable disorders are printed in **bold**.

1.2 Acute Symptoms in the Neonatal Period and Early Infancy (<1 Year)

1.2.1 Clinical Presentation

The neonate has a limited repertoire of responses to severe illness [2–4]. IEM may present with non-specific symptoms such as respiratory distress, hypotonia, poor sucking reflex, vomiting, diarrhea, dehydration, lethargy, seizures; problems which can easily be attributed to infection or some other common cause. Where a previously affected sibling has died, this may have been falsely attributed to sepsis, heart failure, or intraventricular hemorrhage, and it is important to critically review clinical records and autopsy reports when they are available.

In group 1 disorders (IEM that give rise to intoxication), an extremely suggestive clinical picture is that of a baby, born at full-term after a normal pregnancy and delivery, who, after an initial entirely symptom-free period, relentlessly deteriorates for no apparent reason and does not respond to symptomatic therapy. The interval between birth and clinical symptoms may range from hours to weeks, depending on the nature of the metabolic block and the environment. Investigations, routinely performed in sick neonates, including a chest X-ray, CSF examination, bacteriologic studies, and cerebral ultrasound, yield normal results. This unexpected and »mysterious« deterioration after a normal initial period is the most important indication for this group of IEM. Careful re-evaluation of the child's condition is then warranted. In this context signs previously interpreted as non-specific manifestations of neonatal hypoxia, infection, or other common diagnoses take on a new significance. In energy deficiencies (group 2 disorders), clinical presentation is often less evocative and displays variable severity. A clinical algorithm for screening for treatable IEM in neonates is presented in ◘ Table 1.1.

A careful reappraisal of the child is warranted for the following:

Table 1.1. The »sick« neonate: an algorithm for screening for treatable inborn errors of metabolism

Premature Low birth weight	Full term neonates appropriately grown for gestational age			
↓	↓	↓	↓	↓	↓
– Not suggestive but possibility of fortuitous association – If head circumference is small, think of maternal PKU	**Inborn metabolic diseases**	»Traumatic« »Accidental« hypoxia Intracranial injury	Infection	Major electrolyte disturbances: – Hypo/hypercalcemia – Hypo/hypernatremia – Hypo/hyperkaliemia	Isolated/multiple malformations Polymalformation syndromes
↓	↓	↓	↓	↓	↓
First think of **treatable disorders** Emergency treatment must be undertaken in parallel with investigations (Chap. 3)		Clinical history Chest X-ray Cranial ultrasound	»Septic screen« Antibiotics	»Simple metabolic screen« Hormonal, renal investigation	Radiologic investigation Echography Genetic advice

↓	↓	↓	↓	↓
Neurological deterioration (intoxication)	Predominant seizures	Jaundice Liver failure	Cardiac failure Heart beat disorders	Persistent hypoglycemia
↓	↓	↓	↓	↓
MSUD **MMA** **PA** **IVA** **MCD** **UCD**	**B6-responsive seizures** **PNPO** (pyridoxal-P) **MCD** (biotin) **folinic acid resp. seizures** **3PGD** (serine) **GLUT1** (ketotic diet)	**Galactosemia** **HFI** **Tyrosinemia** **CDG type Ib** (with diarrhea) **Bile acid synthesis defects** (with cholestasis) **LCHAD**	**FAO defects**	**Glycogenosis** **PHHI** **FAO defects**

CDG, congenital disorders of glycosylation; *FAO*, fatty acid oxidation; *HFI*, hereditary fructose intolerance; *IVA*, isovaleric acidemia; *LCHAD*, 3-hydroxy long chain acyl-CoA dehydrogenase deficiency; *MCD*, multiple carboxylase deficiency; *MMA*, methylmalonic aciduria; *MSUD*, maple syrup urine disease; *PA*, propionic acidemia; *PHHI*, primary hyperinsulinemic hypoglycemia of infancy; *PKU*, phenylketonuria; *UCD*, urea cycle defects; *PNPO*, pyridox(am)ine-5'-phosphate oxidase deficiency; *3PGD*, 3-phosphoglycerate dehydrogenase deficiency; **bold face**, treatable disorders.

Neurological Deterioration (Coma, Lethargy)

Most inborn errors that result in intoxication or energy deficiency are brought to a doctor's attention because of neurological deterioration. With intoxication, the initial symptom-free interval varies in duration depending on the condition. Typically, the first reported sign is poor sucking and feeding, after which the child sinks into an unexplained coma despite supportive measures. At a more advanced state, neurovegetative problems with respiratory abnormalities, hiccups, apneas, bradycardia, and hypothermia can appear. In the comatose state, characteristic changes in muscle tone and involuntary movements appear. In **maple syrup urine disease (MSUD)** generalized hypertonic episodes with opisthotonus are frequent, and boxing or pedalling movements as well as slow limb elevations, spontaneously or upon stimulation, are observed. Conversely, most non metabolic causes of coma are associated with hypotonia, so that the presence of »normal« peripheral muscle tone in a comatose child reflects a relative hypertonia. Another neurological pattern observed in **organic acidurias** is axial hypotonia and limb hypertonia with large amplitude tremors and myoclonic jerks which are often mistaken for convulsions. An abnormal urine and body odor is present in some diseases in which volatile metabolites accumulate; the most important examples are the maple syrup odor of **MSUD** and the sweaty feet odor of **isovaleric acidemia (IVA)** and **type II glutaric acidemia**. If any of the preceding signs or symptoms are present, metabolic disorders should be given a high diagnostic priority.

In energy deficiencies, the clinical presentation is less evocative and displays a more variable severity. In many conditions, there is no symptom-free interval. The most frequent findings are a severe generalized hypotonia, rapidly progressive neurological deterioration, and possible dysmorphism, or malformations. However, in contrast to the intoxication group, lethargy and coma are rarely initial signs. Hyperlactatemia with or without metabolic acidosis is very frequent. Cardiac and hepatic involvement are commonly associated (► below).

Only a few lysosomal storage disorders present in the neonatal period with neurological deterioration. By contrast, most peroxisomal biogenesis defects present at birth with dysmorphism and severe neurological dysfunction.

Seizures

Five treatable disorders can present in the neonatal period predominantly with intractable seizures: **pyridoxine responsive seizures**, **pyridox(am)ine-5'-phosphate oxidase deficiency**, **folinic acid responsive seizures**, **3-phosphoglycerate dehydrogenase deficiency** responsive to serine supplementation and persistent **hyperinsulinemic hypoglycemia**.

Biotin responsive **holocarboxylase synthetase deficiency** can also rarely present predominantly with neonatal seizures. **GLUT1 deficiency** (brain glucose transporter), responsive to hyperketotic diet, and biotin responsive **biotinidase deficiency** can also present in the first months of life as an epileptic encephalopathy.

Many other non treatable inherited disorders can present in the neonatal period with severe epilepsy: non ketotic hyperglycinemia (NKH), D-2-hydroxyglutaric aciduria, and mitochondrial glutamate transporter defect (all three presenting with myoclonic epilepsy and a burst-suppression EEG pattern), peroxisomal biogenesis defects, respiratory chain disorders, sulfite oxidase deficiency and Menkes disease. In all these conditions, epilepsy is severe, with an early onset, and can present with spasms, myoclonus, partial or generalized tonic/clonic crises.

Hypotonia

Severe hypotonia is a common symptom in sick neonates. It is generally observed in non metabolic inherited diseases (mainly in severe fetal neuromuscular disorders). Only a few inborn errors of metabolism present with isolated hypotonia in the neonatal period and only very few are treatable. Discounting disorders in which hypotonia is part of a constellation of abnormalities, including, for example, major bone changes, dysmorphism, malformations, or visceral symptoms, the most severe metabolic hypotonias are observed in hereditary hyperlactatemia, respiratory chain disorders, urea cycle defects, NKH, sulfite oxidase (SO) deficiency, peroxisomal disorders, and trifunctional enzyme deficiency. Central hypotonia is associated with lethargy, coma, seizures, and neurological symptoms in NKH, SO deficiency, and peroxisomal disorders, and with the characteristic metabolic changes in congenital lactic acidosis and **urea cycle disorders** (hyperammonemia). Severe forms of Pompe disease (alpha-glucosidase deficiency) can initially mimic respiratory chain disorders or trifunctional enzyme deficiency when generalized hypotonia is associated with cardiomyopathy. However, Pompe disease does not strictly start in the neonatal period. Finally, one of the most frequent causes of neonatal hypotonia is Prader-Willi syndrome, where central hypotonia is apparently an isolated symptom at birth which can mimick the hypotonia cystinuria syndrome [4a].

The three neurological presentations are summarized in ◘ Table 1.2.

Hepatic Presentation and Hydrops Fetalis

Three main clinical groups of hepatic symptoms can be identified:

- Hepatomegaly with hypoglycemia and seizures suggest **glycogenosis type I or III**, **gluconeogenesis defects**, or **severe hyperinsulinism**.
- Liver failure (jaundice, coagulopathy, hepatocellular necrosis with elevated transaminases, and hypoglycemia with ascites and edema) suggests **hereditary fructose intolerance** (now very rare since infant formulas are fructose free), **galactosemia**, **tyrosinemia type I** (after

Table 1.2. Neurological presentation

Predominant clinical symptom	Main clinical findings	Biological abnormalities	Most likely diagnoses (disorder or enzyme deficiency)
Neurological deterioration (mostly metabolic and **treatable**)	Lethargy, coma, hiccups Poor sucking, hypothermia Hypotonia, hypertonia Abnormal movements Large amplitude tremor Myoclonic jerks »Burst suppression« Abnormal odor	Ketosis, acidosis Hyperlactatemia Leuconeutropenia Thrombopenia Hyperammonemia Characteristic changes of AAC or OAC	**MSUD** (odor) **MMA, PA, IVA** (odor) **MCD** **Urea cycle defects** **GA type II** (odor)
Seizures (sometimes metabolic, sometimes treatable)	Isolated Generalized	Metabolic ketoacidosis Organic acid profile None None Hypocalcemia Hypomagnesemia Severe hypoglycemia	**MCD** **Pyridoxine responsive seizures** **Folinic acid responsive seizures** **Congenital magnesium malabsorption** **PHHI**
	Generalized Hypsarythmia Severe microcephaly	Low serine (plasma/CSF)	**3PGD**
	Severe hypotonia Myoclonic jerks Burst suppression EEG	Low HVA, 5HIAA in CSF, Vanillactic (urine) Hyperglycinemia None S-sulfocysteine (AAC)	**PNPO** (pyridoxal phosphate responsive seizures) NKH Glutamate transporter Sulfite oxidase
	Facial dysmorphism Malformations Severe hypotonia	VLCFA, phytanic/acid plasmalogens Glycosylated transferrin Sterols in plasma	Peroxisomal defects CDG Cholesterol biosynthesis defects
Severe hypotonia (rarely metabolic) Not treatable	Isolated	None	Prader Willi syndrome Hypotonia cystinuria [4a]
	Fetal distress Hydramnios Arthrogryposis Respiratory failure	None	Severe fetal neuromuscular diseases Steinert Myasthenia Congenital myopathy Sensitivo-motor neuropathy
	Predominant dysmorphism Malformations	VLCFA, phytanic acid plasmalogens Sterols in plasma Tubulopathy Glycosylated transferrin Aberrant protein O-glycosylation Chromosome analyses	Peroxisomal defects Cholesterol defects Lowe syndrome CDG Polymalformative syndromes with muscular dystrophy (Walker Warburg, muscle-eye-brain, etc.) Chromosomal abnormalities
	Cataract Tubulopathy	Hyperlactatemia Enzyme/DNA analyses	Lowe syndrome Respiratory chain
	Cardiomyopathy Macroglossia	Vacuolated lymphocytes Hyperlactatemia Acylcarnitines	Pompe disease Respiratory chain Trifunctional enzyme

AAC, amino acid chromatography; *CDG*, congenital disorders of glycosylation; *GA*, glutaric aciduria; *HVA,* homovanillic acid; *IVA*, isovaleric acidemia; *MCD*, multiple carboxylase deficiency; *MMA*, methylmalonic aciduria; *MSUD*, maple syrup urine disease; *NKH*, non ketotic hyperglycinemia; *OAC*, organic acid chromatography; *PA*, propionic acidemia; *PHHI*, primary hyperinsulinemic hypoglycemia of infancy; *PNPO*, pyridox(am)ine-5'-phosphate oxidase; *VLCFA*, very long chain fatty acids; *3PGD*, 3-phosphoglycerate dehydrogenase; *5HIAA,* 5-hydroxyindoleaceatic acid; **bold face**, treatable disorders.

3 weeks), neonatal hemochromatosis, respiratory chain disorders, and transaldolase deficiency, a disorder of the pentose phosphate pathway which can present with hydrops fetalis. Another disorder described in 15 newborns from Finland displays severe fetal growth retardation, lactic acidosis, failure to thrive, hyperaminoaciduria, very high serum ferritin, hemosiderosis of the liver and early death (GRACILE syndrome). The etiology of this syndrome has been recently identified [5, 6].

- Cholestatic jaundice with failure to thrive is a predominant finding in alpha-1-antitrypsin deficiency, Byler disease, **inborn errors of bile acid metabolism**, peroxisomal disorders, Niemann-Pick type C disease, CDG and citrin deficiency [7, 8].

  With the exception of **long-chain 3-hydroxyacyl-CoA dehydrogenase** (**LCHAD**) deficiency which can present early in infancy (but not strictly in the neonatal period) as cholestatic jaundice, liver failure and hepatic fibrosis, hepatic presentations of inherited fatty acid oxidation disorders and urea cycle defects consist of acute steatosis or Reye syndrome with normal bilirubin, slightly prolonged prothrombin time, and moderate elevation of transaminases rather than true liver failure. One must emphasize that there are frequent difficulties in investigating patients with severe hepatic failure. At an advanced state, many non specific abnormalities secondary to liver damage can be present. Mellituria (galactosuria, glycosuria, fructosuria), hyperammonemia, hyperlactatemia, hypoglycemia after a short fast, hypertyrosinemia (>200 μmol/l), and hypermethioninemia (sometimes higher than 500 μmol/l) are encountered in all cases of advanced hepatocellular disease.

Cardiac Presentation

Some metabolic disorders can present predominantly with cardiac disease. Cardiac failure and a dilated hypertrophic cardiomyopathy, most often associated with hypotonia, muscle weakness, and failure to thrive, suggests fatty acid oxidation disorders, respiratory chain disorders or Pompe disease. Methylglutaconic aciduria is found in Barth syndrome and ketoglutarate excretion in ketoglutarate dehydrogenase deficiency. Several observations suggest that some respiratory chain disorders are tissue specific and are only expressed in the myocardium. CDG type Ia can sometimes present in infancy with cardiac failure due to pericardial effusions, cardiac tamponnade, and cardiomyopathy. Many defects of long-chain fatty acid oxidation can present with cardiomyopathy and/or arrhythmias and conduction defects (auriculoventricular block, bundle branch blocks, ventricular tachycardia) which may lead to cardiac arrest [9, 10].

1.2.2 Metabolic Derangements and Diagnostic Tests

Initial Approach and Protocol for Investigation

As soon as there is clinical suspicion of an IEM, general supportive measures and laboratory investigations should be undertaken concurrently (◘ Table 1.3). Abnormal urine odors can be detected on a drying filter paper or by opening a container of urine which has been closed at room temperature for a few minutes. Although serum ketone bodies reach 0.5–1 mmol/l in early neonatal life, acetonuria, if observed in a newborn, is always abnormal and an important sign of a metabolic disease. The dinitrophenylhydrazine (DNPH) test screens for the presence of alpha-keto acids as occur in MSUD. However, it has now largely been abandoned because of its poor specificity and because amino acid chromatography has become much more readily available. Hypocalcemia and elevated or reduced blood glucose are frequently present in metabolic diseases and the physician should be wary of attributing marked neurological dysfunction purely to these findings.

The metabolic acidosis of organic acidurias is usually accompanied by an elevated anion gap. Urine pH should be below 5; otherwise, renal acidosis is a consideration. A normal blood pH does not exclude hyperlactatemia, as neutrality is usually maintained until serum levels reach 5 mmol/l and more. Ammonia and lactic acid should be determined systematically in newborns at risk. An elevated ammonia level in itself can induce respiratory alkalosis; hyperammonemia with ketoacidosis suggests an underlying organic acidemia (OA), but an isolated hyperammonemia can occur. Elevated lactic acid levels in the absence of infection or tissue hypoxia are a significant finding. Moderate elevations (3–6 mmol/l) are often observed in organic acidemias and in the hyperammonaemias; levels greater than 10 mmol/l are frequent in hypoxia. In most anoxic lactic acidoses, ketosis is absent. Whenever it is possible, the measurement of lactate (L), pyruvate (P), 3-hydroxybutyrate (3OHB), and acetoacetate (AcAc) on a plasma sample immediately deproteinized at the bedside, allows an assessment of the cytoplasmic and mitochondrial redox states through the measurement of L/P and 3OHB/AcAc ratios, respectively. PA, MMA and IVA can induce granulocytopenia and thrombocytopenia, which may be mistaken for sepsis. Transaldolase deficiency and early onset forms of mevalonate kinase deficiency present with severe recurrent hemolytic anemia.

The storage of adequate amounts of plasma, urine, blood on filter paper, and CSF, is an important element in reaching a diagnosis. The utilization of these precious samples should be carefully planned after taking advice from specialists in IEM.

Identification of Five Major Types of Metabolic Distress

Once the above clinical and laboratory data have been collected, specific therapeutic recommendations can be made (▶ Chap. 4). This process is completed within 2–4h and often precludes waiting long periods for the results of sophisticated diagnostic investigations. On the basis of this evaluation, most patients can be classified into one of five types (◘ Table 1.4). The experienced clinician will, of course, have to carefully interpret the metabolic data, particularly in relation to time of collection and ongoing treatment. At the same time it is important to collect all the biologic data listed in ◘ Table 1.3. Some very significant symptoms (such as metabolic acidosis and especially ketosis) can be moderate and transient, largely depending on the symptomatic therapy. Conversely, at an advanced stage, many non-specific abnormalities (such as respiratory acidosis, severe hyperlactatemia, secondary hyperammonemia) can disturb the original metabolic profile. This applies particularly to IEM with a rapid fatal course such as **urea cycle disorders**, in which the initial characteristic presentation of hyperammonemia with respiratory alkalosis shifts rapidly to a rather non-specific picture of acidosis and hyperlactatemia.

In our experience, types I and II (**MSUD, organic acidurias**), type IVa (**urea cycle defects** and **fatty acid oxidation disorders**), nonketotic hyperglycinemia and respiratory chain disorders, encompass more than 80% of the newborn infants with inborn errors of intermediary metabolism.

1.3 Later Onset Acute and Recurrent Attacks (Late Infancy and Beyond)

1.3.1 Clinical Presentation

In about 50% of the patients with inborn errors of intermediary metabolism, disease onset is later. The symptom-free period is often longer than 1 year and may extend into late childhood, adolescence, or even adulthood. Each attack can follow a rapid course ending either in spontaneous improvement or unexplained death, despite supportive measures in the intensive care unit. Between attacks the patient may appear normal. Onset of acute disease may be precipitated by an intercurrent event or may occur without overt cause. Excessive protein intake, prolonged fasting,

◘ **Table 1.3.** Protocol for emergency investigations

	Immediate investigations	Storage of samples
Urine	Smell (distinctive odor) Look (distinctive color) Acetone (Acetest, Ames) Reducing substances (Clinitest, Ames) Keto acids (DNPH) pH (pHstix Merck) Sulfitest (Merck) Electrolytes (Na, K), urea, creatinine Uric acid	Urine collection: collect fresh sample and put it in the refrigerator Freezing: freeze samples collected before and after treatment at –20°C, and collect an aliquot 24 h after treatment. Do not use them without having expert metabolic advice Metabolic investigations: OAC, AAC, orotic acid, porphyrins
Blood	Blood cell count Electrolytes (search for anion gap) Glucose, calcium Blood gases (pH, pCO_2, HCO_3^-, pO_2) Uric acid Prothrombin time Transaminases (and other liver tests) Ammonia Lactate, pyruvate 3-hydroxybutyrate, acetoacetate Free fatty acids	Plasma (5 ml) heparinized at –20°C Blood on filter paper: 2 spots (as »Guthrie« test) Whole blood (10-15 ml) collected on EDTA and frozen (for molecular biology studies) Major metabolic investigations: total homocysteine, AAC, acylcarnitines (tandem MS), OAC, porphyrins, neurotransmitters (HPLC, tandem MS)
Miscellaneous	Lumbar puncture Chest X-ray Cardiac echography, ECG Cerebral ultrasound, EEG	Skin biopsy (fibroblast culture) CSF (1 ml), frozen (neurotransmitters, AA) Postmortem: liver, muscle biopsies (Chap. 3)

AA, amino acid; *AAC*, amino acid chromatography; *CSF*, cerebrospinal fluid; *DNPH*, dinitrophenylhydrazine; *ECG*, electrocardiogram; *EDTA*, ethylenediaminetetra-acetic acid; *EEG*, electroencephalogram; *MS*, mass spectrometry; *HPLC*, high performance liquid chromatography; *OAC*, organic acid chromatography.

Table 1.4. Classification of inborn errors revealed in the neonatal period and early in infancy

Types	Clinical type	Acidosis/ Ketosis	Other signs	Most usual diagnosis (disorder or enzyme deficiency)	Elective methods of investigation
I	**Neurological deterioration**, »Intoxication« type Slow movements Hypertonia	Acidosis – DNPH +++ Acetest –/±	NH_3 N or ↑ ± Lactate N Blood count N Glucose N Calcium N	**MSUD** (distinctive odor)	Aminoacid chromatography (plasma, urine) Blood spot for tandem MS-MS
II	**Neurological deterioration**, »Intoxication« type Fast movements Dehydration	Acidosis ++ Acetest ++ DNPH –/± Ketoacidosis	NH_3 ↑ +/++ Lactate N or ↑ ± Blood count: leucopenia, thrombopenia Glucose N or ↑ + Calcium N or ↓ +	**Organic acidurias (MMA, PA, IVA, MCD)** **Ketolysis defects**	OAC by GLCMS (urine, plasma) Carnitine (plasma) Carnitine esters by tandem MS (urine, plasma) Blood spot for tandem MS-MS
	Neurological deterioration, »energy deficiency« type, with liver or cardiac symptoms	Acidosis ++/± Acetest – DNPH – No ketosis	NH_3 ↑ ±/++ Lactate ↑ ±/++ Blood count N Glucose ↓ +/++ Calcium N or ↓ + Hypoketotic hypoglycemia	**Fatty acid oxidation and ketogenesis defects** (GA II, CPT II, CAT, VLCAD, MCKAT, HMG-CoA lyase)	Idem above Loading test Fasting test Fatty acid oxidation studies on lymphocytes or fibroblasts
III	**Neurological deterioration**, »energy deficiency« type, Tachypnea Hypotonia Lactic acidosis (may be well tolerated)	Acidosis +++/+ Acetest ++/– Lactate +++/+ Lactic acidosis	NH_3 N or ↑ ± Blood count: anemia or N Glucose N or ± Calcium N	Congenital lactic acidoses (pyruvate carrier, PC, **PDH**, Krebs cycle, respiratory chain) **MCD**	Plasma redox states ratios (L:P, 3OHB:AcAc) OAC (urine), AAC (plasma) Polarographic studies Enzyme assays (muscle, lymphocytes, fibroblasts)
IV a)	**Neurological deterioration**, »intoxication« type, Moderate hepatocellular disturbances Hypotonia, seizures, coma	Acidosis – (alkalosis) Acetest –/+ DNPH –	NH_3 ↑ +/+++ Lactate N or ↑ + Blood count N Glucose N Calcium N	**Urea cycle defects** **Triple H syndrome** **Fatty acid oxidation defects** (GA II, CPT II, VLCAD, LCHAD, CAT) **PA, MMA, IVA**	AAC, OAC (plasma, urine) Orotic acid (urine) Liver or intestine enzyme studies (CPS, OTC)
b)	**Neurological deterioration**, Seizures Myoclonic jerks Severe hypotonia	Acidosis – Acetest – DNPH – No major metabolic disturbance	NH_3 N Lactate N or ↑ + Blood count N Glucose N	NKH, SO plus XO **3PGD** **B6-responsive seizures** **PNPO, neurotransmitter defects** Peroxisomal defects Trifunctional enzyme Respiratory chain CDG Cholesterol synthesis defects	AAC (plasma, CSF) AAC (plasma, CSF) OAC OAC, neurotransmitters (plasma, urine, CSF) VLCFA, phytanic acid in plasma Acylcarnitine profile, OAC Lactate (plasma) Glycosylated transferrin (plasma) Sterols (plasma)

Table 1.4 (continued)

Types	Clinical type	Acidosis/ Ketosis	Other signs	Most usual diagnosis (disorder or enzyme deficiency)	Elective methods of investigation
V a)	**Recurrent hypoglycemia with hepatomegaly**	Acidosis ++/– Acetest +/–	Lactate ↑ +/++ NH_3 ↑ +/– Intractable hypoglycemia	**Glycogenosis type I** (acetest –) **Glycogenosis type III** (acetest +) **FBPase** **FAO defects** **PHHI**	Fasting test, Loading test DNA analyses, enzyme studies (liver, lymphocytes, fibroblasts) Organic acids, acylcarnitine Insulin plasma levels
b)	Hepatomegaly Jaundice Liver failure Hepatocellular necrosis	Acidosis +/– Acetest +/–	NH_3 N or ↑ + Lactate / +/++ Glucose N or ↓ ++	**HFI** **Galactosemia** **Tyrosinemia type I** Neonatal hemochromatosis Respiratory chain defects TALDO	DNA analyses, enzyme studies Succinyl acetone Iron-ferritin in salivary glands Organic acids, enzyme/DNA analyses Polyols (HPLC)
c)	**Hepatomegaly** **Cholestatic Jaundice** ± Failure to thrive ± Chronic diarrhea ± osteoporosis ± rickets	Acidosis – Ketosis –	NH_3 N Lactate N Glucose N	Alpha-1-antitrypsin Inborn errors of **bile acid metabolism** Peroxisomal defects CDG Niemann-Pick type C **LCHAD** Mevalonic aciduria Cholesterol metabolism **Cerebrotendinous xanthomatosis** Citrin	Protein electrophoresis Bile acids (plasma, urine, bile by tandem MS) VLCFA, phytanic & pipecolic acid Glycosylated transferrin Fibroblasts studies OAC, acylcarnitine profile OAC Plasma sterols Plasma sterols AAC (citrulline can be normal)
d)	**Hepatosplenomegaly** **»Storage« signs** (coarse facies, ascites, hydrops fetalis, macroglossia, bone changes, cherry red spot, vacuolated lymphocytes) ± Failure to thrive ± Chronic diarrhea ± Hemolytic anemia	Acidosis – Acetest – Ketosis – DNPH –	NH_3 N Lactate N or ↑ Glucose N Hepatic signs ±/++	**Congenital erythropoietic porphyria** GM1 gangliosidosis ISSD (sialidosis type II) I-cell disease Niemann-Pick type IA MPS VII Galactosialidosis CDG Mevalonic aciduria TALDO	Porphyrins Oligosaccharides, sialic acid Mucopolysaccharides Enzyme studies (lymphocytes, fibroblasts) Glycosylated transferrin OAC Polyols (HPLC)

N, normal (normal values = NH_3 < 80 µM; lactate < 1.5 mM; glucose 3.5-5.5 mM); ±, slight; +, moderate; ++, marked; +++, significant/massive; ↑ elevated; ↓ decreased; –, absent (acidosis) or negative (acetest, dinitrophenylhydrazine, DNPH).
L, lactate; *P*, pyruvate; *3OHB*, 3-hydroxybutyrate; *AcAc*, acetoacetate; *GLCMS*, gas liquid chromatography mass spectrometry; *HPLC*, high performance liquid chromatography; *VLCFA*, very-long-chain fatty acids.
AAC, amino acid chromatography; *CAT*, carnitine acylcarnitine translocase; *CDG*, congenital disorders of glycosylation; *CPS*, carbamyl phosphate synthetase; *CPT II*, carnitine palmitoyltransferase II; *FAO*, fatty acid oxidation; *FBPase*, fructose-1,6-bisphosphatase; *GA II*, glutaric aciduria type II; *HFI*, hereditary fructose intolerance; *HMG-CoA*, 3-OH-3-methylglutaryl coenzyme A; *ISSD*, infantile sialic acid storage disease; *IVA*, isovaleric acidemia; *LCHAD*, 3-OH long-chain acyl CoA dehydrogenase; *MCD*, multiple carboxylase; *MCKAT*, medium-chain 3-ketoacylCoA A thiolase; *MMA*, methylmalonic acidemia; *MPS VII*, mucopolysaccharidosis type VII; *MSUD*, maple syrup urine disease; *NKH*, nonketotic hyperglycinemia; *OAC*, organic acid chromatography; *OTC*, ornithine transcarbamylase; *PA*, propionic acidemia; *PC*, pyruvate carboxylase; *PDH*, pyruvate dehydrogenase; *PNPO*, pyridox(am)ine-5′-phosphate oxidase; *SO*, sulfite oxidase; *TALDO*, transaldolase; *VLCAD*, very-long-chain acyl CoA dehydrogenase; *XO*, xanthine oxidase; *3PGD*, 3-phosphoglycerate dehydrogenase; **bold face,** treatable disorders.

Table 1.5. Diagnostic approach to recurrent attacks of coma and vomiting with lethargy

Clinical Presentation	Metabolic derangements and other important signs		Most frequent diagnosis (disorder or enzyme deficiency)	Differential diagnosis
Metabolic coma (without focal neurological signs)	Acidosis (metabolic) pH < 7.20 HCO_3^- < 10 mmol/l pCO_2 < 25 mmHg	Ketosis + (acetest ++)	Respiratory chain defects **MCD**, PC **MMA, PA, IVA, GA I, MSUD*** **Ketolysis defects** **Gluconeogenesis defects**	Diabetes Intoxication Encephalitis
		Ketosis –	**PDH, Ketogenesis defects** **FAO, FBPase**, EPEMA	
	Hyperammonemia NH_3 > 100 µmol/l Respiratory alkalosis pH > 7.45 pCO_2 < 25 mmHg	Normal glucose	**Urea cycle defects*** **Triple H syndrome** **LPI**	Reye syndrome Encephalitis Intoxication
		Hypoglycemia	**FAO (MCAD*)** **HMG-CoA lyase**	
	Hypoglycemia (< 2 mmol/l)	Acidosis +	**Gluconeogenesis defects** **MSUD** **HMG-CoA lyase** **FAO**	Drugs and toxins Ketotic hypoglycemia Adrenal insufficiency GH deficiency Hypopituitarism
	Hyperlactatemia (> 4 mmol/l)	Normal glucose	PC, **MCD**, Krebs cycle defects Respiratory chain* **PDH*** (without ketosis) EPEMA syndrome	
		Hypoglycemia	**Gluconeogenesis defects** (ketosis variable) **FAO** (moderate hyperlactatemia, no ketosis)	
Neurological coma (with focal signs, seizures, or intracranial hypertension)	Biological signs are very variable, can be absent or moderate; ► »Metabolic coma«	Cerebral edema Hemiplegia Extrapyramidal signs	**MSUD, OTC** **MSUD, OTC, MMA, PA,** PGK **GA I, Wilson disease*** **Homocystinuria***	Cerebral tumor Migraine Encephalitis
		Caudate nucleus and putamen necrosis	**BBGD**	
		Stroke-like	**UCD**, **MMA**, **PA**, **IVA*** Respiratory chain (MELAS*) **Homocystinurias*** CDG **Thiamine responsive megaloblastic anemia** **Fabry disease*** (rarely presenting) **Acid maltase*** (rare)	Moya Moya syndrome Vascular hemiplegia Cerebral thrombophlebitis Cerebral tumor
	Abnormal coagulation, Hemolytic anemia	Thromboembolic accidents	AT III, Protein C,S **Homocystinurias*** Sickle cell anemia CDG, PGK	

Table 1.5 (continued)

Clinical Presentation	Metabolic derangements and other important signs		Most frequent diagnosis (disorder or enzyme deficiency)	Differential diagnosis
Hepatic coma (hepatomegaly cytolysis or liver failure) Reye syndrome	Normal bilirubin Slight elevation of transaminases	Steatosis and Fibrosis	**FAO, UCD**	Reye syndrome Hepatitis Intoxication
	Hyperlactatemia	Liver failure	Respiratory chain defects	
	Hemolytic jaundice	Cirrhosis Chronic hepatic dysfunction	**Wilson disease***	
	Hypoglycemia	Exudative enteropathy	Hepatic fibrosis with enteropathy (**CDG Ib**)	

AT III, antithrombin III; *BBGD*, biotin-responsive basal ganglia disease; *CDG*, congenital disorders of glycosylation; *EPEMA*, encephalopathy, petechiae, ethylmalonic aciduria syndrome; *FAO*, fatty acid oxidation; *FBPase*, fructose-1,6-bisphosphatase; *GA*, glutaric aciduria; *GH*, growth hormone; *HMG-CoA*, 3-hydroxy-3-methylglutaryl coenzyme A; *IVA*, isovaleric acidemia; *LPI*, lysinuric protein intolerance; *MCAD*, medium chain acyl-CoA dehydrogenase; *MCD*, multiple carboxylase deficiency; *MELAS*, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; *MMA*, methylmalonic acidemia; *MSUD*, maple syrup urine disease; *OTC*, ornithine transcarbamylase; *PA*, propionic acidemia; *PC*, pyruvate carboxylase; *PDH*, pyruvate dehydrogenase; *PGK*, phosphoglycerate kinase; *UCD*, urea cycle disorders; **bold face**, treatable disorders; * presenting or predominant feature reported in adults.

prolonged exercise, and all conditions that enhance protein catabolism, may exacerbate such decompensations. The diagnostic approach to recurrent attacks of coma, vomiting, ataxia, and psychiatric disturbances, dehydration, Reye and SIDS are presented in ◘ Tables 1.5 to 1.9. Other acute manifestations are listed in Sect. 1.5.

Coma, Strokes and Attacks of Vomiting with Lethargy (◘ Table 1.5)

Acute encephalopathy is a common problem in patients (children and adults) with IEM. All types of coma can be indicative of an IEM, including those presenting with focal neurological signs. Neither the age at onset, the accompanying clinical signs (hepatic, gastrointestinal, neurological, psychiatric etc.), the mode of evolution (improvement, sequelae, death), nor the routine laboratory data, allow an inborn error of metabolism to be ruled out a priori. Two categories can be distinguished:

1. *Metabolic coma without focal neurological signs*
   The main varieties of metabolic comas may all be observed in these late-onset, acute diseases: coma with predominant metabolic acidosis, coma with predominant hyperammonemia, coma with predominant hypoglycemia, and combinations of these three major abnormalities. A rather confusing finding in some organic acidurias and ketolytic defects is ketoacidosis with hyperglycemia and glycosuria that mimics diabetic coma. The diagnostic approach to these metabolic derangements is developed below (► Sect. 1.3.2).
2. *Neurological coma with focal signs, seizures, severe intracranial hypertension, strokes or stroke-like episodes*
   Although most recurrent metabolic comas are not accompanied by neurological signs other than encephalopathy, some patients with **organic acidemias** and **urea cycle defects** present with focal neurological signs or cerebral edema. These patients can be mistakenly diagnosed as having a cerebrovascular accident or cerebral tumor. In these disorders, stopping the protein intake, delivering glucose at high infusion rate and giving »cleansing drugs« (carnitine, sodium benzoate, etc.) can be life saving. Another treatable condition is **biotin-responsive basal ganglia disease** which presents in childhood with a subacute encephalopathic picture of undefined origin including confusion, vomiting, and a vague history of febrile illness [11, 12].

   All severe forms of **homocystinuria** (total homocysteine >100 μmol/l) can cause an acute cerebrovascular accident from late childhood to adulthood. These include **cystathionine-β-synthase deficiency** (usually B6-responsive in the late onset presentations), the severe **MTHFR** defects (folate responsive) and **CblC, CblD** defects (hydroxocobalamin responsive). Patients with **MMA** may, after first presenting with metabolic decompensation, have acute extrapyramidal and corticospinal tract involvement as a result of bilateral destruction of the globus pallidus with variable involvement of the internal capsule. Cerebellar hemorrhage has also been observed in IVA, PA, and MMA.

EPEMA syndrome, the molecular mechanism of which has been recently identified [13], starts in general early in infancy and is characterized by the association of progressive encephalopathy with mental retardation, pyramidal signs, and bilateral lesions in the striatum, resembling Leigh syndrome, relapsing petechiae, orthostatic acrocyanosis, and recurrent attacks of metabolic decompensation with lactic acidosis without ketosis, during which there is an exacerbation of ethylmalonic and methylsuccinic excretions.

Two patients with 3-hydroxyisobutyric aciduria presenting with recurrent episodes of vomiting and ketoacidotic coma have been described [14]. Patients with mitochondrial DNA mutations have presented with cyclical vomiting associated with intermittent lactic acidosis [15, 16]. GA type I frequently presents with an encephalopathic episode, mimicking encephalitis, in association with an intercurrent gastrointestinal or viral infection. Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome is another important diagnostic consideration in such late-onset and recurrent comas. Early episodic central nervous system problems, possibly associated with liver insufficiency or cardiac failure, have been the initial findings in some cases of CDG. **Wilson disease** can rarely present with an acute episode of encephalopathy with extrapyramidal signs.

In summary, all these disorders should be considered in the differential diagnosis of strokes or stroke-like episodes. Vaguely defined and/or undocumented diagnoses such as encephalitis, basilar migraine, intoxication, poisoning, or cerebral thrombophlebitis should therefore be questioned, particularly when even moderate ketoacidosis, hyperlactatemia, or hyperammonemia is present. In fact, these apparent initial acute manifestations are frequently preceded by other premonitory symptoms, which may be unrecognized or misinterpreted. Such symptoms include acute ataxia, persistent anorexia, chronic vomiting, failure to thrive, hypotonia, and progressive developmental delay – all symptoms that are often observed in **urea cycle disorders**, respiratory chain defects, and **organic acidurias**. Late onset forms of **PDH** can present in childhood with recurrent attacks of ataxia, sometimes described by the patient as recurrent episodes of pain or muscular weakness (due to dystonia or to peripheral neuropathy).

Certain features or symptoms are characteristic of particular disorders. For example, macrocephaly is a frequent finding in **glutaric aciduria type I**; unexplained episodes of dehydration may occur in **organic acidurias**; and hepatomegaly at the time of coma is an important although inconsistent finding in **fructose-1,6-bisphosphatase deficiency**. Severe hematologic manifestations and recurrent infections are common in **IVA, PA, and MMA**. Macrocytic anemia may be an important clue indicating a **cobalamin or folate disorder**.

When coma is associated with hepatic dysfunction, Reye syndrome secondary to disorders of **fatty acid oxidation** or the **urea cycle** should be considered. Hepatic coma with liver failure and hyperlactatemia can be the presenting sign of respiratory chain disorders. Finally, hepatic coma with cirrhosis, chronic hepatic dysfunction, hemolytic jaundice, and various neurological signs (psychiatric, extrapyramidal) is a classic, but underdiagnosed manifestation of **Wilson disease**.

Recurrent Attacks of Ataxia (◘ Table 1.6)

Intermittent acute ataxia and disturbed behavior can be the presenting signs of late-onset **MSUD** and **organic acidurias**, where they are associated with ketoacidosis and sometimes with hyperglycemia which can mimic diabetic ketoacidosis. Late onset **ornithine transcarbamylase (OTC) deficiency** and **argininosuccinate synthetase (ASS)** deficiency can present with recurrent attacks of ataxia. Acute ataxia associated with peripheral neuropathy is a frequent presenting sign of **pyruvate dehydrogenase** (**PDH**) deficiency; moderate hyperlactatemia with a normal L/P ratio supports this diagnosis. Hartnup disease (the molecular mechanism of which has been recently identified) is a classical but very rare cause of acute recurrent ataxia.

Acute Psychiatric Symptoms (◘ Table 1.7)

Late-onset forms of congenital hyperammonemia, mainly partial **OTC** deficiency, can present late in childhood or in adolescence with psychiatric symptoms. Because hyperammonemia and liver dysfunction can be mild even at the time of acute attacks, these intermittent late-onset forms of **urea cycle disorders** can easily be misdiagnosed as hysteria, schizophrenia, or alcohol or drug intoxication. **Acute intermittent porphyria** and **hereditary coproporphyria** present classically with recurrent attacks of vomiting, abdominal pain, neuropathy, and psychiatric symptoms. Finally, patients with **homocysteine remethylation defects** may present with schizophrenia-like, folate-responsive episodes. In view of **these possible diagnoses, it is justified to systematically measure ammonia, porphyrins, plasma homocysteine and copper in every patient presenting with unexplained acute psychiatric symptoms**. Episodes of acute psychosis also occur in the newly described autosomal dominant disorder neuroferritinopathy which is associated with low serum ferritin [17, 18].

Dehydration (◘ Table 1.8)

In pediatrics, dehydration is a common consequence of diarrhea caused by a variety of enteral or parenteral acute infections. However, these common infectious diseases can occasionally trigger acute decompensation of an IEM. Moreover, aside from dehydration due to gastrointestinal losses, some IEM can present as recurrent attacks of de-

Table 1.6. Diagnostic approach to recurrent attacks of ataxia/± lethargy

Clinical presentation	Metabolic derangements or other important signs	Additional symptoms	Most frequent diagnosis (disorder or enzyme deficiency)	Differential diagnosis
Acute ataxia	Ketoacidosis Characteristic AAC and OAC profiles	Distinctive odor Neutropenia Thrombopenia Hyperglycemia	**Late onset MSUD** **MMA, PA, IVA**	Diabetes
	Hyperammonemia (sometimes slight elevation) AAC, orotic acid	Respiratory alkalosis Hepatomegaly	**Urea cycle defects (OTC, ASA)**	Intoxication Encephalitis Brain tumor
	Hyperlactatemia (sometimes very moderate and only in post-prandial state)	Normal L/P ratio No ketosis Peripheral neuropathy	**PDH**	Migraine Cerebellitis (varicella) Polymyoclonia Acetazolamide responsive ataxia Acute exacerbation in chronic ataxias
		High L/P ratio Ketosis Cutaneous signs	**MCD** Respiratory chain defects	
	AAC (neutral AA in urines)	Skin rashes, pellagra, sun intolerance	Hartnup disease	

AAC, amino acid chromatography; *ASA*, arginosuccinic aciduria; *IVA*, isovaleric acidemia; *L*, lactate; *LPI*, lysinuric protein intolerance; *MCD*, multiple carboxylase deficiency; *MMA*, methymalonic acidemia; *MSUD*, maple syrup urine disease; *OAC*, organic acid chromatography; *OTC*, ornithine transcarbamylase; *P*, pyruvate; *PA*, propionic acidemia; *PDH*, pyruvate dehydrogenase; **bold face**, treatable disorders.

Table 1.7. Diagnostic approach to recurrent attacks of psychiatric symptoms

Clinical presentation	Metabolic derangements or other important findings	Additional symptoms	Most frequent diagnosis (disorder or enzyme deficiency)	Differential diagnosis
Psychiatric symptoms (hallucinations, delirium, dizziness, aggressiveness, anxiety, schizophrenic-like behaviour, agitation)	Hyperammonemia (sometimes moderate) AAC, orotic acid	Slight liver dysfunction Vomiting Failure to thrive	**Urea cycle defects (OTC, ASA, arginase)** **LPI**	
	Ketoacidosis AAC, OAC	Ataxia, neutropenia	**Organic acid defects, MSUD**	
	Port-wine urine Porphyrins in plasma/urine	Abdominal pain All kinds of neuropathy Vomiting	Acute intermittent **porphyria** **Hereditary coproporphyria**	Hysteria
	Homocystinuria (total homocysteine > 100 µM)	Stroke, seizures Myelopathy	**Methylene tetrahydrofolate reductase**	Schizophrenia
	AAC (neutral AA in urines)	Skin rashes, pellagra	Hartnup disease	
	Low serum ferritin	Dystonia, Parkinsonism, Pallidal necrosis	Neuroferritinopathy [17,18]	Hallervorden-Spatz
	Low serum copper acanthocytosis		**Wilson disease**	
	Foam cells in bone marrow	Vertical ophthalmoplegia	Niemann Pick type C	
	None	Epilepsy, retinitis pigmentosa	Ceroid lipofuscinosis	

AAC, amino acid chromatography; *ASA*, arginosuccinic aciduria; *MSUD,* maple syrup urine disease; *LPI,* lysinuric protein intolerance; *OAC*, organic acid chromatography; *OTC*, ornithine transcarbamylase; **bold face**, treatable disorders.

Table 1.8. Attacks of dehydration

Leading symptoms	Other signs	Age at onset	Diagnosis (disorder or enzyme deficiency)
Severe diarrhea: »gastrointestinal causes«	Severe watery acidic diarrhea Glycosuria	Neonatal	**Glucose galactose malabsorption** **Lactase**
	Hydramnios, no meconium Severe watery nonacidic diarrhea Metabolic alkalosis Low K^+, Cl^-	Congenital	**Congenital chloride diarrhea**
	Severe watery diarrhea	After weaning or when sucrose or starch dextrins are added to the diet	**Sucrase isomaltase**
	Anorexia, failure to thrive Weight loss (before cutaneous lesions and alopecia)	2-4 Weeks or after weaning	**Acrodermatitis enteropathica**
Ketoacidosis: »organic acidurias«	Polyuria Tachypnea Hyperglycemia Glycosuria	Infancy to early childhood	**Diabetic coma** **MMA, PA, IVA** **3-Ketothiolase** Hydroxyisobutyric aciduria
Failure to thrive, anorexia, poor feeding, polydipsia, polyuria: renal tubular dysfunction	Photophobia Renal Fanconi syndrome	Infancy 3-6 months	**Cystinosis**
	Hypernatremia, vomiting Psychomotor retardation Spasticity	Neonatal to first month	**Nephrogenic diabetes insipidus** (X-linked)
	Hyperchloremia Metabolic acidosis Alkaline urine pH	Early in infancy	**RTA type I (distal)** **RTA type II (proximal)** **RTA type IV**
	Hypoglycemia Hepatic glycogenosis Fanconi syndrome	Early in infancy	**Fanconi-Bickel syndrome** (GLUT2 mutation)
	Pulmonary infections Chronic diarrhea Salty sweet	Infancy to early childhood	**Cystic fibrosis**
Salt-losing syndrome: »adrenal dysfunctions»	Severe hyponatremia Ambiguous genitalia	End of first week of life	**Congenital adrenal hyperplasia**
	Unambiguous genitalia	End of first week	**Hypoaldosteronism**
	Ambiguous genitalia	Infancy to early childhood	**Congenital adrenal hypoplasia** **Congenital adrenal hyperplasia, late-onset forms**
	Unambiguous genitalia		Hypo & pseudohypoaldosteronism
	Hypoketotic hypoglycemia		**FAO defects (CPT I and II)**

CPT, carnitine palmitoyl transferase; *FAO*, fatty acid oxidation; *GLUT*, glucose transporter; *IVA*, isovaleric acidemia; *MMA*, methylmalonic aciduria; *PA*, propionic aciduria; *RTA*, renal tubular acidosis; **bold face**, treatable disorders.

hydration secondary to polyuria, hyperventilation or excessive sweating. The main accompanying findings (severe diarrhea, salt wasting, ketoacidosis, failure to thrive, Fanconi syndrome) can be used to classify dehydration due to IEM as shown in Table 1.8.

Reye Syndrome, Sudden Unexpected Death in Infancy (SUDI) and Near-miss (Table 1.9)

Within the last decade, an increasing number of IEM have been described that produce episodes fitting the criteria originally used to define Reye syndrome. There is now con-

Table 1.9. Diseases in which Reye syndrome, sudden unexpected death in infancy (SUDI), and near-miss have been reported

Disorder or Enzyme deficiency	Incidence of the syndrome
Disorders of ureagenesis	Frequent
Partial OTC	Frequent
Partial carbamylphosphate synthetase	Rare
Partial argininosuccinic acid synthetase	Rare
Lysinuric protein intolerance	Rare
Triple H syndrome	Very rare
Disorders of mitochondrial fatty acid oxidation & ketogenesis	Frequent in neonates
Carnitine transport defect	Rare
CPT I	Rare
CPT II	Rare
Translocase	Rare
VLCAD / LCAD	Very rare
LHCAD, trifunctional protein	Rare
MCAD	Rare
Multiple acyl-CoA dehydrogenase	Frequent
3-Hydroxymethylglutaryl-CoA lyase	Rare
Unknown (3-ketoacyl-CoA thiolase?)	Very rare
Organic acidurias	Frequent
3-methylcrotonyl-CoA carboxylase	Very rare
Glutaric aciduria type I	Rare
Respiratory chain defects	Rare
Others (MMA, PA, IVA, biotinidase …)	Rare
Carbohydrate metabolism	Very rare
Hereditary fructose intolerance	
Glycogenosis type I	
Fructose-1,6-bisphosphatase	
Metabolic diseases causing Leigh and Leigh-like syndromes (PDH, PC, respiratory chain defects …)	Very rare
Peroxisomal defects	Very rare

CPT, carnitine palmitoyl transferase; *IVA*, isovaleric acidemia; *LCAD*, long chain acyl-CoA dehydrogenase; *LCHAD*, 3-hydroxy-long chain acyl-CoA dehydrogenase; *MCAD*, medium chain acyl-CoA dehydrogenase; *MMA*, methylmalonic acidemia; *OTC*, ornithine transcarbamylase; *PA*, propionic acidemia; *VLCAD*, very long chain acyl-CoA dehydrogenase; **bold face**, treatable disorders.

siderable evidence that many of the disorders responsible for Reye syndrome were misdiagnosed in the past because of inadequate investigations for IEM. Another important reason for this underestimation is the necessity of collecting blood and urine specimens for metabolic investigations at an appropriate time in relation to the illness since most disorders affecting the mitochondrial pathway, **urea cycle** and **FAO disorders** may produce only intermittent abnormalities. In addition, in contrast to the usual belief, a normal or non specific urinary organic acid and acylcarnitine pattern, even at the time of an acute attack, does not exclude an inherited **FAO disorder**.

True SUDI due to an IEM is, however, a rare event despite the large number of publications on the topic and despite the fact that at least 31 metabolic defects are possible causes. This assertion is not true in the first week of life in which **unexpected death or near-miss is a priori due to a fatty acid oxidation disorder and the investigation of which is mandatory**.

1.3.2 Metabolic Derangements and Diagnostic Tests

Initial Approach, Protocol of Investigation

The initial approach to the late-onset acute forms of inherited metabolic disorders, as with the approach to acute neonatal distress, is based on the proper use of a few screening tests. As with neonates, the laboratory data listed in Table 1.3 must be collected during the acute attack and both before and after treatment.

Main Metabolic Presentations

Metabolic Acidosis (Fig. 1.1)

Metabolic acidosis is a very common finding in pediatrics. It can be observed in a large variety of acquired conditions, including infections, severe catabolic states, tissue anoxia, severe dehydration, and intoxication, all of which should be ruled out. However, these can also trigger an acute decompensation of an unrecognized IEM. The presence or absence of ketonuria associated with metabolic acidosis is the major clinical clue to the diagnosis.

When metabolic acidosis is not associated with ketosis, **PDH deficiency**, **fatty acid oxidation disorders**, and some **disorders of gluconeogenesis** should be considered, particularly when there is moderate to severe hyperlactatemia. All these disorders except **PDH deficiency** have concomitant fasting hypoglycemia. Although **fructose-1,6-bisphosphatase** deficiency is classically considered to give rise to ketoacidosis, some patients have had low concentrations of ketone bodies during hypoglycemia. When metabolic acidosis occurs with a normal anion gap and without hyperlactatemia or hypoglycemia, the most frequent cause is renal tubular acidosis (RTA) type I or II. Pyroglutamic aciduria also can present early in life with permanent, isolated metabolic acidosis, which can be mistaken for RTA type II.

A number of IEM cause a metabolic acidosis with an associated ketosis. The range of serum ketone body concentration varies with age and nutritional state (► Chap. 2). Insulin-dependent **diabetes**, inborn errors of **branched-chain amino acid metabolism**, congenital lactic acidoses such as **multiple carboxylase** and PC deficiencies, inherited defects in enzymes of **gluconeogenesis** and of glycogen synthesis (**glycogen synthase**), and **ketolytic defects** are the main groups of metabolic disorders. The glucose level which can be high, normal, or low is the first parameter to be considered to classify these disorders.

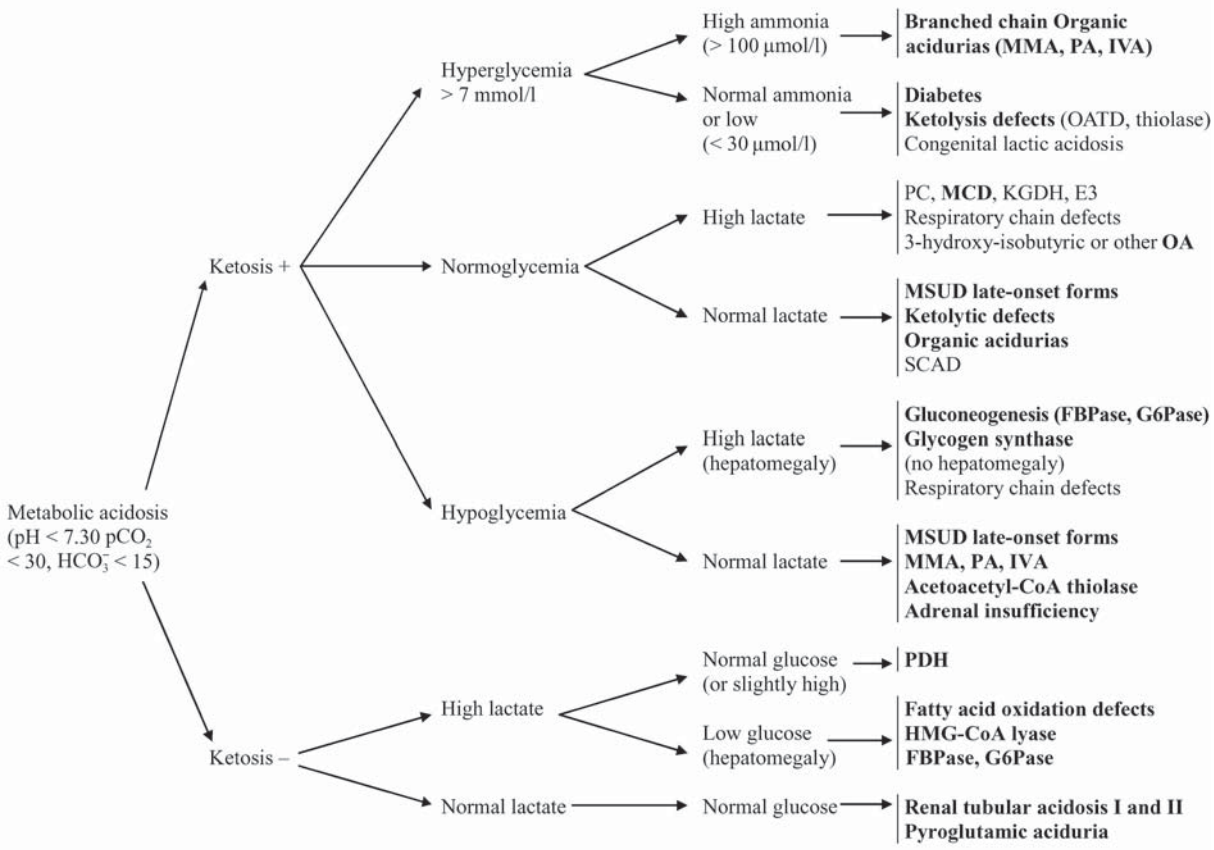

Fig. 1.1. Metabolic acidosis. *E3*, lipoamide oxidoreductase; *FBPase*, fructose-1,6-bisphosphatase; *G6Pase*, glucose-6-phosphatase; *GS*, glycogen synthase; *HMG-CoA*, 3-hydroxy-3-methylglutaryl coenzyme A; *IVA*, isovaleric acidemia; *KGDH*, alpha-ketoglutarate dehydrogenase; *MCD*, multiple carboxylase deficiency; *MMA*, methylmalonic aciduria; *MSUD*, maple syrup urine disease; *OA*, organic aciduria; *OATD*, oxoacid-CoA transferase; *PA*, propionic acidemia; *PC*, pyruvate carboxylase; *PDH*, pyruvate dehydrogenase; *SCAD*, short chain acyl-CoA dehydrogenase; **bold face**, treatable disorders

In the case of hyperglycemia, the classic diagnosis is diabetic ketoacidosis. However, organic acidurias such as **propionic, methylmalonic, or isovaleric acidemia and ketolytic defects** can also be associated with hyperglycemia and glycosuria, mimicking diabetes. The distinction between the different disorders is also based on ammonia and lactate levels, which are generally increased in organic acidemias and normal or low in ketolytic defects.

In the case of hypoglycemia, the first group of disorders to be considered is the **gluconeogenesis defects** and the **glycogenoses**. The main findings suggestive of this group are hepatomegaly and hyperlactatemia, although they are not constant. When there is no significant hepatomegaly, late-onset forms of **MSUD** and **organic acidurias** and **glycogen synthase** (**GS**) deficiency should be considered. A classic differential diagnosis is **adrenal insufficiency**, which can cause a ketoacidotic attack with hypoglycemia.

If the glucose level is normal, congenital lactic acidosis must be considered in addition to the disorders discussed above. According to this schematic approach to inherited ketoacidotic states, a simplistic diagnosis of fasting ketoacidosis or ketotic hypoglycemia should be questioned when there is a concomitant severe metabolic acidosis.

Ketosis (Fig. 1.2)

While ketonuria should always be considered abnormal in neonates, it is a physiological result of catabolism in late infancy, childhood, and even adolescence. However as a general rule, hyperketosis at a level that produces metabolic acidosis is not physiological. Ketosis which is not associated with acidosis, hyperlactatemia, or hypoglycemia, is likely to be a normal physiological reflection of the nutritional state (fasting, catabolism, vomiting, medium-chain triglyceride-enriched or other ketogenic diets). Of interest are ketolytic defects (**succinyl-CoA transferase** and **3-ketothiolase** deficiencies) that can present with persistent moderate ketonuria occurring mainly in the fed state at the end of the day.

Significant fasting ketonuria without acidosis is often observed in **glycogenosis type III** in childhood (with marked hepatomegaly) and in the very rare **GS** defect in infancy (with normal liver size). In both disorders, there is fasting hypoglycemia, and postprandial hyperlactatemia and hyperglycemia.

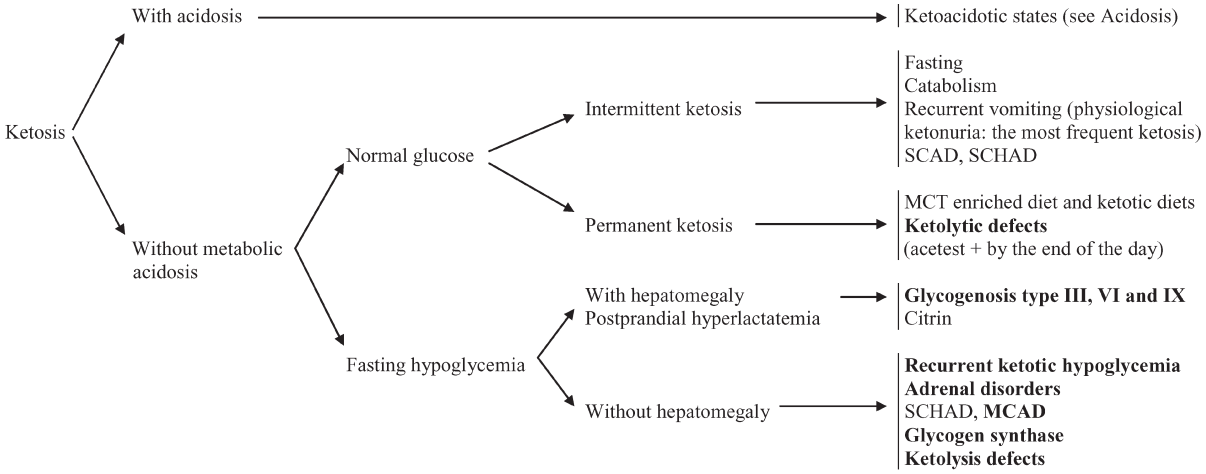

Fig. 1.2. Ketosis (► also Fig. 1.1). *MCAD*, medium chain acyl coenzyme A dehydrogenase; *MCT*, medium chain triglycerides; *SCAD*, short-chain acyl-coenzyme A dehydrogenase; *SCHAD*, hydroxy short-chain acyl-coenzyme A dehydrogenase; **bold face**, treatable disorders

Ketosis without acidosis is observed in ketotic hypoglycemias of childhood (a frequent condition) and in association with hypoglycemias due to **adrenal insufficiency**. **Absence of ketonuria in hypoglycemic states**, as well as in fasting and catabolic circumstances induced by vomiting, anorexia, or intercurrent infections, **is an important observation, suggesting an inherited disorder of fatty acid oxidation or ketogenesis disorder** and can also be observed in hyperinsulinemic states at any age and in growth hormone deficiency in infancy. However, short-chain 3-hydroxy acyl-CoA dehydrogenase (SCHAD), SCAD, and **MCAD** deficiencies can present as recurrent attacks of ketotic hypoglycemia as these enzymes are both sufficiently far down the β-oxidation pathway to be able to generate some ketones from long chain fatty acids [19].

Hyperlactatemia (◘ Table 1.10)

Lactate and pyruvate are normal metabolites. Their plasma levels reflect the equilibrium between their cytoplasmic production from glycolysis and their mitochondrial consumption by different tissues. The blood levels of lactate and pyruvate and the L/P ratio reflect the redox state of the cells.

Blood lactate accumulates in circulatory collapse, in hypoxic insult, and in other conditions involving failure of cellular respiration. These conditions must be excluded before an inborn error of lactate-pyruvate oxidation is sought. Persistent hyperlactatemias can also result from many acquired conditions, such as diarrhea, persistent infections (mainly of the urinary tract), hyperventilation, and hepatic failure. Ketosis is absent in most hyperlactatemias secondary to tissue hypoxia, while it is a nearly constant finding in most inborn errors of metabolism (except in **PDH deficiency**, **glycogenosis type I** and **FAO disorders**). On the other hand, the level of lactate is not discriminating; some acquired disorders are associated with very high levels, whereas it is only moderately raised in some inborn errors of lactate-pyruvate metabolism. Nutritional state also influences the levels of lactate and pyruvate.

Once the **organic acidurias**, **urea cycle defects** (mainly **citrullinemia**), and **fatty acid oxidation defects** that cause secondary hyperlactatemia have been excluded as possible diagnoses, four types of inherited disorders remain to be considered: disorders of liver glycogen metabolism, disorders of liver gluconeogenesis, abnormalities of lactate-pyruvate oxidation, PDH deficiency, Krebs cycle defects, and deficient activity in one of the components of the respiratory chain. The diagnosis of hyperlactatemias is largely based upon two metabolic criteria:

- *Time of occurrence of lactic acidosis relative to feeding:* in disorders of gluconeogenesis (**fructose-1,6-bisphosphatase** and **glucose-6-phosphatase deficiencies**), hyperlactatemia reaches its maximum level (up to 15 mM) when the patient is fasting and hypoglycemic. By contrast, in **glycogenosis types III and VI** and in **glycogen synthase deficiency**, hyperlactatemia is observed only in the postprandial period in patients on a carbohydrate-rich diet. Here, hyperlactatemia never exceeds 7 mM. In pyruvate carboxylase deficiency, hyperlactatemia is present in both the fed and the fasted state, but tends to decrease with a short fast. In disorders of **PDH**, alpha-ketoglutarate dehydrogenase, and respiratory chain function, maximum lactate levels are observed in the fed state (although all hyperlactatemias exceeding 7 mM appear more or less permanent). In these disorders, there is a real risk of missing a moderate (although significant) hyperlactatemia when the level is checked only before breakfast after an overnight fast (as it is usual for laboratory determinations).
- *Determinations of L/P and ketone bodies ratios before and after meals.* These ratios indirectly reflect cytoplasmic (L/P) and mitochondrial (3OHB/AcAc) redox potential states. They must be measured in carefully collected

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Table 1.10. Diagnostic approach to hyperlactatemias

Time of occurence	Main clinical signs	Redox potential states	Diagnosis (disorder or enzyme deficiency)
Only after feeding (or exacerbated after feeding)	Hepatomegaly Fasting ketotic hypoglycemia	Not diagnostic	**Glycogenosis type III** **Glycogen synthase**
	Neurological signs Encephalomyopathy	Normal L/P ratio, no ketosis	**PDH,** pyruvate carrier
		L/P high, 3OHB/AcAc low Postprandial hyperketosis	PC (high citrulline, low glutamine) **MCD** α-KDH (isolated or E3)
		L/P high, 3OHB/AcAc high Postprandial ketosis	Respiratory chain defects (3-methyl-glutaconic aciduria, Krebs cycle intermediates)
		L/P high, No ketosis	Respiratory chain
Only after fasting (or exacerbated after fasting)	Prominent hepatomegaly Hypoglycemia	Not diagnostic	**Glycogenosis type I** **Fructose-1,6-bisphosphatase** (ketosis inconstant)
	Moderate or no hepatomegaly Hypoketotic hypoglycemia	Not diagnostic	**FAO (cardiac, muscle symptoms)** **Fructose-1,6-bisphosphatase**
Permanent	Moderate hyperlactatemia Recurrent attacks of ketoacidosis	Not diagnostic	**Organic acidurias** (MMA, PA, IVA) MAMEL syndrome [27]
	Predominant hyperammonemia	Not diagnostic	**Urea cycle defects** (in neonates)
	Predominant hypoglycemia Hepatomegaly	Not diagnostic	**Glycogenosis type I** **Fructose-1,6-bisphosphatase**
	Neurological signs, encephalomyopathy, important hyperlactatemia (>10 mM)	Highly diagnostic (► above »after feeding«)	Congenital lactic acidemias (► above »after feeding«)

3OHB, 3-hydroxybutyrate; *AcAc*, acetoacetate; *IVA*, isovaleric acidemia; *KDH*, ketoglutarate dehydrogenase; *L*, lactate; *MAMEL*, methylmalonic aciduria, mitochondrial encephalopathy Leigh-like; *MMA*, methylmalonic acidemia; *MCD*, multiple carboxylase deficiency; *P*, pyruvate; *PA* propionic acidemia; *PC*, pyruvate carboxylase; *PDH*, pyruvate dehydrogenase; **bold face**, treatable disorders.

blood samples (► Chap. 2). Three abnormal hyperlactatemia/pyruvicemia profiles are nearly pathognomonic of an inborn error of lactate-pyruvate metabolism:

When hyperpyruvicemia is associated with a normal or low L/P ratio (<10) without hyperketonemia, **PDH deficiency** or pyruvate transporter defect are highly probable, regardless of the lactate level.

When the L/P ratio is very high (>30) and is associated with postprandial hyperketonemia and with a normal or low 3OHB/AcAc ratio (<1.5), a diagnosis of pyruvate carboxylase (PC) deficiency (isolated or secondary to **biotinidase** or **holocarboxylase synthetase deficiency**) or alpha-ketoglutarate dehydrogenase deficiency is virtually certain. In PC deficiency, there is a very characteristic amino acid profile with hyperammonemia, high citrulline and low glutamine.

When both L/P and 3OHB/AcAc ratios are elevated and associated with a significant postprandial hyperketonemia, respiratory chain disorders should be suspected.

All other situations, especially when the L/P ratio is high without hyperketonemia, are compatible with respiratory chain disorders, but all acquired anoxic conditions should also be ruled out (► above).

Hypoglycemia (■ Table 1.11)

Our approach to hypoglycemia is based on four major clinical criteria: liver size, characteristic timing of hypoglycemia (unpredictable, only postprandial or only after fasting), association with lactic acidosis, and association with hyperketosis or hypoketosis. Other clinical findings of interest are hepatic failure, vascular hypotension, dehydration, short stature, neonatal body size (head circumference, weight & height), and evidence of encephalopathy, myopathy, or cardiomyopathy. Based on the liver size, hypoglycemias can be classified into two major groups:

- *Hypoglycemia with permanent hepatomegaly:* Hypoglycemia associated with permanent hepatomegaly is usually due to an inborn error of metabolism. However, all conditions, both acquired or inherited, that are as-

Table 1.11. Hypoglycemia: general approach

Leading symptoms	Other signs	Age at onset	Diagnosis (disorder or enzyme deficiency)
With permanent hepatomegaly			
Permanent short-fast hypoglycemia	Severe liver failure Hepatic necrosis	Neonatal to early infancy	**Galactosemia** **Hereditary fructose intolerance** **Tyrosinemia type I** Neonatal hemochromatosis Respiratory chain defects Other severe hepatic failure
Fibrosis, Cirrhosis	Postprandial hypoglycemia (triggered by fructose), Vomiting	Neonatal to early infancy	**Hereditary fructose intolerance** Glycerol intolerance
	Mental retardation Hypermethioninemia Hepatic failure induced by methionine	Early in infancy	Glycogenosis type IV SAH hydrolase Respiratory chain defects
	Exudative enteropathy Cholangitis attacks Short fast hypoglycemia	Early in infancy	**CDG Ib**
Isolated Hepatomegaly	Fasting hypoglycemia and Lactic acidosis, Ketosis	Infancy	**G6Pase** **FBPase**
	Protuberant abdomen Fasting hypoglycemia and ketosis Postprandial hyperlactatemia	Infancy	**Glycogenosis type III and VI**
Hypotonia	Abnormal glycosylated transferrin	Infancy	CDG
Failure to thrive Chronic diarrhea	Fanconi-like tubulopathy Postprandial hyperglycemia	Infancy	**Fanconi-Bickel syndrome** (GLUT II mutations)
Without permanent hepatomegaly			
With ketoacidosis	Recurrent attacks Hyperlactatemia	Infancy to childhood	**Organic acidurias** Late-onset **MSUD** **Ketolysis defects** Glycerol kinase **FBPase** SCHAD, **MCAD** Respiratory chain defects
	Dehydration, collapse Hyponatremia	Neonatal to childhood	**Adrenal insufficiency** (central or peripheral)
Acidosis without ketosis	Moderate hyperlactatemia Reye syndrome (with muscle/ cardiac symptoms)	Neonatal to infancy	**HMG-CoA lyase** (frequent) **HMG-CoA synthase** (rare) **FAO defects** (frequent) Reye syndrome (idiopathic)
Ketosis without acidosis	Fasting hypoglycemia Low lactate levels Small size for age Macrocephaly	1–6 years	**Recurrent ketotic hypoglycaemia** Adrenal insufficiency SCHAD, **MCAD**, **Glycogen synthase** **Ketolysis defects**
Without acidosis or ketosis	Unpredictable and postprandial hypoglycemia reactive to glucagon	Neonatal to childhood	**Hyperinsulinisms** **Cortisol deficiency** CDG **Factitious or induced illness**
	Short stature, short-fast hypoglycemia	Infancy	**GH deficiency & related disorders**
	Long-fast hypoglycemia Reye syndrome Moderate hepatomegaly Transient cytolysis	Neonatal to infancy	**FAO defects** (frequent) **HMG-CoA lyase** (rare) **FBPase** (rare) **HMG-CoA synthase** (rare)

CDG, congenital disorders of glycosylation; *FAO* fatty acid oxidation disorders; *FBPase*, fructose-1,6-bisphosphatase; *GH*, growth hormone; *G6Pase*, glucose-6-phosphatase; *HMG-CoA*, 3-hydroxy-3-methylglutaryl coenzyme A; *MSUD*, maple syrup urine disease; A; *SAH*, S-adenosyl-homocysteine hydrolase; **bold face**, treatable disorders.

sociated with severe liver failure, can give rise to severe hypoglycemia, which appears after 2-3h of fasting and is associated with moderate lactic acidosis and no ketosis. When hepatomegaly is the most prominent feature without liver insufficiency, gluconeogenesis defects (**glucose-6-phosphatase deficiency, fructose-1,6-bisphosphatase deficiency**) and **glycogenosis type III**, are the most likely diagnoses. Disorders presenting with hepatic fibrosis and cirrhosis, such as hereditary **tyrosinemia type I**, also can give rise to hypoglycemia. The late-onset form of **hereditary fructose intolerance** rarely, if ever, presents with isolated postprandial hypoglycemic attacks. S-adenosylhomocysteine hydrolase deficiency presents with fasting hypoglycemia and hepatocellular insufficiency, often triggered by high protein or methionine ingestion, and is associated with hepatic fibrosis, mental retardation, and marked hypermethioninemia. Respiratory chain disorders can present with hepatic failure and hypoglycemia. **CDG type Ib** (**phosphomannose isomerase** deficiency) with hepatic fibrosis and exudative enteropathy can cause hypoglycemia early in infancy [20, 21].

- *Hypoglycemia without permanent hepatomegaly:* It is important to determine the timing of hypoglycemia and to look for metabolic acidosis and ketosis when the patient is hypoglycemic. Most episodes of hypoglycemia, due to IEM that are not accompanied by permanent hepatomegaly, appear after at least 8h of fasting. This is particularly true for inherited **fatty acid oxidation disorders** except in the neonatal period. Conversely, unpredictable postprandial or hypoglycaemia occurring after a very short fast (2–6h) is mostly due to **hyperinsulinism** and **growth hormone deficiency** or related disorders. When ketoacidosis is present at the time of hypoglycemia, **organic acidurias**, **ketolytic defects**, **late-onset MSUD**, and glycerol kinase deficiencies should be considered. Here, hypoglycemia is very rarely the initial metabolic abnormality. **Adrenal insufficiencies** must be considered in the differential diagnosis, especially when vascular hypotension, dehydration, and hyponatremia are present. Severe hypoglycemia with metabolic acidosis and absence of ketosis, in the context of Reye syndrome, suggests **HMG-CoA lyase deficiency**, **HMG-CoA synthase deficiency** or **fatty acid oxidation disorders**. Fasting hypoglycemia with ketosis occurring mainly in the morning and in the absence of metabolic acidosis suggests recurrent functional ketotic hypoglycemia, which presents mostly in late infancy or childhood in those who were small for gestational age or with macrocephaly. All types of **adrenal insufficiencies** (peripheral or central) can share this presentation. SCHAD and **MCAD** deficiency can on occasions present as recurrent attacks of ketotic hypoglycemia [19] as can **glycogen synthase deficiency**. However, in our experience, this pattern is rarely associated with inborn errors of metabolism.

Hypoketotic hypoglycemias encompass several groups of disorders including **hyperinsulinemic states**, **growth hormone deficiency**, inborn errors of **fatty acid oxidation**, and **ketogenesis defects** (► »Ketosis« above).

Hyperammonemia

The diagnostic approach to hyperammonemia is developed in ► Chap. 20.

1.4 Chronic and Progressive General Symptoms/Signs

As already stated, many acute presentations of inherited disorders that are apparently of delayed onset are preceded by insidious premonitory symptoms and which may have been ignored or misinterpreted. These signs fall schematically into three categories according to whether there is gastrointestinal, muscle or neurological involvement.

1.4.1 Gastrointestinal Symptoms

Gastrointestinal findings (GI) (anorexia, failure to thrive, osteoporosis, chronic vomiting) occur in a wide variety of inborn errors of metabolism. Unfortunately, their cause often remains unrecognized, thus delaying the correct diagnosis. Persistent anorexia, feeding difficulties, chronic vomiting, failure to thrive, frequent infections, osteopenia, and generalized hypotonia in association with chronic diarrhea are the presenting symptoms and signs in a number of constitutional and acquired diseases in pediatrics. They are easily misdiagnosed as cow's milk protein intolerance, celiac disease, chronic ear, nose, and throat infections, late-onset chronic pyloric stenosis etc. Congenital immuno-deficiencies are also frequently considered, although only a few present early in infancy with this clinical picture.

From a pathophysiological point of view, it is possible to define two groups of inborn errors of metabolism presenting with chronic diarrhea and failure to thrive:

- Disorders of the intestinal mucosa or the exocrine function of the pancreas with almost exclusive intestinal effects, for example congenital chloride diarrhea, glucose-galactose malabsorption, lactase and sucrase-isomaltase deficiencies, abetalipoproteinemia type II (Anderson disease), enterokinase deficiency, acrodermatitis enteropathica, and selective intestinal malabsorption of folate and vitamin B_{12}, the latter also causing systemic disease.
- Systemic disorders which also give rise to GI abnormalities.

Table 1.12. Chronic diarrhea, poor feeding, vomiting, failure to thrive

Leading symptoms	Other signs	Age of onset	Diagnosis (disorder or enzyme deficiency)
Severe watery diarrhea Attacks of dehydration	Nonacidic diarrhea, Hypochloremic alkalosis	Congenital to infancy	**Congenital chloride diarrhea**
	Acidic diarrhea, Reducing substances in stools	Neonatal	**Glucose galactose malabsorption** **Lactase**
	Acidic diarrhea, Reducing substances in stools after weaning	Neonatal to infancy	**Sucrase isomaltase**
	Skin lesions, alopecia	Neonatal or post weaning	**Acrodermatitis enteropathica**
Protein losing entero-pathy	Cholangitis crisis Hypoglycemia	Infancy	**CDG type Ib and Ih**
Fat-soluble vitamins malabsorption Severe hypo-cholesterolemia Osteopenia Steatorrhea	Cholestatic jaundice	Neonatal to infancy	**Bile acid synthesis defects** Infantile Refsum
	Hepatomegaly, hypotonia, retinitis pigmentosa, deafness	Infancy	Infantile Refsum CDG type I
	Abdominal distension, ataxia, acanthocytosis, peripheral neuropathy, retinitis pigmentosa	Infancy	**ABL I and II** (no acanthocytes, no neurological signs in type II)
	Pancreatic insufficiency, neutropenia, pancytopenia	Early in infancy	Pearson syndrome Schwachman syndrome
Severe failure to thrive, anorexia, poor feeding, with predominant hepato-splenomegaly	Severe hypoglycemia, inflammatory bowel disease, neutropenia,	Neonatal to early infancy	**Glycogenosis type Ib** (no splenomegaly)
	Hypotonia, vacuolated lymphocytes, adrenal gland calcifications	Neonatal	Wolman disease
	Recurrent infections, inflammatory bowel disease,	Infancy	**Chronic granulomatosis** (X-linked)
	Megaloblastic anemia, neuropathy, homocystin-uria, MMA	1–5 years	**Intrinsic factor**
	Leuconeutropenia, osteopenia, hyperammonemia, interstitial pneumonia,	Infancy	**Lysinuric protein intolerance**
	Recurrent fever, inflammatory bowel syndrome, hyper-IgD	Infancy	Mevalonate kinase
Severe failure to thrive, anorexia, poor feeding, with megaloblastic anemia	Oral lesion, neuropathy, infections, pancytopenia, homocystinuria, MMA	1-2 years	**TC II** **Intrinsic factor**
	Stomatitis, peripheral neuropathy, infections, intracranial calcifications	Infancy	**Congenital folate malabsorption**
	Severe pancytopenia, abnormal marrow precursors, lactic acidosis	Neonatal	Pearson syndrome
Severe failure to thrive, anorexia, poor feeding, no significant hepato-splenomegaly, no megaloblastic anemia	Severe hypoproteinemia, putrefaction diarrhea	Infancy	**Enterokinase**
	Diarrhea after weaning, cutaneous lesions (periorificial), low plasma zinc	Infancy	**Acrodermatitis enteropathica**
	Ketoacidotic attacks, vomiting	Infancy	**Organic acidurias (MMA, PA)** Mitochondrial DNA deletions
	Vomiting, lethargy, hypotonia, hyperammonemia	Infancy	**Urea cycle defects** (mainly **OTC**)
	Frequent infections, lymphopenia,	Infancy	**Adenosine deaminase**
	Developmental delay, relapsing petechiae, orthostatic acrocyanosis	Infancy	EPEMA syndrome [13]

ABL, abetalipoproteinemia; *CDG*, congenital disorders of glycosylation; *EPEMA*, encephalopathy, petechiae, and ethylmalonic aciduria; *MMA*, methylmalonic acidemia; *OTC*, ornithine transcarbamylase; *PA*, propionic acidemia; *TC*, transcobalamin; **bold face**, treatable disorders.

In clinical practice, these groups are sometimes very difficult to distinguish, because a number of specific intestinal disorders can give rise to various systemic clinical abnormalities and vice versa. This is summarized in ◘ Table 1.12.

1.4.2 Muscle Symptoms

Many inborn errors of metabolism can present with severe hypotonia, muscular weakness, and poor muscle mass. These include most of the late-onset forms of urea cycle defects and many organic acidurias. Severe neonatal generalized hypotonia, progressive myopathy with or without an associated nonobstructive idiopathic cardiomyopathy, can be the specific presenting findings in a number of inherited energy deficiencies; the most frequent conditions are mitochondrial respiratory chain disorders and other congenital hyperlactatemias, fatty acid oxidation defects, peroxisomal disorders, muscular glycogenolysis defects, alpha-glucosidase deficiency, and some other lysosomal disorders (► also Sect. 1.2.1 and 1.5.8). Hypotonia, generalized weakness, reduced muscle mass and developmental delay are also the presenting features of the Allan-Herndon-Dudley syndrome due to mutations in the monocarboxylate transporter 8 gene. This X-linked mental retardation syndrome involves the transport of triiodothyronine into neurones and disturbs blood levels of thyroid hormone [22].

1.4.3 Neurological Symptoms

Neurological symptoms are very frequent in inborn errors and encompass progressive psychomotor retardation, seizures, and a number of neurological abnormalities, in both the central and peripheral system, sensorineural defects and psychiatric symptoms.

A large number of inborn errors of intermediary metabolism present with an early and non-specific progressive developmental delay, poor feeding, hypotonia, some degree of ataxia, and frequent autistic features. The list has lengthened rapidly as new laboratory techniques have been applied. The relationship between clinical and biochemical abnormalities is not always firmly established. Many aminoacidopathies that were first described in the late 1950s and 1960s, when plasma and urine amino acid chromatography was systematically used in studying mentally retarded children, must now be questioned as definitely being the cause of neurological disease. This is the case for histidinemia, hyperlysinemia, hyperprolinemia, alpha-amino-adipic aciduria, saccharopinuria, Hartnup »disease« and the recently described acetyl amino aciduria due to amino acylase I deficiency [23a].

A similar picture is now emerging with organic acidurias and it is therefore important to link clinical symptoms and metabolic disturbances. Conversely, it becomes more and more difficult to screen patients on clinical grounds when the clinical symptoms consist only of rather non specific signs such as developmental delay, microcephaly, hypotonia or convulsions. Among the new categories of inborn errors of intermediary metabolism that can present with uninformative clinical manifestations are, for example, adenylosuccinase deficiency, dihydropyrimidine dehydrogenase deficiency, 4-hydroxybutyric aciduria, L-2- and D-2-hydroxyglutaric acidurias, late onset NKH and a number of other inborn errors (► bottom of ◘ Table 1.14). These disorders rarely, if ever, cause true development arrest; rather, they cause progressive subacute developmental delay. Conversely, there is still an important gap between neurological descriptions and biological investigations. Many well-known heritable neurological or polymalformative syndromes have not been considered from a pathophysiological perspective and should be submitted to a comprehensive biochemical evaluation. This is illustrated for example by the story of Canavan disease, in which N-acetylaspartic aciduria was only found in 1988, even though the clinical phenotype had been identified in 1949 and the procedure for identifying N-acetylaspartate in urine was available in 1972.

In the following pages, IEM are listed:

a. according to their age at onset and their association with particular abnormalities, both neurological and extraneurological (► Tables 1.13–1.17) and also
b. alphabetically, under specific associated neurological abnormalities that they can cause (► Sect. 1.4.4).

Of course, these two categorizations are complementary and inevitably involve redundancies. It is recommended that one looks at both.

Progressive Neurological and Mental Deterioration Related to Age (Overview)

◘ Tables 1.13 to 1.17 present a general approach to inborn errors of metabolism involving neurological and/or mental deterioration. Diseases are classified according to their age at onset, the presence or absence of associated extraneurological signs, and the neurological presentation itself; the last is based largely on the clinical classification of Lyon and Adams [24]. Inborn errors of metabolism with neurological signs presenting in the neonate (birth to 1 month; ◘ Table 1.2) and those presenting intermittently as acute attacks of coma, lethargy, ataxia, or acute psychiatric symptoms, were discussed earlier (◘ Tables 1.5 to 1.7).

Early Infancy (◘ Table 1.13)

Three general categories can be identified:

- **Category 1: Disorders Associated with Extraneurological Symptoms.** Visceral signs appear in lysosomal disorders. A cardiomyopathy (associated with early neurological dysfunction, failure to thrive, and hypo-

Table 1.13. Progressive neurological and mental deterioration with extraneurological symptoms (1 to 12 months) (► also Tables 1.2 and 1.4)

Leading symptoms	Other signs	Diagnosis (disorder or enzyme deficiency)
Visceral signs	Hepatosplenomegaly Storage signs, coarse facies	Landing, I-Cell disease Sialidosis type II, Niemann-Pick A Lactosyl ceramidosis
	Hepatosplenomegaly Opisthotonos, spasticity	Gaucher type II
	Hepatomegaly Retinitis pigmentosa	Peroxisomal defects CDG
Hair and cutaneous symptoms	Steely brittle hair	Menkes (X-linked) Trichothiodystrophy
	Trichorrexis nodosa	**Argininosuccinic aciduria**
	Ichthyosis, spastic paraplegia	Sjögren-Larsson syndrome **Serine deficiency syndrome**, CDG
	Alopecia, cutaneous rashes	**Biotinidase** Respiratory chain defects
	Peculiar fat pads on buttocks	CDG
	Cyanosis, hypertonicity	Cytochrome b-5 reductase
	Kernicterus, athetosis	Crigler-Najjar
	Acrocyanosis, petechiae	EPEMA syndrome [13]
Megabloblastic anemia	Failure to thrive, RP	**Folate and cobalamin defects** **UMP synthase**
Cardiac symptoms	Cardiomyopathy Heart failure, heart beat disorders	D-2-hydroxyglutaric acidemia Respiratory chain defects, CDG
Ocular symptoms	Cherry-red spot, hydrops fetalis	Landing, Galactosialidosis, Sialidosis type I
	Myoclonic jerks, macrocephaly	Tay-Sachs, Sandhoff
	Optic atrophy, macrocephaly	Canavan
	Nystagmus, dystonia, stridor	Pelizaeus-Merzbacher (X-linked)
	Retinitis pigmentosa	► Section 1.4.4
	Abnormal eye movements	Aromatic amino acid decarboxylase
	Strabism	CDG
	Supranuclear paralysis	Gaucher, Niemann-Pick type C

CDG, congenital disorders of glycosylation; *EPEMA*, encephalopathy, petechiae, and ethylmalonic aciduria; *RP*, retinitis pigmentosa; *UMP*, uridine monophosphate; **bold face**, treatable disorders.

tonia), sometimes responsible for cardiac failure, is suggestive of respiratory-chain disorders, D-2-hydroxyglutaric aciduria (with atrioventricular block), or CDG. Abnormal hair and cutaneous signs appear in Menkes disease, Sjögren-Larsson syndrome, **biotinidase deficiency**, and respiratory-chain disorders. Peculiar fat pads of the buttocks and thick and sticky skin (like tallow, peau d'orange), and inverted nipples are highly suggestive of CDG. A generalized cyanosis, unresponsive to oxygen, suggests methemoglobinemia, which is associated with severe hypertonicity in cytochrome-b5 reductase deficiency. Kernicterus and athetosis are complications of Criggler-Najjar syndrome. The recently described EPEMA syndrome is characterized by

an orthostatic acrocyanosis, relapsing petechiae, pyramidal signs, mental retardation, and recurrent attacks of lactic acidosis. The presence of megaloblastic anemia suggests an inborn error of **folate and cobalamin** (**Cbl**) metabolism. Ocular abnormalities can be extremely helpful diagnostic signs, for example cherry-red spot, optic atrophy, nystagmus, abnormal eye movements, and retinitis pigmentosa.

- **Category 2: Disorders with Specific or Suggestive Neurological Signs.** Predominant extrapyramidal symptoms are associated with inborn errors of biopterin and aromatic-amino-acid metabolism, **pyridox(am)ine phosphate oxidase**, Lesch-Nyhan syndrome, cytochrome-b5 reductase deficiency, Criggler-Najjar syndrome, the early-onset form of GA type I, and **cerebral creatine deficiency**. Dystonia can also be observed as a subtle but presenting sign in X-linked Pelizaeus-Merzbacher syndrome. It can be also associated with psychomotor retardation, spastic paraplegia and ataxia in the **cerebral folate deficiency syndrome** [25].

  Macrocephaly with a startle response to sound, incessant crying, and irritability are frequent early signs in GM-2 gangliosidosis, Canavan disease, Alexander leukodystrophy, infantile Krabbe disease, and GA type I. Macrocephaly can be also an initial sign in L-2-hydroxyglutaric aciduria and in respiratory-chain disorders due to complex-I deficiency (association with hypertrophic cardiomyopathy).

  Recurrent attacks of neurological crisis associated with progressive neurological and mental deterioration suggest Leigh syndrome, which can present at any age from early in infancy to late childhood. Leigh syndrome is not a specific disorder but, rather, the clinical phenotype of any of several inborn errors of metabolism, some of which still remain to be identified. Recurrent stroke-like episodes often associated with anorexia, failure to thrive, and hypotonia can be presenting symptoms in **urea-cycle defects** (mostly **OTC deficiency**), late-onset **MSUD**, **organic acidurias**, GA type I, CDG and respiratory-chain disorders. Thromboembolic events can be the presenting sign of **classical homocystinuria** and CDG. Angelman syndrome sometimes displays a very suggestive picture, with early-onset encephalopathy, happy-puppet appearance, and epilepsy with a highly suggestive EEG pattern.
- **Category 3: Disorders with Non-specific Developmental Delay.** A large number of inborn errors present with non-specific early progressive developmental delay, poor feeding, hypotonia, some degree of ataxia, frequent autistic features, and seizures. Many IEM can masquerade as a cerebral palsy by presenting as a permanent impairment of movement or posture (◘ Table 1.14). Consequently, it is mandatory to systematically screen such children for those IEM which can be at least partly treatable. In this context, late-onset **subacute forms of hyperammonemia** (usually **OTC** deficiency in girls) can present with an apparently non-specific early encephalopathy and **inborn errors of neurotransmitter synthesis**, especially **dopa-responsive dystonia** due to cyclohydrolase deficiency, tyrosine hydroxylase deficiency, and aromatic-L-amino-acid decarboxylase deficiency, can masquerade as cerebral palsy. Recurrent attacks of seizures unresponsive to anticonvulsant drugs occurring in the first year of life is the presenting symptom of the **blood brain-barrier glucose-transporter (GLUT1)** defect, a disorder that is improved by a hyperketotic diet. The diagnosis relies on the finding of a low glucose level in the CSF while the simultaneous blood glucose level is normal. The new treatable **cerebral folate deficiency syndrome** [25] (improved by folinic acid) should be also systematically screened for.

Late Infancy to Early Childhood (1–5 years) (◘ Table 1.15)

In this period, diagnosis becomes easier. Five general categories can be defined (◘ Table 1.15):

- **Category 1: with visceral, craniovertebral, ocular, or other somatic abnormalities.** These symptoms associated with a slowing or regression of development, suggest mucopolysaccharidosis types I and II, mucolipidosis type III, oligosaccharidosis, Austin disease, Niemann-Pick disease type C, Gaucher disease type III, and lactosyl ceramidosis, all disorders which are usually easy to recognize. Mucolipidosis type IV, which causes major visual impairment by the end of the first year of life, sometimes associated with dystonia, presents with characteristic cytoplasmic membranous bodies in cells. In Sanfilippo syndrome, coarse facies and bone changes may be very subtle or absent. Peroxisomal disorders may present at this age, with progressive mental deterioration, retinitis pigmentosa, and deafness, and in a very similar manner to Usher syndrome type II. Pyrroline-5-carboxylate synthase deficiency presents with slowly progressive neurological and mental deterioration, severe hypotonia, joint laxity, and congenital cataracts.
- **Category 2: with progressive paraplegia and spasticity.** Progressive paraplegia and spasticity are characteristic of six IEM. Metachromatic leukodystrophy and neuroaxonal dystrophy present between 12 and 24 months of age with flaccid paraparesis, hypotonia, and weakness. CSF protein content and nerve conduction velocity are disturbed in the former but normal in the latter. Schindler disease is roughly similar to neuroaxonal dystrophy, though it is often associated with myoclonic jerks. **Arginase deficiency** is a rare disorder that presents early in infancy to childhood (2 months to 5 years) with progressive spastic diplegia, scissoring or tiptoe gait, and developmental arrest. A rapidly progressive flaccid paraparesis resembling subacute degeneration of the cord can be the presenting sign of inherited

Table 1.14. Progressive neurological and mental deterioration (1 to 12 months)

Leading symptoms	Other signs	Diagnosis (disorder or enzyme deficiency)
With suggestive neurological signs		
Extrapyramidal signs	Major parkinsonism Abnormal neurotransmittors	**Inborn errors of biopterin metabolism** **Aromatic amino acid decarboxylase** **Tyrosine hydroxylase, PNPO**
	Choreoathetotis, self-mutilation	Lesch-Nyhan (X-linked)
	Bilateral athetosis, hypertonicity	Cytochrome b5 reductase
	Dystonia, stridor	Pelizaeus Merzbacher (X-linked)
	Kernicterus syndrome	**Criggler-Najjar**
	Acute-onset pseudoencephalitis	**Glutaric aciduria type I**
	Low cerebral creatine	**Creatine deficiency (GAMT)**
	Spastic paraplegia, ataxia, epilepsy	**Cerebral folate deficiency**
	Leigh syndrome	PDH, complex I
Painful pyramidal hypertonia	Opisthotonos	Krabbe, Gaucher III, Nieman-Pick type C
Early epilepsy infantile spasm	Spasticity	NKH, SO, **untreated MSUD & OA** **MCD**, Menkes
Macrocephaly, startle response to sound	Cherry red spot, myoclonic jerks	Tay Sachs, Sandhoff, Canavan, Alexander Vacuolizing leucoencephalopathy
Ocular symptoms	Optic atrophy, incessant crying	Krabbe (infantile)
	Dystonia, choreoathetosis	**GA I**, L-2-hydroxyglutaric aciduria
	Progressive irritability	Respiratory chain, peroxisomal defects
Recurrent attacks of neurological crisis (► also Sect. 1.3.1)	Failure to thrive, hyperventilation attacks	Leigh syndrome (PC, PDH, respiratory chain, MAMEL syndrome [27])
	Stroke-like episodes	**Urea cycle defects, MSUD, OA, GA I** CDG, respiratory chain
	Thromboembolic accidents	**Homocystinurias**, CDG
Without suggestive neurological signs		
Evidence of developmental arrest	Infantile spasms, hypsarrhythmia autistic features	**Untreated PKU, biopterin defects** Peroxisomal defects, Rett syndrome
Non specific symptoms, Apparently non-progressive disorder	Frequent autistic features Poor feeding, failure to thrive	**Hyperammonemia** (late-onset subacute) 4-OH-butyric, L-2-OH-, D-2-OH-glutaric acidurias
	Hypotonia, seizures	Mevalonic aciduria
	With diverse neurological findings simulating cerebral palsy	Adenylosuccinase, pyrimidine defects 3-methylglutaconic, fumarase **Other OA**, **creatine deficiency** **3-PGD**, 3-phosphoserine phosphatase **Homocystinurias**, Salla **Neurotransmittor defects**, Cerebral folate deficiency Angelman, **GLUT1**

CDG, congenital disorders of glycosylation; *GA*, glutaric aciduria; *GAMT*, guanidino acetate methyltransferase; *MAMEL*, methylmalonic aciduria, mitochondrial encephalopathy Leigh-like; *MCD,* multiple carboxylase deficiency; *MSUD*, maple syrup urine disease; *NKH,* non ketotic hyperglycinemia; *OA*, organic acidurias; *PC*, pyruvate carboxylase; *PDH*, pyruvate dehydrogenase; *3-PGD*, 3-phosphoglycerate dehydrogenase; *PNPO*, pyridox(am)ine phosphate oxidase; *SO,* sulfite oxidase; **bold face**, treatable disorders.

Table 1.15. Progressive neurological and mental deterioration (1 to 5 years)

Symptoms	Diagnosis (disorder or enzyme deficiency)
With visceral, craniovertebral, or other somatic abnormalities	
▬ Coarse facies, skeletal changes, hirsutism, corneal opacities	MPS I, MPS II, MPS III, MLP III
▬ Coarse facies, subtle bone changes, lens/corneal opacities, hepatosplenomegaly, vacuolated lymphocytes,	Mannosidosis (gingival hyperplasia) Fucosidosis (angiokeratoma) Aspartylglucosaminuria (joint laxity) Austin (ichthyosis)
▬ Hepatosplenomegaly, progressive dementia, myoclonic jerks	Niemann-Pick type C and related disorders (vertical supranuclear ophtalmoplegia)
▬ Splenomegaly + hepatomegaly, osseous lesions, (ataxia, myoclonus)	Gaucher type III (supranuclear ophtalmoplegia)
▬ Major visual impairment, blindness	Mucolipidosis type IV (corneal clouding)
▬ Retinitis pigmentosa, deafness	Peroxisomal defects, Usher type II
▬ Cataract, joint laxity, hypotonia	Pyrroline-5-carboxylase synthase
With paraplegia, hypotonia, or spasticity due to corticospinal tract involvement or to peripheral neuropathy	
▬ Flaccid paraparesis, pyramidal signs, hyperproteinorrachia	Metachromatic leukodystrophy (abnormal NCV)
▬ Flaccid paraparesis, no change in CSF, optic atrophy	Neuro-axonal dystrophy Schindler (normal NCV)
▬ Progressive spastic diplegia, scissoring or »tiptoe« gait	**Arginase** (high arginine, high orotic) **Cbl C** (subacute cord degeneration) **Triple H** (recurrent attacks of hyper NH_3) Costeff syndrome (OPA3 gene mutation with 3-methylglutaconic aciduria)
With unsteady gait, uncoordinated movements due to cerebellar syndrome, sensory defects or myoclonia	
▬ Without disturbances of organic acid excretion	
– Ataxia, choreoathetosis, oculocephalic asynergia	Ataxia telangiectasia
– Ataxia, difficulty in walking, mental/speech deterioration	GM1 (spastic quadriparesis, pseudobulbar signs) **BBGD** (caudate nucleus, putamen necrosis)
– Ataxia, spinocerebellar degeneration, psychotic behavior	GM2 (Tay-Sachs, Sandhoff) (late infantile form)
– Ataxia, pyramidal signs, vision loss	Krabbe (late infantile, peripheral neuropathy)
– Ataxia, muscular atrophy, peripheral neuropathy	CDG, trifunctional enzyme, peroxisomal defects
– Seizures, myoclonic jerks, postictal coma, transient hemiplegia	Alpers (hepatic signs, hyperlactatemia)
▬ With disturbances of organic and amino acid excretion	
– Progressive ataxia, intention tremor, cerebellar atrophy	L-2-OH-glutaric (spongiform encephalopathy) Combined degeneration of the spinal cord **Cobalamin defects** (CblC, CblE, CblF, CblG)
– Ataxia, peripheral neuropathy, dystonia	**PDH** (moderate hyperlactactemia)
– Ataxia, weakness, RP, myoclonic epilepsy	Respiratory chain, MERFF, methylglutaconic
– Extrapyramidal signs	**Creatine deficiency** (GAMT)
– Ataxia, peripheral neuropathy, RP	**LCHAD** (organic acids, acylcarnitine)
– Acute attacks encephalitis-like, temporal lobe atrophy	GA I (dystonia, macrocephaly)
– Dystonia, athetosis, acute attacks	**MMA, PA, homocystinurias**
– Ataxia, dysarthria, optic atrophy, nystagmus	Ribose-5-phosphate isomerase (polyols)
With seizures and myoclonus, ataxia, frequent falling due to intention myoclonus or to the cerebellar ataxia	
▬ Rapid mental regression, myoclonic jerks, blindness	INCL (early-flattening EEG, CLN1 mutations)
▬ Akinetic myoclonic petit mal, RP, typical EEG pattern	LINCL (misdiagnosed with Lennox-Gastaut)
▬ Rapid regression, myoclonic seizures, spasticity	Schindler (optic atrophy, severe osteoporosis)
▬ Myoclonic epilepsy, volitional and intentional myoclonias, muscular weakness	MERFF, Niemann-Pick C, Gaucher III (ophtalmoplegia, hepatosplenomegaly)
▬ Seizures and myoclonic jerks, uncoordinated movements	Alpers (hepatic symptoms, hyperlactatemia)
Disorders with arrest or regression of psychic and perceptual functions as presenting symptom	
▬ Autistic behaviour, regression of high-level achievements, stereotyped movements of fingers	Rett syndrome (girls), sporadic (acquired microcephaly, secondary epilepsy)
▬ Regression of high-level achievements, loss of speech,	Sanfilippo (hirsutism, agitation)

BBGD, biotin-responsive basal ganglia disease; *Cbl*, cobalamin; *CoA*, coenzyme A; *CSF*, cerebrospinal fluid; *EEG*, electroencephalogram; *GAMT*, guanidino acetate methyltransferase; *Ig*, immunoglobulin; *INCL*, Infantile ceroid lipofuscinosis (CLN1 mutations); *LINCL*, late infantile ceroid lipofuscinosis (CLN2 mutations); *MERRF*, myoclonic epilepsy with ragged red fibers; *MLP*, mucolipidosis; *MPS*, mucopolysaccharidosis; *NCV*, nerve conduction velocity; *OPA*, optic atrophy; *PDH*, pyruvate dehydrogenase; *RP*, retinitis pigmentosa; **bold face**, treatable disorders.

Cbl-synthesis defects. Spastic paraparesis is an almost constant finding in the **triple H syndrome**.

- **Category 3: with unsteady gait and uncoordinated movements** (when standing, walking, sitting, reaching for objects, speaking, and swallowing). Several groups of disorders must be considered. A careful investigation of organic acid and amino acid metabolism is always mandatory, especially during episodes of metabolic stress.
  - Disorders without disturbances of urinary organic acid excretion and lactic acid metabolism are the late-onset forms of GM-1 and GM-2 gangliosidosis, late infantile Krabbe disease, ataxia telangiectasia, and CDG; each presents with signs that are sufficiently characteristic to warrant specific investigation. A severe early-onset encephalopathy with seizures and myoclonic jerks associated with hepatic disease is highly suggestive of Alpers syndrome due to respiratory-chain disorders. **Creatine deficiency** due to guanidinoacetate-methyltransferase deficiency can present in infancy, with an extrapyramidal disorder associated with epilepsy, neurological regression, and failure to thrive.
  - Disorders with disturbances of organic and amino acid metabolism are numerous. PDH deficiency presents frequently with peripheral neuropathy, intermittent ataxia, dystonia and slight or moderate hyperlactatemia (► Hyperlactatemias above). Several respiratory-chain disorders initially cause ataxia, intention tremor, dysarthria, epilepsy, myopathy, and (eventually) multiorgan failure. **LCHAD deficiency**, L-2-hydroxyglutaric aciduria, 3-methylglutaconic aciduria, **MMA**, and **PA** significantly disturb organic acid excretion, although sometimes only slightly and intermittently. In these disorders, the acylcarnitine profile determined (by tandem MS) from blood spots collected on dry filter paper can be very helpful in identifying characteristic abnormalities. GA type I can also present with a permanent unsteady gait due to choreoathetosis and with dystonia developing abruptly after an acute episode resembling encephalitis.
- **Category 4: with predominant epilepsy and myoclonus.** Predominant epilepsy and myoclonus result in ataxia and frequent falling and include two ceroid lipofuscinoses: Santavuori-Hagberg disease (CLN1) and Jansky-Bielchowski disease (CLN2), which is similar to Lennox-Gastaut syndrome (akinetic myoclonic petit mal). Late-onset forms of Niemann-Pick type C and Gaucher disease are easily suspected because of hepatosplenomegaly and supranuclear paralysis. Two other disorders must also be considered: myoclonic-epilepsy with ragged red fibers (MERRF) syndrome and Schindler disease, which is similar to neuroaxonal dystrophy.
- **Category 5: isolated developmental arrest or regression.** Only a few disorders present between 1 and 5 years of age with an isolated developmental arrest or regression of cognitive and perceptual abilities without other significant neurological or extraneurological signs. Sanfilippo disease is one, although regression of high-level achievements, loss of speech, and agitation usually begin later than 5 years of age. Although non-metabolic, Rett syndrome is another such disease; it should be considered when a girl, without a family history, presents between 1 and 2 years of age with autistic behavior, developmental regression, typical stereotyped hand movements, and microcephaly.

Late Childhood to Adolescence (5–15 years)

(◘ Table 1.16)

It is important to distinguish between conditions in which cognitive function is primarily affected and those disorders with more extensive neurological involvement with normal or subnormal intellectual functioning. According to Lyon and Adams [23], there are six clinical categories.

- **Category 1: with predominant extrapyramidal signs** (parkinsonian syndrome, dystonia, choreoathetosis).
- **Category 2: with severe neurological and mental deterioration and diffuse central nervous system involvement.** Category-2 patients have in common severe neurological dysfunction with bipyramidal paralysis, incoordination, seizures, visual failure, impaired school performance, and dementia. In association with splenomegaly or hepatomegaly, these signs suggest Niemann-Pick disease type C or Gaucher disease type III. When visceral signs are absent, they may indicate juvenile metachromatic leukodystrophy, X-linked adrenoleukodystrophy, Krabbe disease, juvenile GM-1 and GM-2 gangliosidoses, or respiratory-chain disorders. Peroxisomal biogenesis defects can also present in the second decade of life with peripheral neuropathy initially mimicking Charcot-Marie-Tooth type II disease, but which then evolves into a pyramidal syndrome, intellectual deterioration, dementia and, shortly thereafter, a neurovegetative state.
- **Category 3: with polymyoclonus and epilepsy**. The juvenile form of ceroid lipofuscinosis (Spielmeyer-Vogt or Batten disease due to CLN3 gene mutations), which presents with loss of sight, retinitis, ataxia, and (at an advanced stage) extrapyramidal signs, should be suspected with the onset of polymyoclonus and epilepsy. After puberty, Lafora disease should also be considered. Gaucher disease type III, late onset GM-2 gangliosidosis, Niemann-Pick disease type C, and respiratory-chain disorders can also begin with polymyoclonus as an early major sign.
- **Category 4: with predominant cerebellar ataxia.** Friedreich ataxia and other hereditary ataxias should be considered and are recognized on clinical and genetic

Table 1.16. Progressive neurological and mental deterioration (5 to 15 years)

Symptoms	Diagnosis (disorder or enzyme deficiency)
With predominant extrapyramidal signs, parkinson syndrome, dystonia, choreoathetosis	
▬ Torsion, dystonia, no mental retardation	**Dystonia musculorum deformans**
▬ Dystonia on lower extremities, gait difficulties, normal IQ	**Segawa (GTP cyclohydrolase)**
	Tyrosine hydroxylase
▬ Lens dislocation, marfanoid morphology	**Classic homocystinuria**
▬ Generalized parkinsonian rigidity, scholastic failure	**Wilson**
▬ Parkinsonism, reading/writing difficulties, alacrima, dysphagia	**Familial glucocorticoid deficiency** (with hypoglycemia)
▬ Dysarthria, dysphagia, cogwhill rigidity	**Biotin responsive basal ganglia disease**
▬ Walking difficulties, dystonic posture, mental regression	Panthotenate kinase (RP, acanthocytosis)
▬ Orofacial dyskinesia	HARP syndrome (panthotenate kinase)
▬ Acute psychosis, pallidal necrosis	Neuroferritinopathy [17,18]
With diffuse central nervous system disorders, seizures, visual failure, dementia	
▬ With hepatosplenomegaly	Niemann Pick type C, Gaucher type III
▬ Without visceral signs	Metachromatic leucodystrophy, X-ALD
	Peroxisomal biogenesis defects
	Krabbe, GM1 and GM2
	Leigh syndrome, respiratory chain defects
With polymyoclonia	
▬ Intellectual deterioration, loss of sight, RP	JNCL (Batten, CLN3 mutations)
▬ Proeminent seizures, myoclonic epilepsy, dementia	Gaucher type III (splenomegaly, osseous signs)
▬ Cerebellar ataxia, cherry red spot	Late GM2 gangliosidosis (Sandhoff, Tay-Sachs)
▬ Hepatomegaly, splenomegaly	Niemann-Pick type C
▬ Myoclonic epilepsy, lactic acidosis	Respiratory chain defects (MERFF, etc.)
With predominant cerebellar ataxia	
▬ Without significant mental deterioration	
– Dysarthria, pes cavus, cardiomyopathy	Friedreich ataxia
– Spinocerebellar degeneration	Other hereditary ataxias, Peroxisomal defects
– Chronic diarrhea, low cholesterol, acanthocytosis	**Abetalipoproteinemia**
– Retinitis pigmentosa, peripheral neuropathy	Refsum, peroxisomal defects, CDG
– Oculocephalic asynergia, conjunctival telangiectasias	Ataxia telangiectasia
▬ With deterioration and dementia	**CTX**, Lafora, GM1, GM2, Gaucher, Niemann-Pick type C, Krabbe
	Metachromatic leukodystrophy, respiratory chain
With predominant polyneuropathy	
▬ Acute attacks	**Porphyrias, tyrosinemia type I**
▬ Progressive	
– With demyelination (low NCV)	Metachromatic leucodystrophy, Krabbe
	β-mannosidase, Refsum, peroxisomal biogenesis
	MNGIE syndrome
– Predominantly axonal (normal NCV)	**LCHAD**, **trifunctional enzyme,** **PDH**, **homocysteine remethylation defects**, **CTX**, peroxisomal biogenesis defects, α-methylacyl-CoA racemase, **serine deficiency**, P5C synthase, **ornithine amino transferase**
	Leigh syndrome, respiratory chain defects
	Abetalipoproteinemia
With psychiatric symptoms as the only presenting sign	
Behaviour disturbances, personality and character changes, mental regression, dementia, schizophrenia before any significant neurological or extraneurologic sign	**OTC**, **homocystinurias** (**CBS, MTHFR, CblC**) Sanfilippo, metachromatic leucodystrophy, Krabbe, Niemann-Pick C, X-ALD Leigh syndrome, JNCL (Batten), Hallervorden-Spatz (PK deficiency), **Wilson**, **CTX**, Huntington chorea (juvenile form) Neuroferritinopathy [17,18]

CBS, cystathionine β-synthase; *CDG,* congenital disorders of glycosylation; *CTX*, cerebrotendinous xanthomatosis; *HARP,* hypobetalipoproteinemia, acanthosis, retinitis pigmentosa, pallidal degeneration; *JNCL*, juvenile neuronal ceroid lipofuscinosis; *MTHFR*, methylene tetrahydrofolate reductase; *NCV,* nerve conduction velocity; *OTC*, ornithinetranscarbamylase; *RP,* retinitis pigmentosa; *X-ALD,* X-linked adrenoleukodystrophy; **bold face**, treatable disorders.

grounds. Abetalipoproteinemia and ataxia telangiectasia are usually suspected because of the associated extraneurological signs. Peroxisomal disorders, CDG, and Refsum disease (which can all present similarly to a peripheral neuropathy and retinitis pigmentosa) can be demonstrated by the analysis of plasma very-long-chain fatty acids, glycosylated transferrin profile, and plasma phytanic acid, respectively. Cerebellar ataxia in association with progressive mental deterioration, dementia, and epilepsy suggests Lafora disease, **cerebrotendinous xanthomatosis**, late-onset forms of gangliosidosis, Krabbe disease, Gaucher disease, Niemann-Pick disease type C, and metachromatic leukodystrophy. Respiratory-chain disorders also can present with a predominant ataxia.

- **Category 5: with predominant polyneuropathy. Porphyrias** and **tyrosinemia type I** can present with an acute attack of polyneuropathy mimicking Guillain-Barre syndrome. Many other disorders can present with a late-onset progressive polyneuropathy that can mimic hereditary ataxia, such as Charcot-Marie-Tooth disease. These include lysosomal diseases (Krabbe disease, metachromatic leukodystrophy, β-mannosidase), peroxisomal disorders (peroxin 7, other peroxisomal biogenesis defects, Refsum disease with demyelination and reduced nerve conduction velocities), defects of energy metabolism (Leigh syndrome, respiratory-chain disorders, PDH deficiency, LCHAD and trifunctional-enzyme deficiencies), abetalipoproteinemia, CDG (► also Sect. 1.4.3).
- **Category 6: with behavioral disturbances as the presenting signs.** Some inborn errors of metabolism can present between 5 and 15 years of age as psychiatric disorders. Behavioral disturbances (personality and character changes), loss of speech, scholastic failure, mental regression, dementia, psychosis, and schizophrenia-like syndrome are the most frequent symptoms. In addition **OTC deficiency** can present with episodes of abnormal behavior and character change until hyperammonemia and coma reveal the true situation (► Recurrent Attacks of Coma above). **Homocystinuria** due to methylenetetrahydrofolate reductase deficiency has presented as isolated schizophrenia. **Searching for these treatable disorders is always mandatory including CTX and Wilson disease.**

Onset in Adulthood (15–70 years)

As metabolic investigations become increasingly common in adult neurological practice, a rapidly increasing number of adults patients with IEM has been identified. When neurologists extend metabolic investigations to late-onset, progressive, neurological deterioration, currently considered to be degenerative, inflammatory, or of vascular origin, it is highly probable that many other disorders will be discovered. Some disorders truely start in adulthood; others present in the pediatric age with symptoms that are not recognised, misdiagnosed or inadequately interpreted. Metabolic diagnosis in adults based on substrate measurements can be very difficult because metabolic changes can be very moderate or even absent. A recent reappraisal of the metabolic profile of the three infantile Refsum disease index cases described in 1986 [26] showed an almost total normalization of the initial characteristic biochemical abnormalities (personal unpublished observation). In ◘ Table 1.17 is the »state of the art« of adult metabolic neurology based upon the personal experience of the adult metabolic clinic of La Pitié Salpétrière hospital and on the literature analysis mostly composed of isolated case reports. There is no doubt that this will change significantly very soon. ◘ Table 1.17 does not describe the full phenotype of the listed disorders, but rather emphasizes the main presenting symptom.

1.4.4 Specific Associated Neurological Abnormalities

Cherry-red Spot

- Cytochrome C oxidase deficiency
- Galactosialidosis (neuraminidase deficiency)
- Gangliosidosis GM1 (Landing)
- Gangliosidosis GM2 (Sandhoff, Tay-Sachs)
- Nephrosialidosis
- Niemann-Pick type A, C and D
- Sialidosis type I

Deafness (Sensorineural)

Detectable in neonatal to early infancy:

- Acyl-CoA oxidase deficiency
- Alport syndrome
- Cockayne syndrome
- Encephalopathy with hyperkinurininuria
- Rhizomelic chondrodysplasia punctata
- Zellweger and variants

Detectable in late infancy to childhood:

- **Biotinidase deficiency (biotin responsive) (untreated or treated late)**
- Infantile Refsum disease (pseudo Usher syndrome)
- Mannosidosis (alpha)
- **Megaloblastic anemia, diabetes and deafness (B1-responsive)**
- Mitochondrial encephalomyopathy
- Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy with ragged red fibers (MERFF), Kearns-Sayre syndrome
- Mucolipidosis type II (I cell disease)
- Mucopolysaccharidosis type I, II and IV
- Neutral lipid storage disorder
- PRPP synthetase superactivity
- Wolframm syndrome

Table 1.17. Progressive neurological and mental deterioration (adulthood)

Diseases	Major presenting signs							
(Disorder or enzyme deficiency)	Parkinson syndrome	Dystonia, chorea	EMG poly-neuropathy	Epilepsy	Psychiatric signs	Spastic paraparesia	Cerebellar ataxia	Multi-systemic
α-mannosidase						+	+	+
α-methylacyl-CoA race-mase			+	+		+		
β-mannosidosis			+		+			+
L-2-OH-glutaric aciduria	+	+		+		+		
Acerulo-plasminemia	+	+			+		+	+
AMN			+			+	+	
ANCL	+			+	+			
Arginase						+		
Biotin responsive encephalopathy		+		+				
Cerebral ALD		+ (chorea)		+	+	+		
Co-enzyme Q10							+	
CTX	+		+	+	+	+	+	+
Dopa responsive dystonia		+				+		
Fabry			+*					+
Gaucher III	+	+ (chorea)		+			+	+
GM1	+	+						
GM2		+	+*		+		+	
GTP cyclohydrolase I	+	+				+		
Hemochromatosis	+							
Homocysteine methyla-tion defects			+	+	+	+		+
Homocystinuria	+	+ +	+		+			+
Huntington chorea	+	+		+	+		+	
Krabbe			+			+		
Lafora				+	+		+	
LCHAD			+					+
Leigh, MELAS, Leber	+	+ +	+	+			+	+
Lesch-Nyhan		+ +			+			
MAO-A					+			
Mevalonate kinase							+	+

Table 1.17 (continued)

Diseases	Major presenting signs							
(Disorder or enzyme deficiency)	Parkinson syndrome	Dystonia, chorea	EMG poly-neuropathy	Epilepsy	Psychiatric signs	Spastic paraparesia	Cerebellar ataxia	Multi-systemic
Mitochondrial defects	+	+	+	+			+	+
MLD		+	+		+	+	+	
MNGIE			+					+
MPS III					+			
Neuraminidase				+				
Neuro-ferritinopathy	+	+			+			
Niemann-Pick C	+	+		+	+		+	
NKH		+ (chorea)				+	+	
Oligosaccharidosis								+
PA		+ (chorea)						
PBD			+				+	+
PDH (E1)	+	+	+				+	
PK		+						
PKU	+				+	+		
Polyglucosan body disease	+		+			+		
Polymerase γ	+		+	+			+	
Porphyria			+*	+	+			
PTP synthase		+						
Refsum			+				+	+
Serine deficiency syndrome			+					
Sjögren-Larsson						+		
Tangier			+*					+
Triple H syndrome						+		
Tyrosine hydroxylase	+					+		
Urea cycle				+	+		+	
Wilson	+	+		+	+			

ALD, adrenoleukodystrophy; *AMN*, adrenomyeloneuropathy; *ANCL*, adult neuronal ceroid lipofuscinosis (CLN4 mutations); *CTX*, cerebrotendinous xanthomatosis; *LCHAD*, 3-hydroxy long chain acyl-CoA dehydrogenase; *MAO*, mono amine oxidase; *MLD*, metachromatic leucodystrophy; *MNGIE*, mitochondrial neuro-gastro-intestinal encephalopathy; *MPS*, mucopolysaccharidosis; *NKH*, non ketotic hyperglycinemia; *PA*, propionic acidemia; *PBD*, Peroxisome biogenesis defects; *PDH*, pyruvate dehydrogenase; *PK*, panthotenate kinase; *PKU*, phenylketonuria; *PTP*, 6-pyruvoyl tetrahydropterin; * polyneuropathy affecting small sensitive fibers and autonomic nervous system; **bold face**, treatable disorders.

Detectable in late childhood to adolescence:
- Beta-mannosidosis
- MERFF, Kearns-Sayre syndromes
- Refsum disease (adult form)
- Usher syndrome type II

Leigh Syndrome

- **Biotinidase deficiency**
- EPEMA syndrome [13]
- Fumarase deficiency
- MAMEL syndrome [26]
- Pyruvate carboxylase deficiency
- **Pyruvate dehydrogenase deficiency**
- Respiratory chain disorders
- Sulfite oxidase deficiency
- 3-methylglutaconic aciduria

Macrocephaly

- Alexander
- Canavan (acetylaspartaturia)
- Gangliosidosis GM2 (Sandhoff, Tay-Sachs)
- **Glutaric aciduria type I**
- Krabbe (infantile form)
- L-2-hydroglutaric aciduria
- Respiratory chain disorders
- Vacuolizing encephalopathy

Microcephaly

Congenital:
- Infant born to untreated PKU mother
- Sulfite oxidase deficiency
- **3P-Glycerate phosphate dehydrogenase** (improved by serine)

Acquired:
- Rett syndrome
- Many untreated disorders in which microcephaly is a symptom of a non specific cerebral atrophy

Neuro-imaging (CT Scan, MRI, ^{1}H-MRS) Abnormalities

(**Bold face**, treatable disorders; *reported in adults as presenting or preponderant symptoms)

Calcifications on CT-scan:
- Aicardi-Goutières syndrome
- **Biopterin metabolism defects**
- Cockayne syndrome
- Congenital lactic acidemias
- **Folic acid metabolism defects**
- GM2 Gangliosidosis
- Kearns-Sayre
- Leigh syndrome
- MELAS syndrome
- Respiratory chain disorders
- 3-hydroxyisobutyric aciduria

White matter hyperintensity:
- With increased head circumference
  - Alexander (anterior)
  - Canavan
  - **Glutaric aciduria type I** (bi-temporal atrophy)
  - L-2-hydroxyglutaric aciduria
  - Mucopolysaccharidosis (with vacuoles)
  - Vacuolizing leucoencephalopathy

- With normal head circumference

  Predominantly periventricular white matter
  - Aicardi-Goutières syndrome (with calcifications)
  - CACH (vanishing white matter disease)
  - **Cerebrotendinous xanthomatosis***
  - Cockayne (with calcifications)
  - **Homocysteine remethylation defects***
  - **Glutaric aciduria type I***
  - Kearns-Sayre
  - L-2-hydroxyglutaric aciduria
  - Menkes
  - Metachromatic leucodystrophy*
  - Mitochondrial cytopathy
  - MNGIE (with supratentorial cortical atrophy)
  - Pelizaeus-Merzbacher (myelination arrest)
  - Peroxisomal biogenesis defects*, PEX-7
  - **PKU** (untreated, reversible)*
  - Polyglucosan body disease*
  - Ribose-5-phosphate isomerase* (arabitol, ribitol)
  - **X-ALD** (posterior)
  - 3-methylglutaryl-CoA lyase*

  Predominant pyramidal tracts
  - Adrenomyeloneuropathy*
  - **Cerebrotendinous xanthomatosis***
  - Krabbe disease*
  - Mitochondrial cytopathies*

  Affecting U fibers
  - Mitochondrial cytopathies*
  - Polyglucosan body disease*
  - Ribose-5-phosphate isomerase* (arabitol, ribitol)
  - L-2-hydroxyglutaric aciduria*

Basal ganglia/brain stem hyperintensities:
- **Biotin-responsive basal ganglia disease** [12] (bilateral necrosis of caudate nucleus and putamen)
- **Cerebrotendinous xanthomatosis***
- GM1 Gangliosidosis*
- Hypoceruleoplasminemia* (diffuse hypointensity)
- Infantile bilateral striatal necrosis [28]
- Leigh syndrome (putamen, caudate nuclei)
- L-2-hydroxyglutaric aciduria
- **Methylmalonic aciduria** (pallidum)
- Mitochondrial cytopathies*
- Neuroferritinopathy* (pallidum) [17, 18]
- PKAN* (Hallervorden-Spatz, HARP syndrome: hypointensity: tiger eye)

- **Pyruvate dehydrogenase deficiency***
- **Wernicke encephalopathy*** (thalami, brain stem)
- **Wilson disease***

Dentate nuclei of the cerebellum (hyperintensities):
- **Cerebrotendinous xanthomatosis***
- L-2-hydroxyglutaric aciduria
- Mitochondrial encephalopathy*
- Polyglucosan body disease*
- Semialdehyde succinate dehydrogenase*
- **Wilson disease***

Gyration abnormalities:
- CEDNIK (snare protein mutation) [29]
- Glutamine synthetase
- Congenital muscular dystrophy: DMC1-C (fukutin related protein), DMC1-D (LARGE protein)
- O-glycosylation disorders: muscle-eye-brain disease, Walker-Warburg syndrome, Fukuyama disease
- Peroxisomal disorders (Zellweger and others)

Corpus callosum agenesis:
- With gyration abnormalities (► above)
- **ACTH deficiency**
- Aicardi syndrome (with calcifications)
- Complex II mitochondrial cytopathies (with leucodystrophy)
- Non ketotic hyperglycinemia
- PDH (with basal ganglia abnormalities)
- 3-hydroxyisobutyric aciduria

Posterior fossa (and olivo-ponto-cerebellar):
- Hypoplasia
  - CDG
  - Congenital muscular dystrophies
  - Joubert syndrome
  - Mitochondrial cytopathies
  - Peroxisomal disorders
- Progressive atrophy
  - Ceroid lipofuscinosis*
  - GM1 Gangliosidosis (Landing)
  - L-2-hydroxyglutaric aciduria
  - Mevalonic aciduria (mevalonate kinase)
  - Neuroaxonal dystrophy (infantile)
  - Schindler
  - Smith-Lemli-Opitz
  - Succinyl semialdehyde dehydrogenase deficiency
  - 3-methylglutaconic aciduria

Stroke and stroke-like episodes:
- CDG
- **Homocystinurias***
- MELAS syndrome*

Nystagmus

With retinitis pigmentosa:
- Abetalipoproteinemia*
- Ceroid lipofuscinosis (CLN1, CLN2, CLN3*, CLN4*)
- **LCHAD***
- Mitochondrial cytopathies (Kearns-Sayre* etc.)
- Peroxisomal defects (infantile to childhood)
- Sjögren-Larsson (fatty acid alcohol oxido-reductase)
- All causes of severe retinitis pigmentosa

With optic atrophy:
- All causes of optic atrophy in adulthood*
- Canavan disease (early sign)
- Ceroid lipofuscinosis (CLN3*, CLN4*)
- Krabbe disease (infantile)
- Leber due to mitochondrial DNA deletions*
- Leigh syndrome (all causes)
- Metachromatic leucodystrophy*
- Mitochondrial cytopathies*
- Neuroaxonal dystrophy – Schindler (infantile)
- Pelizaeus-Merzbacher (presenting sign early in infancy)
- Peroxisomal biogenesis defects*
- Pyruvate dehydrogenase deficiency*
- Ribose-5-phosphate isomerase*
- Sulfite oxidase (infantile)
- X-ALD*
- 3-methylglutaconic aciduria

With corneal opacities, cataract:
- **Fabry disease***
- **Homocystinurias***
- Lowe syndrome (infancy)
- Mucopolysaccharidosis (childhood)
- **Wilson disease***

Opthalmoplegia, Ptosis, Eye Movements, Strabismus (► also Sect. 1.4.3)

Neonatal to early infancy (oculogyric crisis):
- Aromatic amino acid decarboxylase
- CDG Ia (with congenital strabismus)
- Cogan syndrome (ocular contraversion)
- **Pyridox(am)ine-5-phosphate oxidase**
- Tyrosine hydroxylase

Infancy to childhood:
- Ataxia telangiectasia (ocular contraversion, telangiectasia)
- Gaucher type III (horizontal supranuclear paralysis)
- Leigh syndrome (acute attacks of abnormal movements)
- Niemann-Pick C and D (vertical supranuclear paralysis)
- Pyruvate dehydrogenase (acute attacks of abnormal movements)
- Respiratory chain (acute attacks of abnormal movements)

Adulthood:
- **Glutaric aciduria type I**
- GM2 gangliosidosis (abnormal eye movements)
- Mitochondrial cytopathies: Kearns-Sayre (abnormal movements)
- Niemann-Pick C, Gaucher III (► above)
- Non ketotic hyperglycinemia
- Pyruvate dehydrogenase (abnormal movements)
- **Wilson disease**

Peripheral Neuropathy – EMG, NCV Findings

Acute (recurrent attacks):
- **Porphyrias***
- **Tyrosinemia type I**

Chronic:
- Predominantly demyelination (low NCV)
  - Presenting or preponderant
    - Refsum disease (late childhood to adulthood)
    - X-ALD (childhood to adulthood): leucodystrophy
    - AMN (adulthood)
  - Accompanying symptom
    - Austin disease
    - β-mannosidosis
    - Farber lipogranulomatosis
    - **Homocysteine remethylation defects (MTHFR, CblC)**
    - Krabbe (leucodystrophy)
    - Metachromatic leucodystrophy (leucodystrophy)
    - MNGIE syndrome (leucodystrophy)
    - Refsum disease
    - **Tangier disease**
- Predominantly axonal (normal NCV)
  - Presenting or preponderant
    - Abetalipoproteinemia (childhood)
    - α-methylacyl-CoA racemase (adolescence to adulthood)
    - CDG type I (childhood)
    - GM2 gangliosidosis*
    - **LCHAD**, trifunctional (childhood to adolescence)
    - Peroxisomal biogenesis defects (late childhood to adult)
    - Polyglucosan body disease* (leucodystrophy)
    - Pyruvate dehydrogenase (childhood to adulthood)
    - **Vitamin E malabsorption** (tocopherol carrier)
  - Accompanying symptom
    - **Cerebrotendinous xanthomatosis*** (leucodystrophy)
    - Neuroaxonal dystrophy, Schindler (early childhood) (leucodystrophy)
    - **Ornithine amino transferase** (late complications)
    - P5C synthase (late childhood)
    - **Porphyria***
    - Pyroglutamic aciduria (late complication)
    - Respiratory chain (early childhood to adolescence)
    - **Serine deficiency syndrome** (adolescence)
    - Triose phosphate isomerase
  - Affecting small sensitive fibers and the autonomic nervous system
    - **Fabry disease*** (presenting sign)
    - GM2 gangliosidosis*
    - **Porphyria***
    - **Tangier disease***
  - Affecting anterior horn
    - GM2 gangliosidosis, Krabbe disease
    - **Homocysteine remethylation defects (ClbC)**
    - Non ketotic hyperglycinemia
    - Panthotenate kinase (Hallervorden-Spatz) (basal ganglia)
    - Polyglucosan body disease*

Retinitis Pigmentosa

- Aceruleoplasminemia*
- Congenital disorders of glycosylation
- Ceroid lipofuscinosis: CLN1, CLN2; LCN3
- Cobalamin metabolism defects: CblC*
- Gyrate atrophy with ornithine aminotransferase deficiency
- Inborn errors of lipid metabolism:
  - **Abetalipoproteinemia**
  - Sjögren-Larsson syndrome
  - **Vitamin E malabsorption (tocopherol carrier)**,
  - **3-hydroxyacyl-CoA dehydrogenase**
- Panthothenate kinase* (Hallervorden-Spatz, HARP syndrome)
- Peroxisomal biogenesis defects:
  - α-methylacyl-CoA racemase*
  - Classical Refsum disease*
  - Isolated fatty acid oxidation defects
  - Peroxisomal biogenesis defects (Zellweger, NALD, Refsum and variant forms)
- Respiratory chain disorders:
  - Kearns-Sayre syndrome*
  - NARP
  - Other mitochondrial DNA deletions
- Recessive autosomal syndromes (Cockayne, Laurence-Moon-Biedl, Usher type II, Joubert, Senior-Loken etc.)
- »Primary retinitis pigmentosa« X-linked, autosomal recessive or dominant

Self Mutilation, Auto-aggression

- Lesch-Nyhan syndrome
- **Phenylketonuria** (untreated)
- **Tyrosinemia type I** (crisis)
- 3-methylglutaconic aciduria

1.5 Specific Organ Symptoms

A number of clinical or biological abnormalities can be associated with inherited inborn errors of metabolism. Some of these phenotypes are rare and very distinctive (e.g., lens dislocation and thromboembolic accidents in homocystinuria) whereas others are common and rather non-specific (e.g., hepatomegaly, seizures, mental retardation). The most important ones are listed below. The following diagnostic checklist presented is primarily based upon the authors' personal experience and, of course, is not exhaustive. It should be progressively extended by the personal experiences of all readers.

It is important to reemphasise the difference between a syndrome where the underlying pathophysiology has not been described and a disorder where the aetiology is known. Some well-known recessive syndromes (such as Joubert, Usher, Cockayne etc.) have been listed under inborn errors of metabolism, highlighting the need to perform extensive metabolic and genetic investigations. The demonstration of cholesterol synthesis defects in a number of malformative syndromes or the more recent demonstration of O-glycosylation defects in congenital muscular dystrophies illustrate this statement.

1.5.1 Cardiology

Arrhythmias, Conduction Defects (Heart Beat Disorders)

Primitive heart beat disorders:

- **Adrenal dysfunction** (hyperkalemia)
- AMP activated protein kinase (PRKAG2 mutations with cardiac glycogenosis and Wolf-Parkinson-White)
- Triose phosphate isomerase deficiency
- D-2-hydroxyglutaric aciduria (AV block)
- **Fatty acid oxidation disorders** (CPT II, carnitine translocase, LCAD, LCHAD, TF, VLCAD)
- **Hypoparathyroidism** (hypocalcemia)
- Kearns-Sayre syndrome (respiratory chain disorders)
- **Thiamine deficiency-dependent states**

With cardiac/multiorgan failure: ► below
With cardiomyopathy: ► below

Cardiac Failure, Collapse

With tamponade, multiorgan failure:

- Congenital disorders of glycosylation

With apparently primitive heart beat disorders: ► above
With cardiomyopathy: ► below

Cardiomyopathy

- AMP activated protein kinase (presenting sign) [30, 31]
- Barth syndrome
- Congenital disorders of glycosylation (with pericardial effusion, can be the presenting sign)
- Congenital muscle dystrophies
- D-2-hydroxyglutaric aciduria
- **Fabry disease**
- **Fatty acid oxidation disorders** (presenting sign)
- Friedreich ataxia (presenting sign)
- **Glycogenosis type III** and IV
- GM1 gangliosidosis
- Isobutyryl-CoA dehydrogenase
- **Methylmalonic aciduria (Cbl C)**, malonic aciduria
- Mucopolysaccharidosis
- Muscle glycogen synthase (presenting sign) [32]
- Pompe disease, Danon disease (presenting sign)
- **Propionic acidemia**
- Respiratory chain disorders (presenting sign)
- **Selenium deficiency**
- Steinert disease – myotonic dystrophy
- **Thiamine deficiency** (presenting sign)
- **Thiamine-responsive anemia**
- 3-methylglutaconic aciduria

1.5.2 Dermatology

Acrocyanosis (Orthostatic)

- EPEMA syndrome [13]

Alopecia

Age at onset: neonatal to infancy

- **Acrodermatitis enteropathica**
- **Biotin-responsive multiple carboxylase defects**
- **Calciferol metabolism defects** (vitamin-D-dependent rickets)
- **Congenital erythropoietic porphyria**
- Conradi-Hünermann syndrome
- Ehlers-Danlos type IV
- **Essential fatty acid deficiency**
- **Hepatoerythropoietic porphyria**
- Menkes disease (X-linked)
- **Methylmalonic and propionic acidurias**
- Netherton syndrome
- **Zinc deficiency**

Age at onset: adulthood

- **Porphyria cutanea tarda**
- Steinert

Angiokeratosis

- Aspartylglucosaminuria
- β-mannosidosis
- **Fabry disease** (presenting sign)
- Fucosidosis
- Galactosialidosis
- Kanzaki disease
- Schindler disease (adult form)

Brittle Hair

- **Argininosuccinic aciduria**
- **Citrullinemia**
- Menkes syndrome
- Pollitt's syndrome
- Trichothiodystrophy

Hyperkeratosis

- CEDNIK (neuro-cutaneous syndrome: keratosis on palms and soles) [29]
- Ichthyosis (► below)
- **Tyrosinemia type II** (keratosis on palms and soles)

Ichthyosis (with Congenital Erythrodermia)

- Austin disease
- CEDNIK (neuro-cutaneous syndrome: SNARE protein mutation) [29]
- Conradi-Hünermann syndrome (chondrodysplasia punctata X-linked)
- Multisystemic triglyceride storage disease
- Netherton syndrome
- **Refsum disease (adult form)**
- **Serine deficiency syndrome**
- Sjögren-Larsson syndrome
- Steroid sulfatase deficiency (X-linked)

Laxity (Dysmorphic Scarring, Easy Bruising)

Inborn errors of collagen:

- Cutis laxa
- Ehlers-Danlos syndrome (nine types)
- Occipital horn syndrome
- Pyrroline-5-carboxylate synthase

Nodules

- Congenital disorders of glycosylation
- Farber lipogranulomatosis

Pellagra

- **Hartnup disease**

Photosensitivity and Skin Rashes

Age at onset: neonatal to childhood

- **Congenital erythropoietic porphyria**
- **Erythrohepatic porphyria**
- **Erythropoietic protoporphyria**
- **Hartnup disease**
- Mevalonic aciduria (with fever and arthralgia)
- Respiratory chain disorders
- Xeroderma pigmentosa (nine varieties)

Age at onset: adulthood

- **Hereditary coproporphyria**
- **Porphyria variegata**
- **Porphyria cutanea tarda**

Pili Torti

- Menkes disease
- Netherton syndrome

Telangiectasias - Purpuras - Petechiae

- Ethylmalonic aciduria (EPEMA syndrome)
- Prolidase deficiency

Trichorrhexis Nodosa

- **Argininemia**
- **Argininosuccinic aciduria**
- **Lysinuric protein intolerance**
- Menkes disease
- Netherton syndrome

Ulceration (Skin Ulcers)

- Prolidase deficiency

Vesiculo-Bullous Skin Lesions

- **Acrodermatitis enteropathica**
- **Biotinidase deficiency** (biotin-responsive)
- **Holocarboxylase synthetase deficiency** (biotin-responsive)
- **Methylmalonic, propionic acidemias** (isoleucine deficiency)
- **Zinc deficiency**

Xanthoma

- Apo CII (eruptive)
- Apolipoprotein A1 (planar)
- **Familial dominant hypercholesterolemia**:
  - homozygote (childhood)
  - heterozygote (adulthood)
- Dysbetalipoproteinemia (hyperlipoproteinemia type III)
- Hepatic lipase
- Lipoprotein lipase (eruptive)
- Sitosterolemia (childhood)

1.5.3 Dysmorphism

Coarse Facies

Age at onset: present at birth
- Galactosialidosis (early infancy)
- I-cell disease
- Landing
- Sialidosis type II
- Sly (mucopolysaccharidosis (MPS) type VII) (rare)

Age at onset: early infancy
- Austin
- Fucosidosis type I
- Hurler (MPS type IH)
- Mannosidosis
- Maroteaux-Lamy (MPS type V)
- Salla disease
- Sialidosis type II
- Sly (MPS type VII)

Age at onset: childhood
- Aspartylglucosaminuria
- Hunter (MPS type II)
- Pseudo-Hurler polydystrophy
- Sanfilippo (MPS type III)

Dysplasia, Dysmorphic

Maternal metabolic disturbances (untreated pregnancy):
- **PKU** (dysmaturity, heart defect, microcephaly, specific face, hypotrophy)
- Alcohol (dysmorphic, hypotrophy)
- **Diabetes** (macrosomia)
- Drugs (dysmorphic, hypotrophy)
- **Vitamin deficiencies** (riboflavin)

Inborn errors affecting the fetus:
- Carnitine palmitoyl transferase II deficiency (renal cysts)
- D-2-hydroxyglutaric aciduria
- Glutaric aciduria type II (MADD) (renal cysts)
- Inborn errors of collagen
- **Hyperinsulinism** (macrosomia, dysmorphia)
- Hypoparathyroidism
- Hypophosphatasia
- Leprechaunism
- Lysosomal storage disorders (hydrops fetalis)
- Mevalonic aciduria (mevalonate kinase deficiency)
- Peroxisomal biogenesis defects (renal cysts, migration defects)
- Chondrodysplasia punctata
- Pyruvate dehydrogenase deficiency
- Respiratory chain defects
- Serine synthesis (microcephaly)
- Transaldolase deficiency (hydrops fetalis)

Malformations

- 3-OH-isobutyryl-CoA deacylase deficiency (limbs, vertebrae)
- Cholesterol synthesis defects:
  - Smith-Lemli-Opitz
  - Conradi-Hünermann-Happle syndrome
  - Desmosterolosis
  - Greenberg dysplasia
  - Antley-Bixler syndrome
  - Mevalonic aciduria
  - CHILD syndrome
  - Lathosterolosis
- Glutamine synthetase
- Non-ketotic hyperglycinemia
- O-glycosylation and related defects:
  - Walter-Warburg (POMT1)
  - Muscle-eye-brain disease (POMGMT),
  - Fukuyama (Fukutin)
  - DMC1-C (fukutin related protein)
  - DMC1-D (LARGE protein)

Intra-uterine Growth Retardation

- Fetal alcoholic syndrome
- Infants born to mothers with untreated phenylketonuria
- Cholesterol biosynthesis defects
- Lysosomal storage disorders
- Many non-metabolic polymalformative syndromes
- Peroxisomal disorders
- Respiratory chain disorders
- Transaldolase deficiency

1.5.4 Endocrinology

Diabetes (and Pseudodiabetes)

- Abnormal pro-insulin cleavage
- **Diabetes, deafness and thiamine responsive megaloblastic anemia**
- Diabetes type II: fatty acid oxidation disorders, Kir 6.2, glucokinase
- **Organic acidurias (methylmalonic, propionic, isovaleric acidemias, ketolysis defects)**
- Respiratory chain disorders – Wolfram syndrome

Hyperinsulinism

- **SUR1 and KIR6.2 mutations (potassium channel)**
- **Glucokinase overactivity**
- **Glutamate dehydrogenase overactivity**
- Short chain L-3-OH-acyl-CoA dehydrogenase
- Wiedemann-Beckwith syndrome

Hyperthyroidism

- Glutaric aciduria type I (glutaryl-CoA dehydrogenase deficiency)

Hypogonadism – Sterility
- CDG type I
- Galactosemia

Hypoparathyroidism
- **Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency**
- Respiratory chain disorders
- **Trifunctional enzyme deficiency**

Hypothyroidism
- Allan-Herndon-Dudley syndrome (monocarboxylate transporter 8) [22]

Salt-Losing Syndrome
- **Disorders of adrenal steroid metabolism**
- **Fatty acid oxidation disorders** (carnitine palmitoyl transferase II)
- Respiratory chain disorders (mitochondrial DNA deletions)

Sexual Ambiguity
- Congenital adrenal hyper- and hypoplasia
- Disorders of adrenal steroid metabolism

Short Stature – Growth Hormone Deficiency
- Respiratory chain disorders

1.5.5 Gastroenterology

Abdominal Pain (Recurrent)

With flatulence, diarrhea, lose stools:
- **Lactose malabsorption**
- **Congenital sucrase isomaltase deficiency**

With vomiting, lethargy, ketoacidosis:
- **Urea cycle defects** (OTC, ASA)
- **Organic acidurias** (MMA, PA, IVA)
- **Ketolysis defects**
- Respiratory chain disorders
- **Diabetes**

With neuropathy, psychiatric symptoms:
- MNGIE syndrome
- **OTC** (late onset)
- **Porphyrias**
- **Tyrosinemia type I**

With hepatomegaly and splenomegaly:
- Cholesterol ester storage disease
- Lipoprotein lipase deficiency
- **Lysinuric protein intolerance**
- Hemochromatosis
- Mevalonate kinase deficiency

With pain in extremities:
- **Fabry disease**
- δ-aminolevulinate dehydratase deficiency
- **Sickle cell anemia**

With hemolytic anemia:
- **Coproporphyria**
- Hereditary spherocytosis
- **Sickle cell anemia**
- Nocturnal paroxysmal hemoglobinuria

With Crohn disease (and pseudo-Crohn):
- **Glycogenosis type 1b**
- **Trifunctional enzyme deficiency**
- **Carnitine transporter** (OCTN2)

With inflammatory syndrome (fever rash, IC reactive protein):
- HyperIgD syndrome (mevalonate kinase deficiency)

Acute Pancreatitis
- Hyperlipoproteinemia type I and IV
- **Lysinuric protein intolerance**
- **Organic acidurias** (MMA, PA, IVA, MSUD)
- Respiratory chain disorders (Pearson, MELAS)

Chronic Diarrhea, Failure to Thrive, Osteoporosis
(► Table 1.12)

Hypocholesterolemia
- Abetalipoproteinemia type I and II
- Congenital disorders of glycosylation type I
- Infantile Refsum disease
- Mevalonic aciduria
- Peroxisomal disorders
- Smith-Lemli-Opitz syndrome
- **Tangier disease** (alpha-lipoprotein deficiency)

HELLP Syndrome (Baby Born to Mothers with)
- **Carnitine palmitoyl transferase I deficiency**
- **LCHAD deficiency** and other fatty acid β-oxidation disorders
- Respiratory chain defects

Intestinal Obstruction
- MNGIE syndrome (mitochondrial cytopathy)

1.5.6 Hematology

Acanthocytosis
- Abetalipoproteinemia
- Hallervorden-Spatz syndrome (panthothenate kinase)
- Inborn errors of cobalamin **(Cbl C)**
- Wolman disease

Anemias (Macrocytic)

- **Hereditary orotic aciduria**
- Inborn errors of cobalamin metabolism:
  - **Imerslund-Gräsbeck syndrome**
  - **Intrinsic factor deficiency**
  - **TC II deficiency**
  - **Cbl C, Cbl E, Cbl G**
  - **Methionine synthase deficiency**
- Inborn errors of folate metabolism:
  - Dihydrofolate reductase deficiency,
  - Glutamate formimino transferase deficiency
  - **Congenital folate malabsorption**
- Mevalonic aciduria
- Pearson syndrome (due to mitochondrial DNA deletion) (dyserythropoiesis)
- Respiratory chain disorders
- **Thiamine responsive megaloblastic anemia**

Anemias (Non-macrocytic, Hemolytic or Due to Combined Mechanisms)

- Abetalipoproteinemia
- **Carnitine transport defect**
- **Congenital erythropoietic porphyria**
- **Erythropoietic porphyria**
- **Erythropoietic protoporphyria**
- **Galactosemia**
- Hemochromatosis
- Lecithin cholesterol acyltransferase deficiency
- Mevalonic aciduria
- Pyroglutamic aciduria
- Red blood cells glycolysis defects
- Severe liver failure
- Transaldolase deficiency
- **Wilson disease**
- Wolman disease

Bleeding Tendency, Hemorragic Syndromes

- Gaucher disease
- **Glycogenosis type Ia and Ib**
- Inborn errors with severe liver failure
- Primitive disorders of homeostasis
- Severe thrombocytopenia

Pancytopenia – Thrombocytopenia – Leucopenia

- Aspartylglucosaminuria
- CDG IIf (CMP sialic acid transporter)
- **Gaucher type I** and III
- **Glycogenosis type Ib** (neutropenia)
- **Inborn errors of cobalamin metabolism**
- **Inborn errors of folate metabolism**
- Johansson-Blizzard syndrome
- **Lysinuric protein intolerance**
- **Organic acidurias** (methylmalonic, propionic, isovaleric)
- Other conditions with large splenomegaly
- Pearson syndrome
- Respiratory chain disorders
- Schwachman syndrome
- Transaldolase deficiency

Vacuolated Lymphocytes

- Aspartylglucosaminuria
- Austin disease
- Ceroid lipofuscinosis
- I-cell disease (mucolipidosis type II)
- Landing disease (GM1)
- Mucopolysaccharidosis
- Niemann-Pick type Ia
- Pompe disease
- Sialidosis
- Wolman disease

Hyperleucocytosis (>100.000/mm^3)

- Leucocyte adhesion deficiency syndrome (CDG IIc: GDP fucose transporter 1)

Hemophagocytosis

- Gaucher disease
- **Lysinuric protein intolerance**
- Niemann-Pick

1.5.7 Hepatology

Cholestatic Jaundice

- α-1-antitrypsin deficiency
- **Arginase deficiency**
- Byler disease
- Congenital disorders of glycosylation
- **Cerebrotendinous xanthomatosis**
- Cholesterol synthesis defects (Smith-Lemli-Opitz)
- Citrin deficiency
- COG 7 deficiency
- Cystic fibrosis
- **Galactosemia**
- **Inborn errors of bile acid metabolism**
- **Long-chain 3-hydroxyacyl-CoA dehydrogenase**
- α-methylacyl-CoA racemase
- Mevalonic aciduria
- Niemann-Pick type C
- Peroxisomal disorders
- Transaldolase deficiency
- **Tyrosinemia type I**

Cirrhosis

- Alpers progressive infantile polydystrophy
- Alpha-1-antitrypsin deficiency
- **Arginase deficiency**
- Congenital disorders of glycosylation
- Cholesterol ester storage disease

- Cystic fibrosis
- **CDG Ib**
- **Galactosemia**
- **Gaucher disease**
- Glycogenosis type IV
- Hemochromatosis
- **Hereditary fructose intolerance**
- **Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency**
- Niemann-Pick disease
- Peroxisomal disorders
- S-adenosylhomocysteine hydrolase deficiency
- Sitosterolemia
- Transaldolase deficiency
- **Tyrosinemia type I**
- **Wilson disease**
- Wolman disease

Liver Failure (Ascites, Edema) (► also Reye Syndrome, Sect. 1.3.1)

Age at onset: congenital (hydrops fetalis)
- Barth hemoglobin
- CDG
- **Erythropoietic porphyria**
- Galactosialidosis
- GM1 gangliosidosis (Landing)
- Mevalonic aciduria
- Mucopolysaccharidosis type VII
- Niemann-Pick A and C
- Sialidosis type II
- Transaldolase deficiency

Age at onset: neonatal to early infancy
- **Fatty acid oxidation disorders**
- **Fructose-1,6-bisphosphatase deficiency**
- **Hereditary fructose intolerance**
- **Galactosemia**
- Mevalonic aciduria
- Mitochondrial DNA depletion (DOGK)
- **Neonatal hemochromatosis** (prevented by immunoglobulin to the pregnant mother)
- Respiratory chain disorders
- **Tyrosinemia type I** (after 3 weeks)

Age at onset: infancy
- Same defects as in neonatal period
- ACAD 9
- Alpha-1-antitrypsin deficiency
- Congenital disorders of glycosylation
- Cholesterol ester storage disease
- Cystic fibrosis
- Familial hepatic fibrosis with exudative enteropathy (**CDG Ib**)
- **Ketogenesis defects**
- Pyruvate carboxylase deficiency
- S-adenosylhomocysteine hydrolase deficiency
- **Urea cycle defects**
- Wolman disease

Age at onset: childhood to adolescence
- **Wilson disease**

1.5.8 Immune System

Inflammatory Syndrome
- Hyper-IgD syndrome
- Mevalonate kinase deficiency

Macrophage Activating Syndrome
- **Gaucher disease**
- **Lysinuric protein intolerance**
- Niemann-Pick disease
- **Propionic acidemia**

Severe Combined Immune Deficiency
- Adenosine deaminase deficiency
- Purine nucleoside phosphorylase deficiency
- **Hereditary orotic aciduria**

1.5.9 Myology

Exercise Intolerance, Myoglobinuria, Cramps, Muscle Pain, Elevated CK

Glycolytic defects (muscle glycogenosis):
- Phosphorylase deficiency (McArdle)
- Phosphofructokinase deficiency
- Phosphoglycerate kinase deficiency
- Phosphoglycerate mutase deficiency
- Lactate dehydrogenase deficiency
- **Glucose-6-phosphate dehydrogenase deficiency**
- Phosphorylase b kinase deficiency

Fatty acid oxidation defects:
- **Carnitine palmitoyl transferase II**
- **VLCAD, LCHAD, translocase, trifunctional**
- SCHAD (restricted to muscles), MCKAT
- Others undescribed (CPT I, SCAD ?)

Miscellaneous:
- **Channelopathies** (hyperkalemic paralysis)
- Duchenne and Becker muscular dystrophies
- Idiopathic familial recurrent myoglobinuria
- Lipoamide dehydrogenase deficiency
- Acid maltase (adult)
- Myoadenylate deaminase deficiency
- Respiratory chain disorders

Myopathy (Progressive)

- Adenylate deaminase deficiency
- **Fatty acid oxidation disorders**
- Glycogenosis type II (acid maltase deficiency)
- Glycogenosis type III
- Multisystemic triglyceride storage disease
- Respiratory chain disorders (Kearns-Sayre and others)
- Steinert disease

1.5.10 Nephrology

Hemolytic Uremic Syndrome

- **Inborn errors of cobalamin metabolism** (Cbl C, Cbl G)

Nephrolithiasis/Nephrocalcinosis

- APRT deficiency (2-8 dihydroxyadenine)
- **Cystinuria** (cystine)
- Hereditary hyperparathyroidism (calcium)
- Hereditary renal hypouricemia (uric acid)
- **Hyperoxaluria type I and II** (oxalic)
- Lesch-Nyhan (uric acid)
- Molybdenum cofactor deficiency (xanthine)
- PRPP synthase superactivity (uric acid)
- **Renal tubular acidosis type I**
- **Xanthine oxidase deficiency** (xanthine)
- Familial juvenile hyperuricemic nephropathy (uromodulin mutation)

Nephrotic Syndrome

- Respiratory chain disorders

Nephropathy (Tubulointerstitial)

- **Glycogenosis type I**
- **Methylmalonic aciduria**
- Respiratory chain disorders (pseudo Senior-Loken syndrome)

Polycystic Kidneys

- Congenital disorders of glycosylation
- CPT II deficiency
- Glutaric aciduria type II
- Zellweger syndrome

Tubulopathy

Fanconi syndrome:

- **Galactosemia – hereditary fructose intolerance**
- Respiratory chain disorders (complex IV or mito DNA deletion)
- **Tyrosinemia type I**
- Bickel-Fanconi syndrome: GLUT2 mutations
- Lowe syndrome (OCRL1 X-linked mutations)
- **Cystinosis**

Renal tubular acidosis:

- **Renal tubular acidosis type I** (distal)
- **Renal tubular acidosis type II** (proximal)
- Pyruvate carboxylase deficiency
- **Methylmalonic aciduria**
- **Glycogenosis type I**
- **Carnitine palmitoyl transferase I deficiency**
- Dent disease (CLCN5 mutations)

Urine – Abnormal Color

- Alkaptonuria (black)
- Indicanuria (blue)
- Myoglobinuria (red)
- Porphyria (red)

Urine – Abnormal Odor

- Dimethylglycine dehydrogenase (fish)
- 3-methyl-crotonylglycinuria (cat)
- Glutaric aciduria type II (sweaty feet)
- **Isovaleric acidemia** (sweaty feet)
- **MSUD** (maple syrup)
- **Phenylketonuria** (musty odor)
- Trimethylaminuria (fish)
- **Tyrosinemia type I** (boiled cabbage)

1.5.11 Neurology (► Sect. 1.4.2)

1.5.12 Ophthalmology (► also Cherry-red Spot, Ophthalmoplegia, and Retinitis Pigmentosa, Sect. 1.4.4)

Cataracts

Detectable at birth (congenital):

- Cockayne syndrome
- Lowe syndrome (OCRL1 X-linked mutation)
- Peroxisomal biogenesis defects (Zellweger and variants)
- Phosphoglycerate dehydrogenase deficiency
- Rhizomelic chondrodysplasia punctata
- Sorbitol dehydrogenase deficiency

Detectable in the newborn period (1st week to 1st month):

- **Galactosemias**
- Marginal maternal galactokinase deficiency
- Peripheral epimerase deficiency (homozygotes and heterozygotes)

Detectable in infancy (1st month to 1st year):

- Alpha-mannosidosis
- Galactitol or sorbitol accumulation of unknown origin
- Galactokinase deficiency
- Hypoglycemia (various origins)
- P5C synthase deficiency
- Respiratory chain disorders
- Sialidosis

Detectable in childhood (1 to 15 years):
- **Diabetes mellitus**
- Dominant cataract with high serum ferritin
- **Hypoparathyroidism**
- **Lysinuric protein intolerance**
- Mevalonic aciduria
- Neutral lipid storage disorders (unknown cause)
- Pseudo-hypoparathyroidism
- Sjögren-Larsson syndrome
- **Wilson disease**

Detectable in adulthood (> 15 years):
- Carriers for Lowe syndrome
- **Cerebrotendinous xanthomatosis**
- **Fabry disease**
- Glucose-6-phosphate dehydrogenase deficiency
- **Heterozygotes for GALT and galactokinase**
- **Homocystinurias**
- **Lactose malabsorbers**
- Mevalonate kinase
- Mitochondrial cytopathies
- **Ornithine aminotransferase deficiency**
- PEX 7
- Refsum disease
- Steinert dystrophy (cataract can be presenting sign)
- **Tangier disease**

Corneal Opacities (Clouding)

Visible in early infancy (3 to 12 months):
- **Tyrosinemia type II** (presenting sign)
- **Cystinosis** (presenting sign)
- Hurler, Sheie (MPS I)
- I-cell disease (mucolipidosis type II)
- Maroteaux-Lamy (MPS VI)
- Steroid sulfatase deficiency

Visible in late infancy to early childhood (1 to 6 years):
- Mucolipidosis type IV (presenting sign)
- Alpha-mannosidosis (late-onset form)
- Lecithin cholesterol acyltransferase deficiency
- Morquio (MPS IV)
- Pyroglutamic aciduria (presenting sign)
- **Tangier disease**

Visible in late childhood, adolescence to adulthood:
- **Fabry disease** (X-linked)
- Galactosialidosis (juvenile form)
- **Wilson disease** (green Kaiser Fleischer ring)

Ectopia Lentis (Dislocation of the Lens)

- **Classical homocystinuria** (downwards dislocation)
- Sulfite oxidase deficiency
- Marfan syndrome (upwards dislocation)
- Marchesani syndrome

Keratitis, Corneal Opacities

- **Tyrosinemia type II**
- **Fabry disease** (X-linked)

Microcornea

- Ehlers-Danlos type IV

1.5.13 Osteology

Osteopenia

- **Cerebrotendinous xanthomatosis**
- CDG
- **Glycogenosis type I**
- **Homocystinuria**
- I-cell disease (mucolipidosis type II)
- Infantile Refsum disease
- **Lysinuric protein intolerance**
- **All organic acidurias** (chronic forms)

Punctate Epiphyseal Calcifications

- Beta-glucuronidase deficiency
- Chondrodysplasia punctata rhizomelic type
- Conradi-Hünermann syndrome
- Familial resistance to thyroid hormone
- Peroxisomal disorders (Zellweger and variants)
- Spondyloenchondromatosis
- Warfarin embryopathy

Exostosis (Hereditary Multiple)

- O-glycosylation defects (EXT1-EXT2)

1.5.14 Pneumology

Hyperventilation Attacks

- Gazeous alkalosis
- **Hyperammonemias**
- Joubert syndrome
- Leigh syndrome (idiopathic or due to various inborn errors)
- Metabolic acidosis
- Rett syndrome (only girls)

Pneumopathy (Interstitial)

- **Gaucher disease**
- **Lysinuric protein intolerance**
- Niemann-Pick type B

Stridor

- **Biotinidase deficiency**
- Hypocalcemia
- Hypomagnesemia
- **MADD** (riboflavin responsive)
- Pelizaeus-Merzbacher

Pulmonary Hypertension

- **Glycogenosis type I**
- Non ketotic hyperglycinemia

1.5.15 Psychiatry (► Sect. 1.3.1 and 1.4.3)

1.5.16 Rheumatology

Arthritis – Joint Contractures – Bone Necrosis

- Alkaptonuria
- Familial Gout
- Farber disease
- **Gaucher type I**
- **Homocystinuria**
- I-cell disease, Mucolipidosis type III
- Lesch-Nyhan syndrome
- Mevalonic aciduria (recurrent crisis of arthralgia)
- Mucopolysaccharidosis type IS
- PRPP synthetase superactivity, HGPRT deficiency
- Uromoduline mutation (familial hyperuricemic nephropathy)

Bone Crisis

With bone changes (rickets):

- **Calciferol metabolism deficiency**
- **Hereditary hypophosphatemic rickets**

With hemolytic crises and abdominal pain:

- **Porphyrias**
- **Sickle cell anemia**
- **Tyrosinemia type I**

With progressive neurological signs:

- **Gaucher type III**
- Krabbe disease
- Metachromatic leucodystrophy

Apparently isolated (presenting symptom):

- **Fabry disease**
- Gaucher type I

1.5.17 Stomatology

Glossitis, Stomatitis

- **Clb F**
- **Folate malabsorption**
- **Intrinsic factor deficiency**
- **Transcobalamin II**

Macroglossia

- Beckwith-Wiedemann syndrome
- Congenital muscular dystrophies (DMC1C)
- Complex IV deficiency
- Pompe disease

Hypodontia

- Leucoencephalopathy with ataxia [33]

1.5.18 Vascular Symptoms

Raynaud Syndrome

- **Fabry disease**

Thromboembolic Accidents – Stroke-like Episodes (► also Sect. 1.3.1)

- CDG
- Ehlers-Danlos type IV
- **Fabry disease**
- **Homocystinuria** (all types)
- Menkes disease
- **Organic acidurias** (methylmalonic, propionic)
- Respiratory chain disorders (MELAS and others ...)
- **Urea cycle disorders** (OTC deficiency)

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