Inborn Errors of Metabolism - Early Detection, Key Symptoms and Therapeutic Options

2nd edition

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in collaboration with
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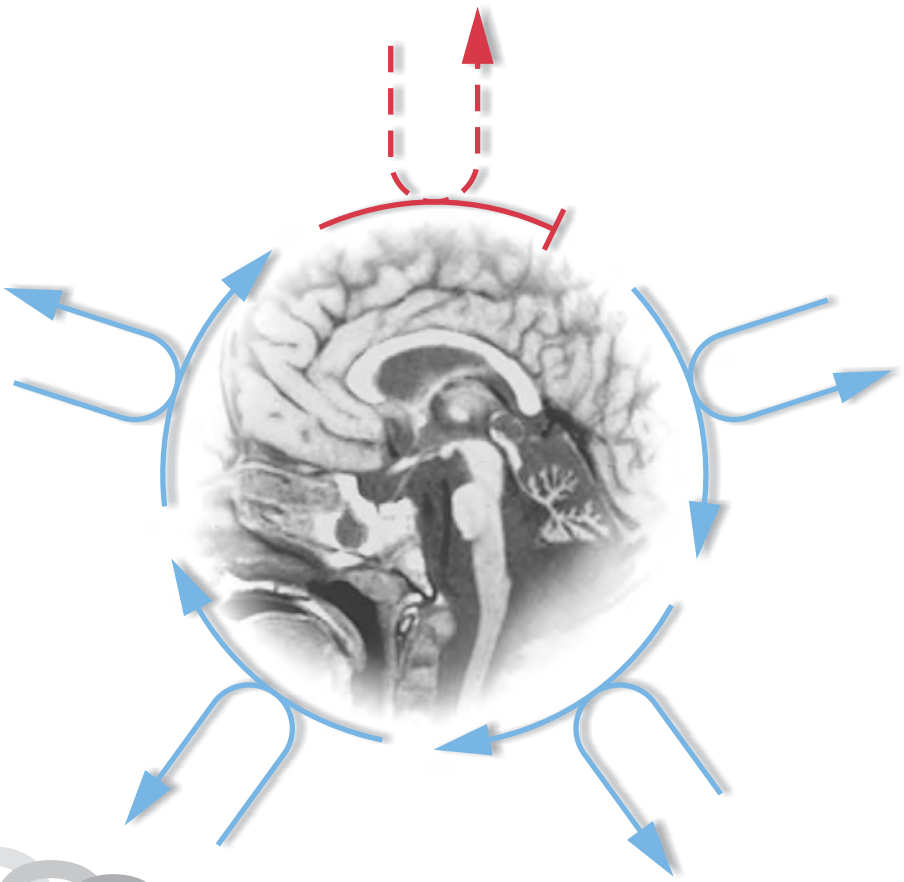

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UNI-MED Verlag AG, one of the leading medical publishing companies in Germany, presents its highly successful series of scientific textbooks, covering all medical subjects. The authors are specialists in their fields and present the topics precisely, comprehensively, and with the facility of quick reference in mind. The books will be most useful for all doctors who wish to keep up to date with the latest developments in medicine.

Preface and acknowledgements

This book, in its second revised and updated edition, is intended to provide an overview of the broad spectrum of inborn errors of metabolism. It is aimed at colleagues working in hospitals as well as in practice, and in particular physicians treating children and adolescents. Since the number of adult patients with inborn errors of metabolism is steadily increasing, this book is also of interest to general practitioners, internal specialists and neurologists.

The clinical symptoms of inborn errors of metabolism are frequently unspecific, but are very complex in the sense of a multi-organ involvement. In the case of acute, life-threatening symptoms, rapid diagnosis can be life-saving. Development and prognosis of affected children often depends on early diagnosis and adequate therapy. However, the number of special diagnostic parameters, differential diagnoses and treatment options is manifold and difficult for physicians not specialised in this field.

In addition to newborn screening tests, this book covers important biochemical and clinical symptoms of differential diagnoses. The most frequent metabolic diseases are presented in a brief and clear form. Special attention was paid to short tables, differential diagnosis flowcharts, special metabolic diagnostics, therapy and emergency procedures. Chapter 7 provides references to further literature as well as internet links.

I would like to thank my co-workers, who have done invaluable work in the course of the revision and updating of this book and have a substantial share in the success of this book. Special thanks go to the publishers who have once again ensured the professional implementation and graphic design for this edition.

Notes and suggestions for improvement or supplementation are, as always, welcome.

Duesseldorf, March 2017 *Prof. Dr. Ertan Mayatepek*

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Contents

1. Newborn screening

Newborn screening started with the so-called "Guthrie test" in the 1960s. This screening test allowed the presymptomatic detection of phenylketonuria for the first time. Newborn screening is a population screening, which allows early detection of a defined inborn error of metabolism or endocrine disease in all children of one population. With the help of newborn screening, treatment can be introduced as soon as a positive screening result is available. Expansion of newborn screening has become possible due the development of tandem mass spectrometry (MS/MS) as a diagnostic tool. According to the current German paediatric guidelines ("Kinder-Richtlinien des Bundes"), expanded newborn screening was introduced nationally in 2005 and reliably tests for 14 treatable diseases. The expanded newborn screening comprises a selection of metabolic and endocrine diseases, which are listed in Table 1.1. Cystic fibrosis was recently included in 2016.

MS/MS allows simultaneous quantification of a number of metabolic markers (acylcarnitines) according to their specific mass. This analysis can be performed in dried blood spots, and only a few droplets of blood are necessary. The time of collection of blood is very important (☞ Figure 1.1). The ideal collection time is between 48 and 72 hours after birth. The blood should not be collected before 36 hours of life and not after 72 hours of life. This is important because certain diseases, especially several fatty acid oxidation defects, can only be detected during catabolism. Blood should be collected before blood transfusion or corticosteroid or dopamine therapy. If blood is collected be-

Diseases	Method of analysis	Biochemical marker	Incidence
Endocrine disorders			
Congenital adrenal hyperplasia	Immunoassay	17-OH progesterone	1:15,000
Congenital hypothyroidism	Immunoassay	TSH	1:4,000
Fatty acid oxidation defects			
MCAD deficiency	MS/MS	**C8**, C6, C10:1, C8/C10 ratio	1:10,000
VLCAD deficiency	MS/MS	**C14:1**, C14:2, C14	1:80,000
LCHAD/TFP deficiency	MS/MS	**C16 OH**, C18:1OH	1:170,000
CACT deficiency	MS/MS	C16, C18, low C0	<1:200,000
CPT 1 deficiency	MS/MS	**high C0**, C0/(C16+C18) ratio	<1:200,000
CPT 2 deficiency	MS/MS	C16, C18, low C0	<1:200,000
Amino acid disorders			
Phenylketonuria/ hyperphenylalaninaemia	MS/MS	Phenylalanine, Phe/Tyr ratio	1:6,000
MSUD	MS/MS	Leucine/isoleucine, valine	1:150,000
Organic acid disorders			
Glutaric aciduria type I	MS/MS	**C5 DC (glutaryl carnitine)**, C5DC/C8 ratio	1:130,000
Isovaleric aciduria	MS/MS	**C5 (isovaleryl carnitine)**, C5/C8 ratio	1:100,000
Other metabolic disorders			
Biotinidase deficiency	Colorimetrical	Enzyme activity	1:30,000
Galactosaemia	Photo- and fluorometrical	Enzyme activity, galactose	1:70,000

Table 1.1: Metabolic and endocrine diseases included in the German newborn screening programme.

Diseases	Alarm	Phenotype	Action
Endocrine disorders			
Congenital adrenal hyperplasia	High	Virilisation, symptoms of salt wasting	Immediate transfer to Paediatric centre with endocrinology department
Congenital hypothyroidism	Moderate	Generally asymptomatic at 3rd to 5th day of life	Further diagnostic procedures and treatment by Paediatric endocrinologist within 1-2 days
Fatty acid oxidation defects			
MCAD deficiency	Moderate	Generally asymptomatic	Contact metabolic centre, out-patient work-up within 1-2 days
VLCAD deficiency	High	Generally asymptomatic, poss. metabolic encephalopathy	Immediate transfer to metabolic centre
LCHAD/TFP deficiency	High	Metabolic encephalopathy	Immediate transfer to metabolic centre
CACT deficiency	High	Reye-like syndrome, cardiomyopathy, liver function disorder, shock or asymptomatic	Immediate transfer to metabolic centre
CPT 1 deficiency	High		Immediate transfer to metabolic centre
CPT 2 deficiency	High		Immediate transfer to metabolic centre
Amino acid disorders			
Phenylketonuria	Moderate	Asymptomatic	Contact metabolic centre, admission within 1-2 days
MSUD	High	Metabolic encephalopathy at 4 days of life	Immediate transfer to metabolic centre
Organic acid disorders			
Glutaric aciduria type I	Moderate	Generally asymptomatic	Transfer to metabolic centre within 1-2 days
Isovaleric aciduria	High	Generally asymptomatic, poss. metabolic encephalopathy	Immediate transfer to metabolic centre
Other metabolic disorders			
Biotinidase deficiency	Moderate	Generally asymptomatic	Contact metabolic centre, out-patient work-up within 1-2 days
Galactosaemia	High	Hepatopathy, impaired coagulation	Immediate transfer to the hospital

Table 1.2: Procedure in case of a positive screening result.

fore 36 hours of life, screening has to be repeated at a later time. In premature babies (born before 32 gestational weeks), blood should also be collected between 36 and 72 hours of life. However, additional screening has to be performed at a corrected age of 32 weeks of gestation. The dried blood spot card has to be transferred to a screening laboratory as soon as possible. Pathological results are reported to the sender immediately (often by phone). Table 1.2 demonstrates which time frame is advisable to initiate further diagnostic procedures and treatment if the screening result is positive. In all cases of metabolic diseases, the next metabolic centre must be contacted. Highly urgent cases need immediate diagnostic work-up and start of treatment. In moderately urgent cases, further diagnostic procedures and treatment need to be initiated within one to two days.

As soon as the positive screening result is communictaed, a second dried blood spot has to be collected and sent to the screening laboratory. However, the acylcarnitine analysis and other screening tests only allow a tentative diagnosis of disease. In every patient with a pathological screening result further diagnostic workup is necessary in order to confirm or exclude the diagnosis.

With the exception of galactosaemia, none of these metabolic disorders requires complete cessation of breastfeeding. It is even preferable to include breast milk as a high quality protein source in the diet (as a reduced form of breastfeeding).

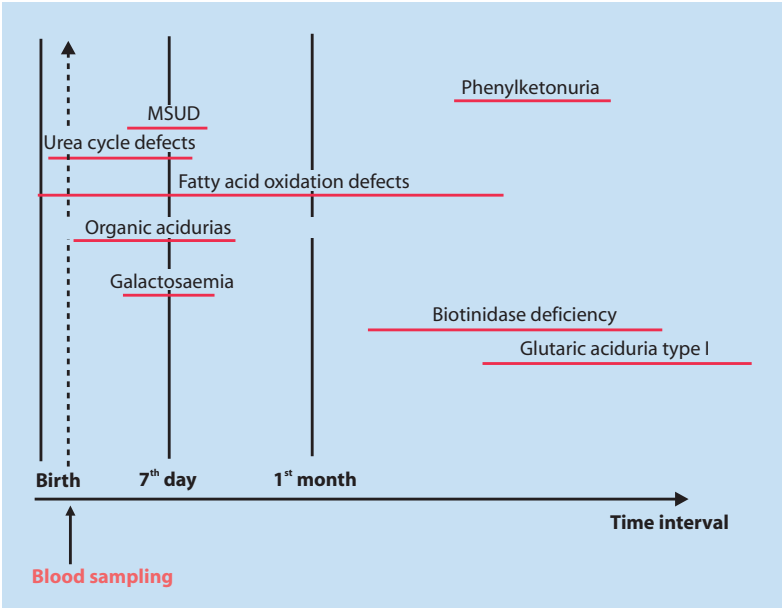


Figure 1.1: Age at symptomatic presentation in different inborn errors of metabolism.

2. Diagnostic procedures

2.1. Biochemical investigations

Simple tests in urine

Simple metabolic tests in a spot urine sample may already provide clues for the diagnosis of metabolic diseases. Some examples include:

- **Reducing substances in urine,** particularly for detection of sugars, e.g. galactose in classical galactosaemia, fructose in hereditary fructose intolerance or glucose in Fanconi syndrome
- **Nitroprusside test (Brand reaction)** for detection of sulphur-containing acids (disulphides), e.g. cystine in cystinuria or homocystine in homocystinuria
- **Sulphite test** for detection of sulphite oxidase and molybdenum cofactor deficiencies in fresh urine

Special metabolic investigations

☞ Table 2.1

Substance	Indication	Sample	Handling of sample
Amino acids (plasma)	Selective screening, e.g. aminoacidaemia, hyperammonaemia, suspected disorders of energy metabolism	Plasma (fasting, EDTA, 0.5-1 ml)	Centrifuge and freeze supernatant, ship on dry ice
Amino acids (urine)	Renal disorders, suspected Fanconi syndrome	Urine (5-10 ml)	Preserve with 2 drops of chloroform or freeze
Amino acids (CSF)	Suspected neurometabolic diseases, especially epileptic encephalopathies	CSF and EDTA plasma (0.5-1 ml each)	Freeze CSF at –70°C, ship on dry ice together with a plasma sample
Acylcarnitines	Neonatal screening and selective screening, suspected fatty acid oxidation defect or organic aciduria	Dried spot on filter paper ("Guthrie card")	Ship at room temperature
Carnitine status	Suspected disorder of intermediary metabolism, primary and secondary carnitine deficiency, control of therapy	Serum/EDTA plasma (1 ml) and in some cases urine (5 ml)	Centrifuge immediately and ship
Organic acids	Selective screening, organic aciduria or other disorders of intermediary metabolism, unexplained metabolic crisis (e.g. hypoglycaemia, metabolic acidosis, coma), suspected neurometabolic disease	Urine (5-10 ml)	Preserve with 2 drops of chloroform, ship at room temperature
Orotic acid	Suspected urea cycle defects (e.g. OTC deficiency), suspected orotic aciduria	Urine (5-10 ml)	Preserve with 2 drops of chloroform, ship at room temperature
Homocysteine	Suspected (mild) hyperhomocysteinaemia, thromboembolic events, vascular diseases, progredient neuropathy, unclear retardation, microcephaly, megaloblastic anaemia	Plasma (fasting; EDTA, 1 ml)	Centrifuge immediately, ship of supernatant on dry ice
Lactate	Suspected disorders of energy metabolism	Blood (perchloric acid extraction where required), CSF	Ship supernatant on dry ice
Free fatty acids, β-hydroxy-butyrate	Assessment of free fatty acid metabolism in hypoglycaemia or during fasting test	Plasma/serum (fasting; 1 ml)	Centrifuge immediately, ship supernatantt on dry ice

Guanidinoacetate, creatine, creatinine	Suspected disorder of creatine metabolism	EDTA plasma (1 ml), urine (5-10 ml) or 24 h-urine collection (10 ml), CSF (1 ml)	Preserve urine with 2 drops of chloroform, ship plasma and CSF on dry ice
Isolelectric focussing of transferrin (IEF)	Suspected disorder of protein glycosylation (CDG)	0.5 ml serum (or dried blood spot), no plasma	Centrifuge Serum immediately and ship on dry ice
Galactose and galactose metabolites	Suspected disorder of galactose metabolism (neonatal screening!)	Dried blood spot, EDTA full blood (2 ml), plasma, urine	Details should be clarified with the laboratory
Investigations for lysosomal disorders	Suspected lysosomal storage disease, mucopolysaccharidosis, oligosaccharidosis. Quantification of glycosaminoglycans, oligosaccharides, free neuraminic acid	Urine (10 ml)	Preserve with 2 drops of chloroform
Investigations for peroxisomal disorders	Suspected peroxisomal disorder	Investigation of very long-chain fatty acids (VLCFA), phytanic acid, pristanic acid: plasma (1 ml); Plasmalogens: EDTA full blood (2 ml)	Plasma: Centrifuge immediately and ship supernatant on dry ice
Purines and pyrimidines	Suspected disorder of purine- or pyrimidine metabolism, e.g. renal and/or neurological symptoms (retardation, seizures, autism)	Urine (5 ml, morning sample) or 24 h-urine collection (keep cool and dark)	Preserve with 2 drops of chloroform or ship on dry ice. Record medication!
Bile acid metabolites	Suspected bile acid synthesis defects	Urine (5 ml)	Preserve with 2 drops of chloroform
Pterines	Hyperphenylalaninaemia, BH_4 test, suspected neurotransmitter defect	Urine (5 ml, protected against light and heat), serum (1 ml), CSF (1 ml); DHPR activity: dried blood card, CSF with special stabilisation	Centrifuge blood immediately, freeze immediately, ship supernatant on dry ice
Biogenic amines and metabolites	Progredient mental retardation, dystonia or dystonia-parkinsonism, severe treatment-resistant epilepsy of unknown origin	CSF (4 x 0.5-1 ml); special preparation (rostro-caudal gradient!)	Before lumbar puncture always contact laboratory for instructions. Freeze immediately, store at –70°C. Ship on dry ice
Sterol analysis	Suspected disorder of cholesterol biosynthesis, e.g. Smith-Lemli-Opitz (SLO) syndrome	EDTA-plasma (1 ml)	Centrifuge and ship supernatant immediately

Table 2.1: Specific metabolic investigations.

2.2. Biopsies, enzymology, histopathology

Biopsies are usually obtained for enzyme studies (especially fibroblasts, liver and muscle) and for histology (e.g. liver, muscle, conjunctiva) and sometimes for electron microscopy. Before samples are obtained, modalities should always be discussed with the metabolic laboratory or pathological institute. Some enzyme studies are available in lymphocytes, making biopsies dispensable.

2.3. Mutation analyses

Mutation analyses should be performed to obtain a primary diagnosis or confirmation of diagnosis in disorders which cannot be confirmed by biochemical or enzymatic methods alone. Ideally 2-5 ml EDTA blood (do not centrifuge!) should be shipped within 24 hours at room temperature. If no blood sample is available, a dried blood spot, fibroblasts or biopsies or similar may be used.

2.4. Function tests

A metabolic profile with repeated measurements of relevant metabolites (e.g. glucose, lactate) throughout one day and different function tests (a selection is given in Table 2.2) provides diagnostic pointers to disturbed metabolic pathways and information about exogenous factors.

2.5. Neuroradiological investigations

Within the last years radiological investigations of the brain with neuroimaging and functional imaging techniques (e.g. MRT, PET, SPECT, *in vivo* MR spectroscopy) have substantially increased the understanding of neurometabolic and neurodegenerative diseases (☞ Table 2.3).

Moreover, investigations with *in vivo* MR spectroscopy (MRS) and semi-quantitative analysis of different metabolites (e.g. creatine, lactate) can al-

Test	Indication	Remarks
Glucose challenge	Suspected disorder of mitochondrial energy metabolism, glycogen synthase deficiencies	Oral application of 2 g/kg glucose (max. 50 g), lactate, glucose, acid-base status every 30 min, duration 3 h, urine sampling over 2 h
Fasting test	Unclear, recurrent hypoglycaemia, assessment of fasting tolerance	Duration depending on age, e.g. <6 months: max. 8 h; 1-2 years: max. 18 h; always use i.v. line! Obtain samples in hypoglycaemia or if clinical symptoms occur (e.g. free fatty acids, β-hydroxybutyrate, amino acids, acylcarnitines, organic acids) and stop fasting!
Glucagon stimulation test	Suspected glycogen storage disease, congenital hyperinsulinism, disorders of gluconeogenesis	Requirements: blood glucose <3.5 mmol/l (<60 mg/dl); glucagon (500 µg) i.m., after this regular measurements of glucose (normal increase >1.4 mmol/l (25 mg/dl) during 45 min
Forearm ischaemia test	Patients with muscle cramps on exertion (e.g. suspected disorder of glycogenolysis)	Painful, high cooperation necessary, not possible in young children. Determination of lactate, ammonia, NH_3 and CK after ischaemia (blood pressure cuff) of the arm muscles
Tetrahydrobiopterin-(BH_4) test	Hyperphenylalaninaemia (confirmed BH_4 cofactor deficiency or BH_4-responsive form of phenylketonuria)	Oral load with 20 mg/kg BH_4, blood sampling for Phe/Tyr after 0, 4, 8, 12, 16 and 24 h, urine collection for pterines over 8 h (protect from light)
Phenylalanine challenge	Suspected disorder of biogenic amine or pterine metabolism, unclear dystonic movement disorder	Oral load with 100 mg/kg L-phenylalanine; blood sampling after 1, 2,4 and 6 h for Phe/Tyr and pterines

Table 2.2: Function tests.

ready provide important diagnostic clues for a suspected inborn error of metabolism.

- (Progressive) cerebellar atrophy or hypoplasia
- Disturbances of white matter (e.g. leukodystrophy, spongiform encephalopathy)
- Involvement of basal ganglia (e.g. necrosis, atrophy)
- Vascular insult (unilateral atrophy)
- Subdural haematoma
- Frontotemporal atrophy
- Dysgenesis or agenesis of corpus callosum
- Abnormalities of gyral morphology and neuronal migration
- Generalised cerebral atrophy

Table 2.3: MRI abnormalities of the brain which can be associated with inborn errors of metabolism.

2.6. *Post-mortem* investigations

In the case of sudden unexpected death in childhood, *post-mortem* samples (☞ Table 2.4) should be collected for metabolic screening. Diagnosis of inborn errors of metabolism in these cases is important as it may guide genetic testing and counselling of family members.

Indicated investigations depend, among others, on the details of patient history, clinical symptoms and available laboratory results. Basic diagnostics include amino acids, acyl carnitines and organic acids.

It is important to consider that because of autolytic processes interpretation of obtained results in *post-mortem* samples might be difficult or even impossible.

Material	Remarks
Plasma and serum	~5 ml, in separate fractions, freeze at –80°C
Blood spot on filter paper (Guthrie-card)	Storage at room temperature
Full blood	5-10 ml, anticoagulation with EDTA, freeze without centrifuging (for DNA isolation)
Urine	Freeze in separate fractions at –80°C
CSF	0.5-1 ml; freeze in separate fractions at –80°C
Fibroblasts	Skin biopsy, may be taken up to 24 h post mortem; storage in culture medium or 0.9% NaCl at room temperature for 1-2 days; do not cool or freeze!
Liver	Several biopsies, freeze immediately (at –70°C or in liquid nitrogen); for electron microscopy asservation in glutaraldehyde
Muscle (skeletal or consider heart)	If possible during the first hour post-mortem; requirements see liver

Table 2.4: Asservation of samples for post-mortem investigations.

3. Biochemical key symptoms

3.1. Hyperammonaemia

Hyperammonaemia is a key symptom of a number of inborn errors of metabolism. Each child suspected of an acute metabolic disease should receive early testing of blood ammonia levels. Age-specific reference values for ammonia have to be considered (☞ Table 3.1).

Newborns (umbilical cord artery)	50-160 µmol/l (85-270 µg/dl)
1st day of life	30-145 µmol/l (50-245 µg/dl)
5th-6th day of life	30-135 µmol/l (50-230 µg/dl)
<1 month	27-63 µmol/l (45-109 µg/dl)
Infants and children	25-50 µmol/l (40-85 µg/dl)
Adults	10-55 µmol/l (20-90 µg/dl)

Table 3.1: Age-related reference values for ammonia in plasma.

Uncuffed venous or arterial blood sampling is important. Capillary plasma is not suitable. The sample has to be collected in a precooled tube for immediate anticoagulation, transported on ice and be analysed immediately. Since the ammonia concentration in tissue, erythrocytes, thrombocytes, etc. is considerably higher than in blood, lysis can lead to falsely increased levels. If in doubt, blood sampling has to be repeated.

Acute metabolic crises with hyperammonaemia can lead to cerebral oedema due to swelling of astrocytes. Irreversible impairment of neurons will result in severe neurological deficits. Acute hyperammonaemia and encephalopathic crises have a high mortality rate, especially in newborns and infants.

In all neonates with ammonia levels >200 µmol/l there is an urgent suspicion of an underlying inborn error of metabolism. Clinical symptoms are generally non-specific, including lethargy, poor sucking, vomiting, muscular hypotonia, irritability, apnoea or seizures up to coma.

Urea cycle defects are the most common cause of severe hyperammonaemia. These are characterised by recurrent encephalopathies (☞ Chapter 5.6). Since there is only a short time interval from the onset of the first symptoms to possible irreversible brain damage, a rapid diagnosis and efficient treatment is of special importance. In about 30% of all cases of hyperammonaemia in newborns, the underlying cause is an organic aciduria. Ammonia concentration is very high (>1,000 µmol/l) in urea cycle defects as well as in organic acidurias in most cases. Ammonia levels can therefore not be used to distinguish between these two disease groups. In addition, the differential diagnosis also includes some types of fatty acid oxidation disorders. In these defects, ammonia is usually not as high as in urea cycle defects or organic acidurias. Other inborn errors of metabolism cause hyperammonaemia rather infrequently, and usually concentrations of ammonia are not excessively increased (e.g. tyrosinaemia type I, disorders of energy metabolism, galactosaemia, hyperinsulinism-hyperammonaemia syndrome, glutamatedehydrogenase overactivity). In addition, drug-induced hyperammonaemia has to be excluded (e.g. caused by valproate or chemotherapy).

Early diagnosis and prompt initiation of therapy is essential for the long-term prognosis. Laboratory results should be available within a few hours (independent of time of day). A few basic investigations (e.g. blood gases, glucose, ketone bodies in urine) and some specific investigations such as

- Amino acids in plasma
- Acylcarnitines in dried blood spots and
- Organic acids including orotic acid in urine

already allow a suspected diagnosis. An algorithm for differential diagnostic work-up in cases of hyperammonaemia is shown in Figure 3.1.

An overview of the three most frequent groups of inborn errors of metabolism presenting with hyperammonaemia and their typical laboratory findings is shown in Table 3.2.

Principles of emergency therapy in hyperammonaemia include:

- Immediate stop of protein intake

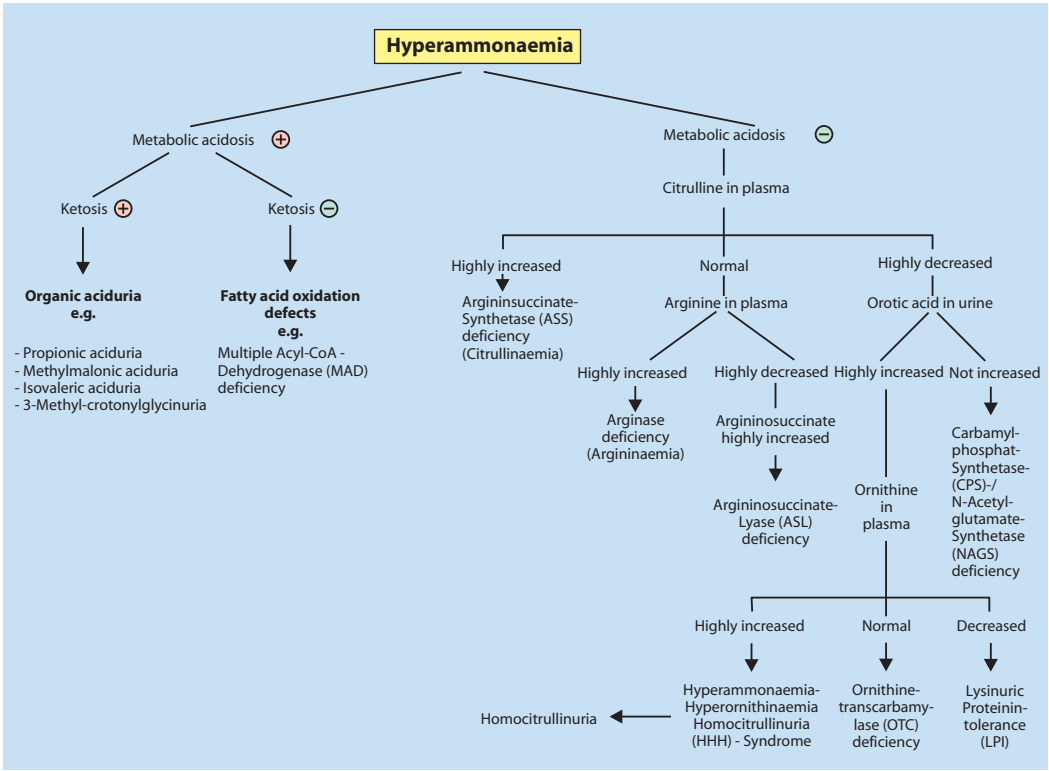


Figure 3.1: Differential diagnostic algorithm in cases of hyperammonaemia caused by an inborn error of metabolism.

Investigation	Urea cycle defects	Organic acidurias	Fatty acid oxidation defects
Blood gases	Respiratory alkalosis (initial)	Metabolic acidosis	Metabolic acidosis
Transaminases	Increased	Increased	Increased
Glucose	Normoglycaemia	Normoglycaemia	Hypoglycaemia
Creatine kinase	Normal	Normal	In some cases increased
Ketone bodies	+/–	+++ (massive ketosis)	Hypoketosis
Acylcarnitines	Normal	Propionylcarnitine increased (in propionic aciduria and methylmalonic aciduria), isovalerylcarnitine increased (in isovaleric aciduria)	Diagnostically relevant! Disorder-specific acylcarnitine profiles
Amino acids	In some cases diagnostically relevant!	No specific profile	Normal
Organic acids	In some cases orotic aciduria	Diagnostically relevant!	In some cases dicarbonic aciduria

Table 3.2: Typical laboratory findings which are relevant in cases of hyperammonaemia.

- Parenteral high dose supplementation of glucose (additional administration of insulin) with the main goal to achieve an anabolic state
- Ammonia detoxification (e.g. drugs like phenylacetate or -butyrate and/or sodium benzoate; if ammonia exceeds 400 µmol/l, immediate introduction of extracorporal detoxification, e.g. haemodialysis, haemofiltration)
- Substitution of intermediates of the urea cycle (arginine or citrulline) for enhancement of turnover in urea cycle defects
- Assistance of mitochondrial metabolism with carnitine (after exclusion of fatty acid oxidation defects)
- Forced diuresis (high amounts of fluid, diuretics)

Details for therapy of single inborn errors of metabolism are given in the referring chapters (urea cycle defects (☞ Chapter 5.6), organic acidopathies (☞ Chapter 5.7), fatty acid oxidation defects (☞ Chapter 5.10)).

3.2. Hypoglycaemia

Hypoglycaemia is defined as blood glucose <45 mg/dl. The clinical presentation of hypoglycaemia can be variable (☞ Table 3.3).

Newborns	Infants/children/adults
• Poor sucking or refusal to feed • Pallor • Tachypnoea • Shivering • Hyperexcitability • Apnoea, cyanosis • Hypotonia • Seizures • Coma	• Hunger, abdominal pain • Pallor, sweating • Nausea, vomiting • Weakness, lethargy • Headache, impaired vision • Abnormal behaviour • Unconsciousness • Seizures • Coma

Table 3.3: Clinical symptoms of hypoglycaemia.

Overall, the most common cause of genetic hypoglycaemia is congenital hyperinsulinism. For further diagnostic work-up, the time of hypoglycaemia in relation to food intake is important (☞ Figure 3.2).

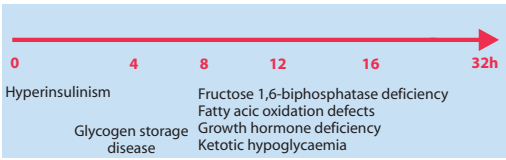


Figure 3.2: Causes of hypoglycaemia in relation to food intake.

Clinical parameters as well as the age of the patient are also diagnostically relevant. Hepatomegaly may point to a glycogen storage disease. Long-chain fatty acid oxidation diosorders may present with cardiomyopathy and/or skeletal myopathy. Hypoglycaemia in a macrosomic newborn suggests congenital hyperinsulinism. Increased glucose demand is also suggestive for congenital hyperinsulinism. Ketotic hypoglycaemia occurs due to immature gluconeogenesis. Symptoms become manifest after prolonged fasting or infections with reduced food intake. Ketotic hypoglycaemia occurs during infancy and loses its relevance after preschool age.

Baseline investigations during hypoglycaemia comprise:

- Glucose
- β-Hydroxybutyrate in blood and/or ketone bodies in urine (ketone test strips)
- Lactate
- Insulin
- Free fatty acids (if possible)
- Acylcarnitines in dried blood spots

A glucagon challenge (500 µg or 30-100 µg/kg s.c.) may be diagnostic in cases of suspected GSD type I. Glucagon does not result in an increase in blood glucose during hypoglycaemia in GSD type I. Instead, significant hyperlactataemia is observed.

Treatment of hypoglycaemia consists of adequate glucose supply to achieve blood glucose concentrations of about 100 mg/dl (=5.5 mmol/l). Long-term treatment depends on the underlying metabolic defect (see respective chapters).

3.3. Metabolic acidosis

Metabolic acidosis is a frequent finding in paediatric patients. It is found in severe infections, advanced catabolic states, tissue hypoxia, dehydration or intoxication. These causes have to be excluded before an inborn error of metabolism

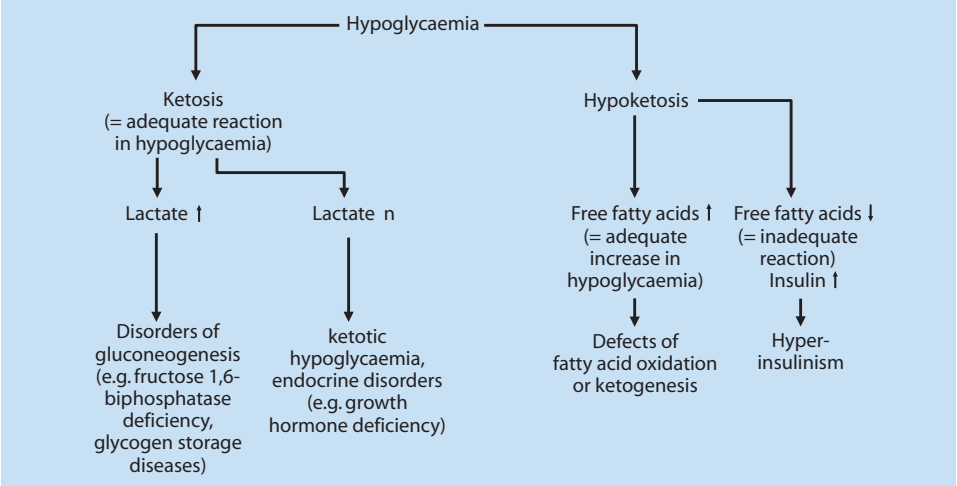


Figure 3.3: Diagnostic algorithm in case of hypoglycaemia.

should be considered as a the primary underlying cause. However, these states could also trigger the acute decompensation of an undiagnosed inborn error of metabolism.

Metabolic acidosis is mainly characterised by a decreased pH (<7.30) and low plasma bicarbonate (<15 mmol). Because of compensatory hyperventilation a decreased P_{CO2} (<30 mmHg) is common.

It is important to differentiate between renal loss of bicarbonate (e.g. renal Fanconi syndrome), intestinal loss of bicarbonate (e.g. diarrhoea) or an increased production of organic acids (e.g. lactate, ketones). In the latter case an increased anion gap (definition: sodium – (chloride + bicarbonate), normal 7-16 mval/l) is present.

The following investigations are indicated for differential diagnosis of metabolic acidosis caused by an inborn error of metabolism:

- Lactate in blood
- Ketones in urine
- 3-Hydroxybutyrate in blood
- Organic acids in urine
- Carnitine status in blood
- Acylcarnitines in dried blood spots
- Amino acids in plasma

A simplified diagram for differential diagnosis of metabolic acidosis is shown in Figure 3.4.

3.4. Hyperlactataemia

Lactate accumulates as a consequence of central or peripheral ischaemia. This may occur due to increased physical exercise, following epileptic seizures, or in cardiomyopathy, sepsis and other severe general diseases. Other causes of hyperlactataemia should be ruled out before metabolic investigations are initiated. Blood lactate concentrations can also be elevated as a result of difficult blood collection in a screaming child or prolonged use of a tourniquet. Concomitant ketosis points to a metabolic defect, with exception of fatty acid oxidation defects and pyruvate dehydrogenase deficiency which are not accompanied by ketosis. If neurological symptoms are present, CSF lactate values should be determined.

Baseline investigations in hyperlactataemia include:

- Glucose
- Blood gas analysis
- 3-Hydroxybutyrate (blood) and/or ketone bodies in urine (Ketostix)
- Amino acids, especially alanine (plasma)
- Acylcarnitines (dried blood spot)
- Organic acids (urine)

The assessment of pyruvate is generally not necessary. In exceptional cases it may be determined for the lactate/pyruvate ratio.

The time of hyperlactataemia in relation to food intake is diagnostically relevant (☞ Table 3.4). Dis-

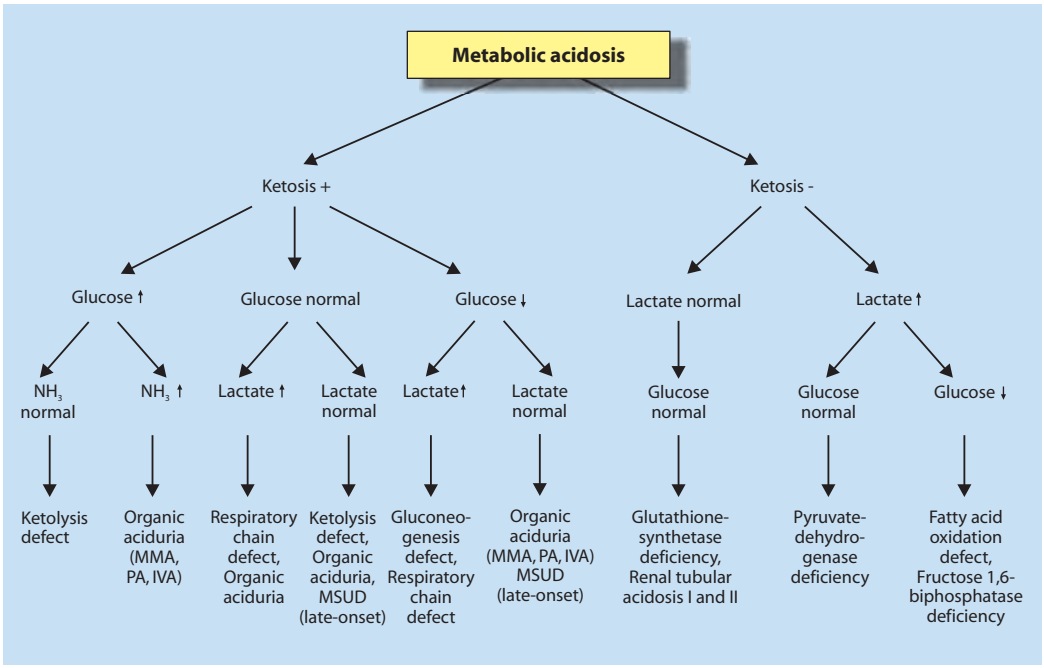


Figure 3.4: Differential diagnosis algorithm in cases of metabolic acidosis caused by an inborn error of metabolism.

orders of the tricarboxylic acid (TCA) cycle and the respiratory chain present with permanent hyperlactataemia, which is aggravated after meals and intake of carbohydrates. This is especially true for pyruvate dehydrogenase deficiency. The concentration of blood lactate can also be relevant for further diagnostic work-up. In disorders of the TCA cycle and the respiratory chain, blood lactate is usually >10 mmol/l. In disorders of gluconeogenesis (e.g. GSD type I, fructose 1,6-biphosphatase deficiency) blood lactate can also increase up to 15 mmol/l during hypoglycaemia. In GSD type II or IV, or glycogen synthase deficiency, lactate usually does not exceed 7 mmol/l.

Treatment of hyperlactataemia depends on the underlying metabolic defect (see respective chapters).

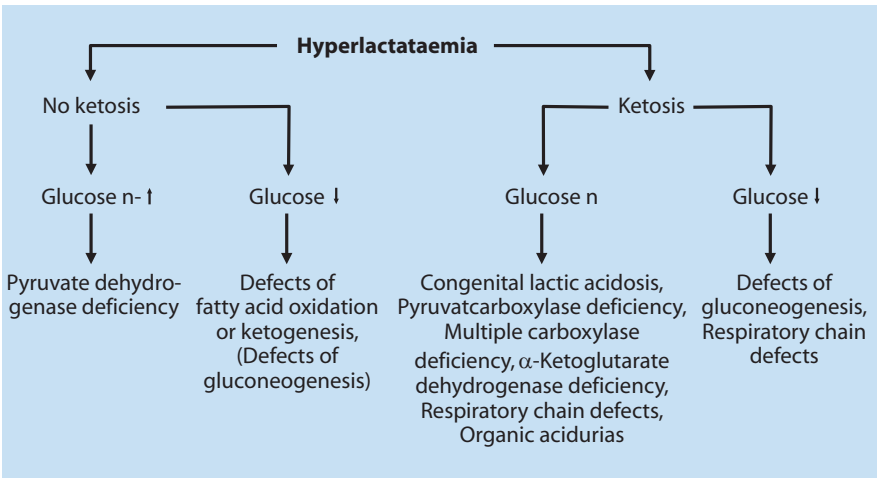


Figure 3.5: Diagnostic algorithm in case of hyperlactataemia.

Time of hyperlactataemia	Diagnostic marker	Diagnosis
Postprandial increase of lactate	Hepatomegaly	GSD type III
	Ketotic hypoglycaemia after fasting	Glycogen synthase deficiency
	Neurological symptoms, lactate/pyruvate ratio normal	Pyruvate dehydrogenase deficiency
	Neurological symptoms, encephalomyopathy, lactate/pyruvate ratio elevated	Pyruvate carboxylase deficiency
		Other disorders of the TCA cycle
		Respiratory chain defects
Fasting-induced post-prandial decrease of blood lactate	Hepatomegaly, hypoglycaemia	GSD type I
	Hypoglycaemia after fasting	Fructose 1,6-biphosphatase deficiency
	Pathological acylcarnitines	Fatty acid oxidation defects
Permanent hyperlactataemia	Neurological symptoms, encephalomyopathy, lactate/pyruvate ratio elevated	Pyruvate dehydrogenase deficiency
		Pyruvate carboxylase deficiency
		Other disorders of the TCA cycle
		Respiratory chain defects
	Episodic ketoacidosis, hyperammonaemia	E.g. organic aciduria
	Hyperammonaemia	E.g. urea cycle defects

Table 3.4: Hyperlactataemia in relation to food intake.

4. Clinical key symptoms

4.1. The critically ill neonate – metabolic emergencies in the neonate

Frequently, inborn errors of metabolism manifest as acute metabolic crises in newborns. In a neonate with an inborn error of metabolism clinical symptoms are often non-specific (☞ Table 4.1). Early diagnosis and initiation of adequate treatment are of utmost importance to improve outcome.

- Lethargy
- Altered consciousness
- Coma
- Irritability
- Seizures
- Poor sucking or refusal to feed
- Vomiting
- Loss of weight
- Respiratory dysfunction, tachypnoea
- Hypothermia
- Muscular hypotonia
- Hepatomegaly
- Cardiomyopathy
- Multiorgan failure

Table 4.1: Clinical symptoms in neonates in case of an inborn error of metabolism.

Patients with inborn errors of metabolism often deteriorate after an initial symptom-free period of several hours or days. Family history might be helpful in some cases (consanguinity, previous miscarriages or neonatal deaths). Clinical deterioration despite symptomatic treatment is typical.

Initial **basic (emergency) diagnostics include:**

- **Blood:** Acid–base status and anion gap [Na – (Cl + HCO_3^-)], blood cell count, glucose, transaminases, clotting studies, ammonia, lactate, uric acid, electrolytes, creatine kinase, creatinine, (plus rule out sepsis)
- **Urine:** Ketone testing strips (Note: ketonuria is an indicator for a metabolic disease in the neonate!), pH, colour, odour, reducing substances

Supplementary samples should always be taken before starting emergency treatment for further specific investigations. The most important **initial specific investigations** include:

- **Blood:** Amino acids (plasma), acylcarnitine profile (dried blood spots)
- **Urine:** Organic acids, orotic acid

It is of special importance to diagnose those metabolic diseases which can be effectively treated. The most important inborn disorders presenting as acute metabolic crisis in the neonatal period as are listed in Table 4.2.

As soon as a metabolic disorder is suspected, an immediate stop of all potential toxic substances (e.g. protein, fat, galactose) is necessary. Initially, a 10% glucose infusion (150 ml/kg per day = 10 mg/kg per min, about 60 kcal/kg per day) is started with adequate electrolyte substitution.

The results of the basic (emergency) diagnostics should be available within 30 minutes. In case of hypoglycaemia, hyperammonaemia, metabolic acidosis or hyperlactatemia treatment has to be specified (see related chapters). In case of non-specific or unclear results and ongoing suspicion of a metabolic disease, the glucose/electrolyte infusion has to be continued, and further specific investigations (see above) are initiated. Results should be available within 24 hours. It is in any case recommended to contact a metabolic specialist for advice. Until the results of specific investigations are available, glucose, lactate, ammonia, acid–base status and electrolytes should be monitored regularly. Not all inborn errors of metabolism which manifest as an acute metabolic crisis in newborns are routinely determined through newborn screening tests.

Therefore, it may be helpful to contact the screening laboratory and make specific enquiries if such a disorder is suspected.

A list of the most important drugs used for the treatment of metabolic emergencies with dosages is given in Chapter 6 (☞ Table 6.8).

	Ammonia	Metab. acidosis	Blood glucose	Lactate	Ketosis	Routine labs	Metab. specific diagnostics
Urea cycle defects	↑↑	n/↑	n	-	-	Transaminases n/↑	Amino acids in plasma, orotic acid in urine
Organic acidurias	↑↑	↑↑	↓/n/↑	n/↑	↑↑	Urea n/↑, poss. pancytopenia	Acylcarnitine profile, organic acids in urine
Fatty acid oxidation disorders	n/↑	n/↑	↓	n/↑	-	Elevated transaminases, CK und urea	Acylcarnitine profile, poss. organic acids in urine
Respiratory chain disorders	n/↑	↑↑	n/↓	↑↑	n/↑	Poss. elevated transaminases, CK, urea	Keep samples for specific diagnostic tests
MSUD	n/↑	↑↑	n/↓	n/↑	↑↑		Amino acids in plasma
Classic galactosaemia			↓			Elevated transaminases and bilirubin, signs of liver synthesis dysfunction, poss. haemolytic anaemia	Galactose and galactitol in urine (test for reducing substances positive), galactose in plasma, galactose-1-phosphate in erythrocytes, enzyme activity in erythrocyte
Hereditary tyrosinaemia type I						Transaminases ↑, AFP ↑↑, signs of liver synthesis dysfunction, poss. signs of renal tubulopathy	Amino acids in plasma, succinyl acetone in dried blood spots/urine

Table 4.2: Characteristic laboratory results in inborn error of metabolism with manifestation as acute metabolic crisis in neonates.

Acute liver failure	Classical galactosaemia, hereditary tyrosinaemia type 1, mitochondrial disorders, urea cycle defects, citrin deficiency, fatty acid oxidation disorders, CDG
Suspicious body odour	MSUD (maple syrup odour), isovaleric aciduria (odour of sweaty feet)
Heart failure	Disorders of fatty acid oxidation, mitochondriopathies, propionic acidaemia, glycogenosis type 2, glycogenosis type 3, mucopolysaccharidoses
Hydrops fetalis	Lysosomal storage diseases, CDG, mevalonic aciduria, transaldolase deficiency
Coma	Urea cycle defects, organic acidurias, MSUD, classic galactosaemia, mitochondriopathies, hyperinsulinism, ketolysis defects, gluconeogenesis defects
Seizures	Urea cycle defects, organic acidurias, hyperinsulinism, non-ketotic hyperglycinaemia, peroxisomal disorders, pyridoxine-dependent seizures, creatine deficiency syndromes, mitochondriopathies

Table 4.3: Major signs of inborn errors of metabolism presenting as acute metabolic crisis in the neonatal period.

4.2. Acute and chronic encephalopathies

Neurological symptoms are one of the most frequent complications of inborn errors of metabolism. Some of the more frequent inborn errors of metabolism in which neurological symptoms usually are a prominent feature are listed in Table 4.4 according to age.

Acute encephalopathy always represents an emergency for diagnostic as well as therapeutic work-up. The initial emergency diagnostic tests include:

- Blood gas analysis
- Electrolytes (anion gap) in plasma
- Blood glucose
- Ketone bodies in urine
- Transaminases, creatine kinase, coagulation studies
- Ammonia
- Plasma lactate
- Plasma amino acids
- Acylcarnitines (dried blood spots on filter paper)
- Organic acids in urine

Diagnostic work-up of chronic encephalopathy usually is more complex and time-consuming. One of the key questions is whether other organ systems apart from the central or peripheral nervous system are involved (☞ Figure 4.2). Liver and spleen may be affected (hepatosplenomegaly), but also skin, connective tissues, eyes, bones or muscles may be involved. If exclusively neurological symptoms are present it is important to differentiate between white matter disease and grey matter disease (☞ Figure 4.1).

In addition to the laboratory tests listed above, the following investigations should be considered:

- Mucopolysaccharides and oligosaccharides in urine
- Imaging studies of the brain (magnetic resonance tomography)
- Electrophysiological investigations (e.g. visual or acoustic evoked potentials, in special cases nerve conduction velocities, electromyographic studies)
- X-ray of selected bones (e.g. to discover dysostosis multiplex)
- Opthalmological examination
- Further investigations are indicated according to clinical symptoms (e.g. VLCFA, homocysteine).

4.3. Psychomotor impairment

Since numerous metabolic diseases can lead to irreversible brain damage with a progressive chronic course, a large group of metabolic disorders must be taken into account in the differential diagnosis. In several metabolic disorders psychomotor impairmentdevelops in the course of time and does not have to be a primary symptom. The most important groups and some examples of disorders are listed in Figure 4.2.

A detailed clinical history before commencement of treatment is essential. It will elucidate at which age psychomotor impairment was recognised, whether there are phases in which the child lost

Disease	Age of manifestation		
	Newborns	Infants and toddlers	Children and adolescents
Urea cycle defects	++++	+ (OTC-deficient heterocygotes)	(+)
Organic acidurias	++++	+	(+)
Maple syrup urine disease	++++	++	+
Fatty acid oxidation defects	++	++++	(+)
Non-ketotic hyperglycinaemia	++++	0	0
Mitochondrial disorders	+++	++	+

Table 4.4: Inborn errors of metabolism in which neurological symptoms usually are a prominent feature (if untreated) sorted according to their typical age of presentation.

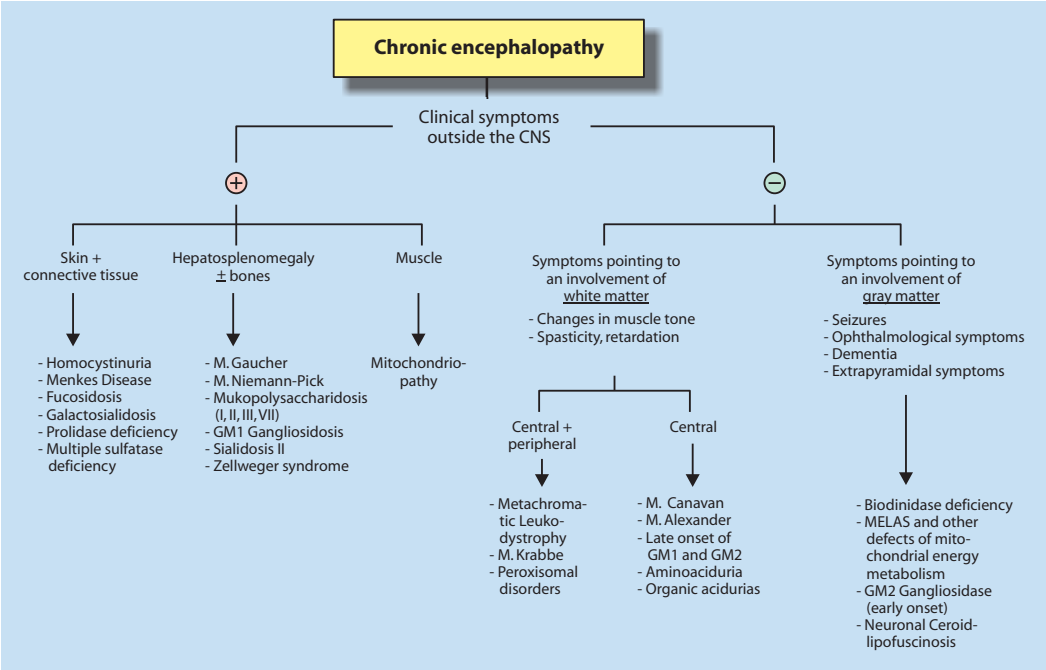


Figure 4.1: Differential diagnostic in case of a chronic encephalopathy.

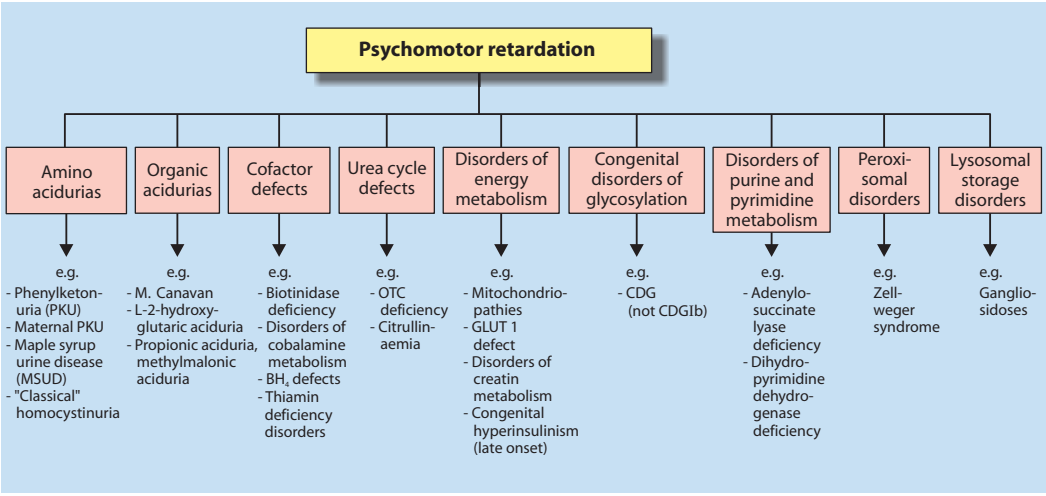


Figure 4.2: Differential diagnosis of psychomotor impairment and inborn errors of metabolism.

skills which were (partially) regained or whether there is stagnation or regression of skills. Careful clinical and paraclinical investigations will assist in differential diagnosis (e.g. dysmorphic signs, organomegaly, involvement of multiple organ systems, epilepsy, opthalmological abnormalities, macro- or microcephaly, abnormal hair).

Basic investigations in cases of psychomotor impairment include:

- Full blood count, differential blood count
- Electolytes in plasma
- Plasma glucose (in the fasting state)
- Blood gas analysis
- Uric acid

- Creatinine
- Transaminases
- Creatine kinase
- Ammonia
- Plasma lactate

In most cases additional investigations, such as ultrasound, X-ray or MRI, are necessary for assessment of specific organ systems (e.g. abdomen, skeletal system), in order to be able to request more tailored laboratory investigations.

- Magnetic resonance imaging of the brain
- Ultrasound examinations of abdomen, heart and urogenital tract
- Opthalmological examination (e.g. cherry red spot)
- In some cases *in-vivo*-MR-spectroscopy of the brain
- In some cases electroencephalography (EEG)
- In some cases X-ray (e.g. dysostosis multiplex?)
- In some cases audiogram, brainstem evoked response audiometry

Table 4.5: Paraclinical investigations for work-up of psychomotor impairment.

Further biochemical assessment of psychomotor impairment depends on the patient history and clinical findings, in particular the neurological abnormalities. Table 4.6 shows some biochemical investigations which may be performed in many cases of unclear psychomotor impairment.

- Amino acids (plasma)
- Homocysteine (plasma)
- Guanidoacetate, creatine, creatinine (urine, plasma)
- Isoelectric focussing of transferrin (serum or dried blood spots on filter paper)
- Purines, pyrimidines (urine)
- Peroxisomal diagnostic tests (e.g. very long chain fatty acids (VLCFA), phytanic acid, plasmalogens) (plasma)
- Copper, coeruloplasmin (suspected Wilson's disease or Menke's disease)
- Acylcarnitines (dried blood spots on filter paper)
- Organic acids, orotic acid (urine)
- Biotinidase activity in serum, if not tested in newborn screening
- Mucopolysaccharides (glycosaminoglycans) (urine)
- Oligosaccharides (urine)
- Free uraminic acid (urine)
- Lumbar puncture with analysis of glucose, lactate, amino acids). In particular if seizures and ataxia are present: glucose in CSF and plasma (fasting) to rule out glucose transporter 1 (GLUT1) deficiency

Table 4.6: Additional biochemical investigations in psychomotor impairment (selection).

4.4. Cardiomyopathy

Cardiomyopathy is a leading symptom found in many metabolic diseases. Other signs accompanying cardiomyopathy in metabolic diseases include neurological symptoms, signs of a storage disease, recurrent episodes of metabolic crisis, skeletal myopathy or hepatomegaly. Cardiomyopathy may be the leading clinical sign, e.g. in the early-onset forms of fatty acid oxidation defects, Pompe disease, Barth syndrome, respiratory chain defects or CDG. In lysosomal storage diseases, a multisystemic involvement of visceral organs and usually also of the nervous system is found. The glycogen storage diseases type III and type IV manifest themselves by hepatomegaly and possibly hypoglycaemias. In the case of organoacidopathies (in particular, propionaciduria), cardiomyopathy is a companion symptom. As a rule, it develops as a re-

sult of poor metabolic metabolism during preschool age. There are some biochemical parameters that may allow a first classification. Baseline diagnostic parameters include:

- (Differential) blood count
- (Fasting) glucose
- Acid–base status
- Transaminases
- Creatine kinase
- Coagulation factors
- Lactate
- Ammonia
- Ketones in urine (Ketostix)

According to the clinical and biochemical pattern further laboratory investigations have to be performed (☞ Table 4.7).

Treatment and prognosis of cardiomyopathy depend on the underlying disease. In fatty acid oxidation defects, cardiomyopathy is, e.g., completely reversible with sufficient MCT intake.

4.5. Dysmorphias

The spectrum of dysmorphias in the context of inherited metabolic diseases is broad. A selection of stigmata which may be found in inherited metabolic diseases is given in Table 4.8.

Besides these distinctive features, numerous alterations may be found in several metabolic diseases later in life. Hence, inherited metabolic diseases have to be taken into account when diseases with dysmorphic phenotype are subject of investigations. However, dysmorphias are found in only very few cases. In the context of metabolic diseases

Disorder	Age of onset	Clinical and biochemical parameters	Diagnostic procedures
Fatty acid oxidation defects (included in newborn screening test)	Pre screening era: 0-1 years	Pathological acylcarnitines, elevated CK	Acylcarnitines (dried blood spot), enzyme analysis, molecular analysis
Pompe disease	0-1 years	Typical ECG and echocardiography	Oligosaccharides (urine), vacuoles in lymphocytes, enzyme analysis, molecular analysis
Respiratory chain defects	No preferred age	Lactic acidosis, elevated alanine	Amino acids (plasma), lactate/pyruvate ratio, muscle biopsy (respiratory chain)
Barth syndrome	0-2 years	Neutropenia, 3-methylglutaconic aciduria	Organic acids (urine)
CDG syndromes	First years of life	Multisystemic disorder	Isoelectrical focussing (IEF) of transferrin
MPS I, II and VI	No preferred age	Signs of storage diseases	Mucopolysaccharidosis (glycosaminoglycanes) in urine
Glycogen storage disease type III, IV	No preferred age, onset accompanied by skeletal myopathy	Hepatomegaly, (hypoglycaemia), elevated transaminases, elevated CK in muscle involvement	Type III: enzyme analysis, molecular genetic testing; type IV: liver biopsy, molecular genetic testing, enzyme analysis
Organic acidurias (propionic aciduria, methylmalonic aciduria)	Preschool age	Episodes of metabolic derangement, metabolic acidosis	Organic acids (urine)

Table 4.7: Clinical and biochemical parameters and confirmatory diagnostic procedures in case of cardiomyopathy.

Organ system	Dysmorphic symptom	Inherited metabolic diseases (examples)
Skeleton	Dysostosis multiplex	Mucopolysaccharidoses/oligosaccharidoses
	Dwarfism	Mucopolysaccharidoses Peroxisomal diseases
	Proximal shortening of limbs	Rhizomelic chondrodysplasia punctata
	Variable dysplasias of the skeleton	Refsum disease Disturbances of sterol synthesis (i.e. CHILD syndrome)
Feet	Syndactyly toe II/III	Smith-Lemli-Opitz (SLO) syndrome
Face	High forehead	Peroxisomal diseases Mucopolysaccharidoses
	Prominent forehead	Alagille syndrome
	Flat, broad root of the nose	Peroxisomal diseases Mucopolysaccharidoses
	Epicanthus	Peroxisomal diseases
	Hypertelorism	Alagille syndrome
	Ear abnormalities	Peroxisomal diseases Mucopolysaccharidoses
	Variable facial malformations	Glutaric aciduria type II Desmosterolosis Antley-Bixler syndrome Mitochondriopathies (e.g. PDH deficiency)
CNS	Microcephaly	Smith-Lemli-Opitz syndrome Defects of serine synthesis Rhizomelic chondrodysplasia punctata Dihydropyrimidin-dehydrogenase deficiency GABA-transaminase deficiency
	Macrocephaly	Glutaric aciduria type I Canavan disease GM_2 gangliosidosis
	Cerebellar atrophy	Mevalonic aciduria, CDG syndromes
	Hydrocephalus	α-Mannosidosis

Table 4.8: Selection of dysmorphic signs and associated metabolic diseases.

dysmorphias can be found in particular in the following diseases:

- Peroxisomal diseases
- Congenital disorders of glycosylation (CDG)
- Lysosomal storage diseases
- Disturbances of sterole synthesis
- Disturbances of energy metabolism

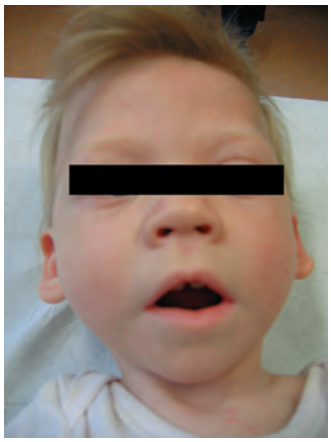


Figure 4.3: Typical facial appearance in Smith-Lemli-Opitz (SLO) syndrome.

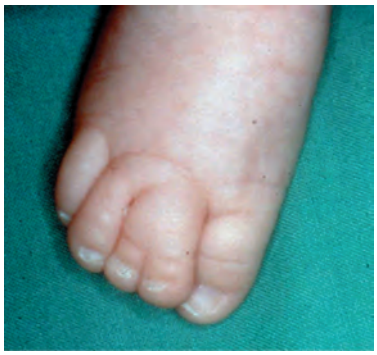


Figure 4.4: Syndactyly in Smith-Lemli-Opitz (SLO) syndrome.

4.6. Hepatopathy

In many inborn errors of metabolism the liver is considerably affected. Therefore, in the presence of any liver disease of the newborn child, but also in infants and children, an inborn error of metabolism has to be considered.

If hepatopathy of unknown origin is present, a detailed **medical history** should be collected, including family history, the question of parental consanguinity, nutritional history, age at onset of symptoms, and finally drug intake.

Physical examination is done with particular attention to icterus, hepatomegaly, splenomegaly, ascites, bleeding tendency, failure to thrive, or syndromal signs.

First line investigations in unknown liver disease

Transaminases, γ-GT, conjugated and unconjugated bilirubin, alkaline phosphatase, cholinesterase, blood clotting, ammonia, glucose, albumin, creatinine, urea, uric acid, blood gas analysis, lactate, and in some cases also ferritin, α-fetoprotein and bile acids.

Subsequent abdominal **ultrasound** including the urinary tract should be performed with special emphasis on liver size, density, evidence of a gall bladder. If liver cirrhosis is suspected, portal vein flow needs to be evaluated. Medical history and the first-line investigations will allow categorisation into one of the following four groups of disorders:

- Cholestatic liver disease with conjugated hyperbilirubinaemia
- Acute or subacute hepatocellulary necrosis
- Liver cirrhosis
- Hepatomegaly

Further special metabolic work-up should be initiated depending on the underlying disease (☞ Table 4.9).

4.7. Non-immune fetal hydrops

Apart from severe anaemia, heart defects and infectious diseases, a number of genetic diseases may be associated with non-immune fetal hydrops. Nevertheless, it is not unusual that despite comprehensive investigations an underlying cause cannot be found. The percentage of inherited metabolic diseases which may manifest with fetal hydrops is small. After exclusion of the most frequent causes by studying haematological parameters, karyotype, signs of infections, cardiac ultrasound etc. the metabolic diseases mentioned in Table 4.10 should be taken into account.

Cardinal symptom	Age at manifestation	Considered disorder	Typical findings/advanced analysis
Cholestatic liver disease	<3 months	α1-antitrypsin deficiency	α1-antitrypsin ⇓, isoelectric focusing
		Cystic fibrosis	Positive sweat test
		Tyrosinaemia type I	AFP ⇑; succinylacetone increased
		Niemann-Pick type C	Foam cells detected in the bone marrow, enzyme analysis
		Peroxisomal disorder	VLCFA, plasmalogen analysis
		Defect of bile acid synthesis	Bile acid profile
	>3 months	Progressive familial intrahepatic cholestasis	γ-Glutamyl transferase increased or normal depending on subform
		Rotor syndrome	Mild icterus
		Dubin-Johnson syndrome	Mild icterus
Acute or subacute hepato-cellulary necrosis	<3 months	Neonatal haemo-chromatosis	Ferritin ⇑⇑⇑, AFP ⇑⇑⇑, liver biopsy
		Galactosaemia	Galactose, galactose-1-P ⇑
		Tyrosinaemia type I	AFP ⇑; Succinylacetone ⇑
		Urea cycle defect	Ammonia ⇑⇑⇑
		Respiratory chain defect	Lactate ⇑⇑
		Long chain fatty acid oxidation disorder	(Glucose ⇓), liver values and CK ⇑, pathological acylcarnitine profile
		Niemann Pick type A, B	Foam cells detected in bone marrow, enzyme analysis
	3 months - 2 years	Hereditary fructose intolerance	Renal tubular dysfunction, medical history (start of supplementary food), glucose ⇓
		Tyrosinaemia type I	AFP ⇑; succinylacetone ⇑
		Long chain fatty acid oxidation defect	Pathological acylcarnitine profile, transaminases and CK ⇑
		Respiratory chain defect	Lactate ⇑⇑
		Urea cycle defect	Ammonia ⇑⇑⇑
	>2 years	Wilson's disease	Copper n-⇓; coeruloplasmin n-⇓, copper excretion in urine ⇑, copper concentration in liver biopsy ⇑
		α1-antitrypsin deficiency	α1-antitrypsin ⇓, IEF pathological bands
		Long chain fatty acid oxidation defect	Pathological acylcarnitine profile, liver values and CK ⇑

Cardinal symptom	Age at manifestation	Considered disorder	Typical findings/advanced analysis
Cirrhosis	<1 year	Glycogen storage disease type IV	Enzyme analysis, molecular genetic testing, glycogen concentration in liver biopsy ⇑⇑
		Galactosaemia	Galactose, galactose-1-P ⇑
		Neonatal haemochromatosis	Ferritin ⇑⇑⇑, AFP ⇑⇑⇑, liver biopsy
		Tyrosinaemia type I	AFP ⇑; succinylacetone ⇑
	>1 year	α1-antitrypsin deficiency	α1-antitrypsin ⇓, IEF pathological
		Wilson' disease	Copper n-⇓; coeruloplasmin n-⇓, copper excretion in urine ⇑, copper concentration in liver biopsy ⇑
Hepatomegaly	<3 months	Lysosomal storage disorder	Foam cells detected in bone marrow, enzyme analysis, urinary glycosaminoglycans and oligosaccharides
		CDG type I a	IEF of transferrin pathological
		Defects of gluconeogenesis	Glucose ⇓, lactate ⇑, acidosis
		Mevalonic aciduria	Dysmorphic features, ataxia, recurrent episodes of fever of unknown origin, CK ⇑, IgD ⇑, mevalonic acid in urine ⇑
		Long chain fatty acid oxidation defect	Pathological acylcarnitine profile, transaminases and CK ⇑
		Glycogen storage disease type I	Glucose ⇓, lactate ⇑, uric acid ⇑, mutational analysis
	3 months up to 2 years	Defects of gluconeogenesis	Glucose ⇓ , lactate ⇑, acidosis
		Lysosomal storage disorder	Foam cells detected in bone marrow, enzyme analysis
		Long chain fatty acid oxidation defect	Pathological acylcarnitine profile, transaminases and CK ⇑
		α1-antitrypsin deficiency	α1-antitrypsin ⇓, IEF pathological
	>2 years	Haemochromatosis	Ferritin ⇑⇑⇑, AFP ⇑⇑⇑, hyperpigmentation, hypogonadism, cardiomyopathy, mutational analysis
		Cystic fibrosis	Pathological sweat test, molecular genetic testing
		Lysosomal storage disorder	Foam cells detected in bone marrow, enzyme analysis, urinary oligosaccharides; ophthalmoscopic examination: cherry-red spot
		Long chain fatty acid oxidation defect	Pathological acylcarnitine profile, transaminases and CK ⇑

Table 4.9: Differential diagnosis of metabolic disease with liver affection.

- GM_1-gangliosidosis
- Sialidosis
- Galactosialidosis
- Wolman's disease (☞ Fig. 4.6)
- Sialic acid storage disease
- Smith-Lemli-Opitz (SLO) syndrome
- Congenital disorders of glycosylation (CDG)
- Mitochondriopathies
- Acute neuronopathic Gaucher's disease
- Niemann-Pick disease type C
- Mucolipidosis type II (I-cell disease)
- Multiple sulphatase deficiency
- Mucopolysaccharidosis type I, IVa, VII
- Mevalonic aciduria
- Zellweger syndrome
- Glycogen storage disease type IV
- Primary carnitine deficiency

Table 4.10: Inherited metabolic diseases which may present with fetal hydrops (selection).

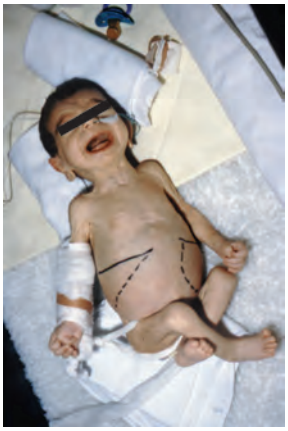


Figure 4.5: Infant with Wolman's disease, a lipid storage disease presenting with hepatosplenomegaly, diarrhoea, distended abdomen and failure to thrive. The disease may be associated with fetal hydrops and the course usually is fatal within the first year of life.

In case of fetal hydrops, lysosomal storage diseases belong to the major causes which have to be clarified. Affected newborns typically show a markedly increased birth weight and distinctive swelling of the limbs. During the first days of life a clear reduction of birth weight can be observed. Severely affected patients often die from respiratory insufficiency, cardiac failure or coagulopathy. Pronounced hepatosplenomegaly, dysostosis multiplex, vacuolated lymphocytes in blood smear or ascites and storage cells in bone marrow are suggestive for the presence of a lysosomal storage disease. Definite diagnosis requires enzymatic analyses.

4.8. Psychiatric symptoms

Little is known about psychiatric symptoms in the context of inherited metabolic diseases, and only a few systematic investigations on this issue have been performed. It is conceivable that a considerable number of patients with inherited metabolic diseases suffer from psychiatric disturbances, in particular depression. Patients have an increased risk when they suffer from diseases which

- have a chronic (progressive) course,
- in part are painful and
- in many cases show morphological defects of the central nervous system.

Of note, most information regarding psychiatric problems in inherited metabolic diseases refers to children, rather than adults. Experiences in adult patients are limited and are mainly based on single cases.

An exploratory overview on psychiatric symptoms in the context of inherited metabolic diseases is given in Table 4.11.

Psychiatric symptom	Inherited metabolic disease	Diagnostic procedure
Behavioural disturbances	Aspartylglucosaminuria	Enzymatic analysis
	Neuronal ceroidlipofuscinosis	(Electron-)microscopy (fibroblasts, leucocytes): typical storage cells, enzymatic analysis
	X-chromosomal adrenoleuco-dystrophy	VLCFA in serum
	Urea cycle defects (e.g. heterozygote OTC deficiency)	Amino acids in plasma, orotic acid in urine, molecular genetic testing
Hyperkinetic behaviour	Mucopolysaccharidosis type III	Enzymatic analysis
Psychosis	γ-glutamyltranspeptidase deficiency	Glutathione in urine
	Wilson's disease	Coeruloplasmin, copper (serum, urine, liver)
	Lysosomal storage diseases	Enzymatic analysis
	Acute intermittent porphyria (AIP)	Porphyrins in urine
Depression	Fabry disease	Enzymatic analysis
	Wilson's disease	Coeruloplasmin, copper (serum, urine, liver)
Schizophrenia	Acute intermittent porphyria (AIP)	Porphyrins in urine
	MTHFR deficiency	Amino acids in plasma, homocysteine
Automutilation	Lesch-Nyhan syndrome	Urate in serum
Aggression	Mucopolysaccharidosis III	Enzymatic analysis
	Monoaminooxidase deficiency	Biogene amines in cerebrospinal fluid and urine
	Succinatesemialdehyde-dehydrogenase deficiency	Organic acids in urine
Autism	Creatine deficiency syndromes	Guanidinoacetate in plasma MR-spectroscopy (*in vivo*)
	Adenylosuccinate-lyase deficiency	Purines in urine
	Succinatesemialdehyde-dehydro-genase deficiency	Organic acids in urine
	SLO syndrome	Steroles in plasma
	Organic acidurias (e.g. mevalonic aciduria)	Organic acids in urine
Dementia	Acoeruloplasminaemia	Coeruloplasmin in serum
	Choreoacanthocytosis	Acanthocytosis in blood smear
	Mitochondriopathies (e.g. MELAS)	Lactate
	Lysosomal storage diseases	Enzymatic analysis

Table 4.11: Psychiatric symptoms in the context of inherited metabolic diseases.

4.9. Ophthalmological problems

The eye as an "upstream part of the CNS" usually is not accessible to diagnostic procedures and therefore cannot give decisive hints for the diagnosis of inherited metabolic diseases. Blindness as the most severe ophthalmological manifestation is only found in very few cases (☞ Tab. 4.12).

Symptom	Metabolic disease
Blindness	Niemann-Pick disease type A and B
	Peroxisomal diseases
	Krabbe disease
	2-Methyl-2-hydroxybutyryl-CoA-dehydrogenase deficiency
	Neuronal ceroidlipofuscinosis

Table 4.12: Selection of metabolic diseases associated with blindness.

Cornea, lens, retina and optic nerve on the other hand are often affected in inherited metabolic diseases. The differential diagnosis in retinitis pigmentosa is of particular interest (☞ Tab. 4.13).

Symptom	Metabolic disease
Variable corneal lesions	Tyrosinaemia type II
Corneal crystals	Cystinosis
Cataract	Defect of serine synthesis
	"Classical" galactosaemia (GALT deficiency)
	Galactokinase deficiency
	Lysosomal storage diseases
	Peroxisomal disease (Zellweger syndrome)
	Chondrodysplasia punctata, Conradi-Hünermann syndrome
	Cerebrotendinous xanthomatosis
	Apolipoprotein A-I deficiency
	Tangier disease
	Fish eye disease
Dislocation of the lens	"Classical" homocystinuria
	Sulphite oxidase deficiency/ molybdenum-cofactor deficiency
Optic atrophy	Canavan disease
Retinitis pigmentosa	Neuronal ceroidlipofuscinosis
	Peroxisomal diseases
	LCHAD/TFP deficiency
	Sjögren-Larsson syndrome
	Vitamin B_{12} deficiency
	Primary vitamin E deficiency
	CDG syndromes
Cherry-red macula spot	Lysosomal storage diseases (e.g. GM_1- or GM_2 gangliosidosis)

Table 4.13: Selection of metabolic diseases which have to be taken into account in patients with ophtalmological problems.

4.10. Haematological problems

Disorders of erythrocytes

A number of congenital metabolic disorders can be associated with disorders of the erythrocytes, especially in conjunction with anaemia. A selection of corresponding diseases and erythrocyte abnormalities is shown in Table 4.14.

More than 95% of macrocytic anaemias are caused by acquired deficiency of vitamin B_{12} and folate. However, many congenital disorders of vitamin B_{12} and folate metabolism are associated with macrocytic anaemia (but not MTHFR deficiency, see Section 5.4.2).

Haemolytic anaemias can be due to deficiencies of enzymes involved in the processes involved in glycolysis or the pentosephosphate cycle or or can be caused by porphyria or disturbed erythrocyte nucleotide metabolism.

Disorders of leucocytes and thrombocytes

Changes in the blood cell count like pancytopenia, thrombocytopenia or leukopenia are found in Gaucher disease type I and III, glycogen storage disease type I non-a (as neutropenia, ☞ Chapter 5.11.3.1), congenital disorders of cobalamin and folate metabolism, lysinuric protein intolerance and some organic acidopathies (e.g. MMA, PA, IVA, ☞ Section 5.7).

Vacuolised lymphocytes are found, e.g., in metabolic disorders such as Pompe disease, mucopolysaccharidoses, Niemann-Pick disease type I a, c or GM1. Hyperleucocytosis (>100,000/µl) is a typical finding in leukocyte adhesion deficiency syndrome (SLC35C1-CDG, formerly CDG type IIc). Haemophagocytosis is observed in CblC deficiency, Gaucher disease, lysinuric protein intolerance or Niemann-Pick disease.

Macrocytic anaemia	Anaemia (except macrocytic forms)	Acanthocytosis
• Disorders of the cobalamin metabolism (e.g., Cbl C, D, E, F, G, trans-cobalamin II deficiency) • Disorders of folate metabolism (e.g., mevalonic aciduria, Pearson's syndrome, congenital folate malabsorption, thiamine-responsive megaloblastic anaemia) • Hereditary orotic aciduria	• Porphyria (e.g., congenital erythropoietic porphyria) • Carnitine transporter defect • Galactosaemia • Haemochromatosis • Glutathione synthetase deficiency • Transaldolase deficiency	• Disorders of cobalamin metabolism (Cbl C) • Wolman disease • Hallervorden-Sparrow syndrome (pantothenate kinase deficiency)

Table 4.14: Selection of disorders of the erythrocytes in the context of congenital metabolic diseases.

5. Selection of metabolic diseases (symptoms, diagnosis, treatment)

5.1. Phenylketonuria (PKU)

Definition

PKU is the most frequent disorder of amino acid metabolism and is caused by hepatic phenylalanine hydroxylase deficiency (PAH).

Incidence

1:6,000 in Germany.

Pathogenesis

Deficiency of PAH causes inadequate conversion of phenylalanine (Phe) to tyrosine (Tyr) and accumulation of Phe in different body fluids. High levels of phenylalanine are toxic, especially for brain cells. Phe is broken down by alternative metabolic pathways to phenylketones, which are ultimately excreted in the urine, giving the disease its name. High levels of phenylalanine interfere with the transport of aromatic and neutral amino acids via cell membranes (e.g., the blood–brain barrier). They also inhibit protein synthesis, increase myelin turnover, and inhibit the synthesis of neurotransmitters such as serotonin, dopamine and noradrenaline. To catalyse the reaction of Phe to Tyr, PAH must be activated by tetrahydrobiopterin (BH_4). BH4 is converted to dihydrobiopterin (BH_2), which is recylced with the help of dihydopteridine reductase (DHPR). Increased Phe levels can therefore not only be caused by a reduced activity of PAH (which is found in 98% of patients presenting with elevated Phe levels), but also by deficiencies in the biosynthesis or regeneration of BH_4 (BH_4 deficiency, "Atypical PKU").

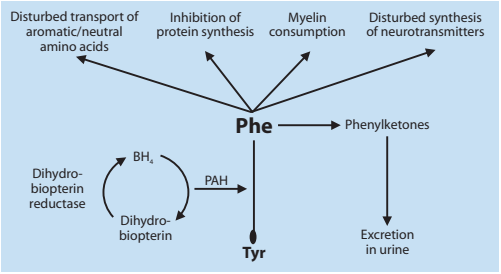


Figure 5.1: Consequence of disturbed metabolism of phenylalanine in Phenylketonuria (PKU). Phe=phenylalanine; Tyr=tyrosine; PAH=phenylalanine hydroxylase; BH_4=tetrahydrobiopterine.

Clinical spectrum

Based on Phe plasma levels and PAH residual activity, classical PKU and milder variants can be distinguished (☞ Table 5.1). Mild forms of hyperphenylalaninaemia, with Phe plasma levels not exceeding 600 mmol/l on a normal (i.e., not phenylalanine-reduced) diet, generally do not need therapeutic intervention.

	Phenylalanine in plasma	Residual PAH activity
Classical PKU	>1,200 µmol/l (>20 mg/dl)	<1%
Mild PKU	>600-1,200 µmol/l (>10-20 mg/dl)	1-3%
Mild hyperphenylalaninaemia (HPA)	>120-600 µmol/l (>2-10 mg/dl)	3-10%

Table 5.1: Clinical classification in phenylalanine hydroxylase (PAH) deficiency.

Untreated patients with classical PKU or those with insufficient therapy can develop a wide spectrum of neurological signs.

Age	Clinical symptoms
Infancy	• EEG changes (e.g. hypsarrhythmia) • Hypopigmentation of skin, hair and eyes • Eczematous skin changes • "Mousy" body odour
From early childhood	• Mental retardation • Behavioural disturbances such as hyperactivity, autoaggression, autism and psychosis • Seizures • Pyramidal tract signs and Parkinson-like symptoms • Gait ataxia

Table 5.2: Clinical consequences of untreated and/or insufficiently treated PKU.

Early treated patients with well-controlled Phe levels do not develop such symptoms and are phenotypically not different from healthy children.

Special forms

1. Maternal PKU

Elevated maternal Phe concentrations during pregnancy can cause severe damage to the unborn child. In order to prevent damage to the unborn child (miscarriage, growth retardation, microcephaly, heart failure, intellectual disability, etc.), Phe concentrations should be strictly maintained between 120 and 360 µmol/l before conception and throughout pregnancy.

2. Defective biosynthesis or regeneration of tetrahydrobiopterin (BH_4)

BH_4 not only acts as a cofactor for PAH, but also for tyrosine hydroxylase and tryptophan hydroxylase. Apart from increased concentrations of Phe, BH_4 deficiency causes a deficiency of neurotransmitters (e.g. dopamine, serotonin) and accumulation of abnormal pterines. Clinical symptoms caused by dopamine and serotonin deficiency (e.g. infantile Parkinson syndrome, dystonia, intellectual disability). Diagnosis can be made by performing an oral BH_4-loading test, analyses of pterines in urine or dried blood spots and determination of dihydropteridine reductase (DHPR) activity. Treatment includes oral administration of neurotransmitter precursors (L-DOPA/carbidopa/5-OH-tryptophan), combined with BH_4 and/or a Phe-resctricted diet if needed.

Diagnosis

Increased concentrations of Phe in newborn screening lead to the suspected diagnosis of PKU. BH_4 deficiency, which may also present with elevated Phe concentrations in newborn screening, needs to be ruled out. This is done by performing a BH_4 test and by analysing the pterins (from urine or dried blood) and DHPR activity (in dried blood).

Treatment

Once the diagnosis of PKU has been confirmed, therapy has to be started as soon as possible in order to prevent irreversible damage to the CNS. The mainstay of PKU treatment is to reduce dietary Phe intake. A Phe-free medical formula is given to lower initially massively elevated Phe levels. Breastfeeding can be continued. Apart from the normal benefits of breastfeeding, mother's milk provides an excellent source of natural protein, and its Phe concentration is lower than that of standard commercial infant formula.

To avoid deficiency of essential amino acids because of the diet, these amino acids have to be added as Phe-free amino acid supplements. Modern amino acid mixtures are enriched with trace elements, vitamins and minerals. Hence, deficiencies of these micronutrients are not expected if the compliance with the amino acid supplement is good.

Sapropterine dihydrochloride (synthetic BH_4) leads to an increase in the activity of PAH in some of the patients with PKU, so that phenylalanine tolerance is increased and the dietary regime may be relaxed. The response to sapropterine dihydrochloride (10-20 mg/kg per day) must be tested individually for each patient.

Monitoring

Recommendations for monitoring are based on patients' age and on the concentrations of Phe in plasma. In patients with poor metabolic control or

during intercurrent illness, biochemical and clinical monitoring should take place more frequently.

An overview of Phe target values recommended in Germany is given in Table 5.3.

Age	Recommended Phe levels	
	mg/dl	µmol/l
0-10 years	0.7-4.0	42-240
11-16 years	0.7-15	42-900
>16 years	0.7-20	42-1,200

Table 5.3: German recommendations for Phe plasma levels in PKU patients.

Table 5.4 shows the recommended frequency of clinical and biochemical controls in PKU.

Age	Biochemical control	Clinical control
0-12 months	every 1-2 weeks	every 3 months
1-9 years	every 2-4 weeks	every 3-6 months
10-15 years	every 4 weeks	every 6 months
>15 years	every 2-3 months	every 6-12 months

Table 5.4: Recommendations for monitoring of PKU according to age.

Prognosis

In patients with good dietary compliance, the prognosis of PKU is excellent, and patients cannot be distinguished from healthy individuals.

5.2. Maple syrup urine disease (MSUD)

Definition

Maple syrup urine disease (MSUD) is caused by a deficiency of branched-chain ketoacid-dehydrogenase complex. This multienzyme-complex comprises three different subunits (E1-E3). Loss of function of one single subunit E1a, E1b or E2 results in this metabolic disease. The enzyme catalyses the second step of the degradation pathway of the branched-chain amino acids leucine, isoleucine and valine (☞ Figure 5.2).

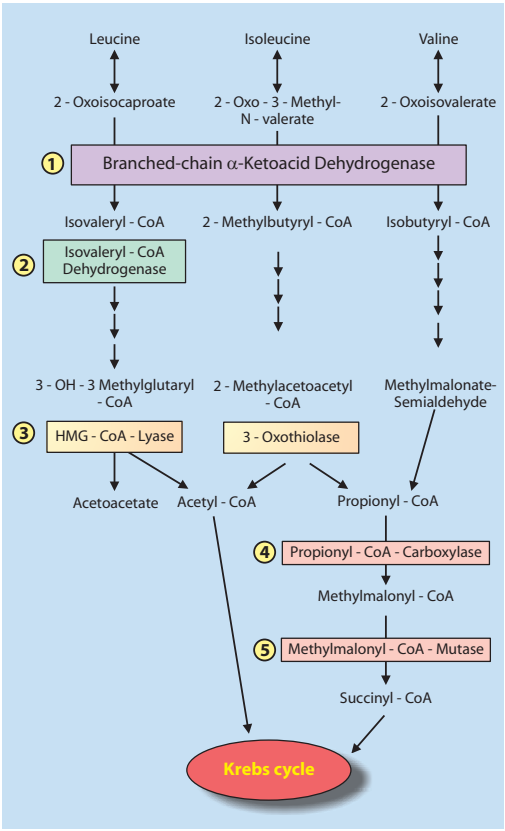


Figure 5.2: Metabolic pathway of branched-chain amino acids. 1= Maple syrup urine disease (MSUD), 2=Isovaleric aciduria, 3=HMG-CoA-lyase deficiency, 4=Propionic aciduria, 5=Methylmalonic aciduria.

Incidence

1:150,000.

Pathomechanism

There is a continuum of severe classical forms with almost undetectable residual activity (<2%) to mild variant forms with residual enzyme activity of up to 40%. Leucine and in particular the direct degradation product 2-oxoisocaproic acid are the most important neurotoxic substances in MSUD. Isoleucine, valine and their analogous 2-oxoacids have less neurotoxic effect. The severity of damage to the brain depends on the extent and duration of the increase in toxic metabolites.

Clinical spectrum

Patients affected by the classical form of MSUD already show signs of severe encephalopathy in the first few days of life. As a rule, newborns become lethargic by the fourth day of life, and show poor sucking, hyporeflexia and trunk hypotonia with increased muscular tone of the extremities. As a sign of the cerebral oedema a bulging fontanelle is observed. As leucine levels increase, progression of the neurological symptoms occurs with the onset of seizures and impaired consciousness. In addition, a maple syrup-like or "sweetish-caramel-like" odour of the child can be noticed. Untreated newborns with classical MSUD die within the first days of life.

In older children with diagnosed MSUD, drowsiness or an uncertain gait pattern as a sign of a movement and coordination disorder are clinical signs of metabolic decompensation.

20-30% of the patients present with mild (variant) forms of the MSUD. These are characterised by developmental delay, episodic, partly progressive neurological disorders or recurrent metabolic decompensation.

Diagnosis

MSUD is part of the neonatal screening program (elevated leucin/isoleucin and valine). The most important diagnostic test for MSUD is the measurement of plasma amino acid concentrations. In addition, the presence of alloisoleucine, produced by tautomerisation from isoleucine and typically not present in healthy individuals is characteristic for this disease. Branched-chain ketoacids can also be found in the urine. Different from other organic acidurias, in MSUD no other laboratory signs of metabolic decompensation point towards this underlying metabolic disorder.

Treatment

Emergency treatment is based on withdrawal of natural protein and the promotion of anabolic metabolism. A high-calorie diet with special infant formula free of branched-chain amino acids is initiated. Additionally, intravenous glucose may be given in cases of poor nutritional tolerance.

In hyperglycaemia intravenous insulin (starting at 0.05 IU/kg/h) is given simultaneously. The goal is a calorie intake of approximately 130 kcal/kg body weight. Isoleucine and valine must be supplemented at an early stage (high doses approximately 12 hours after initiation of therapy, dose 80-100 mg/kg), even if their plasma levels are still increased, so as not to be limiting factors for protein synthesis. Under this regime, the increased amino acids usually fall within their normal range within a few days. Frequently extracorporeal detoxification (haemodialysis/haemofiltration) can be avoided with this therapy regimen.

As part of the continuous therapy the daily leucine intake and thus the amount of natural protein is massively restricted.

The supply of leucine is individually adjusted and checked by regular analyses of plasma amino acids. For this purpose weekly controls are necessary during infancy. Later, controls of the amino acids are necessary every 2 to 4 weeks. The aim is to achieve leucine levels between 80 and 250 (-300) µmol/l.

To avoid protein deficiency, a leucine, isoleucine and valine-free amino acid mixture is substituted in the classical form. Often supplementation of valine and isoleucine is also necessary. The individual leucine intake is reduced for a few days during illness or in the case of dietary errors which lead to increased leucine levels.

Prognosis

Prognosis depends on the initial brain damage at manifestation and on the long-term metabolic control. After early and successful treatment the prognosis is satisfactory. For variant forms prognosis is usually good.

5.3. Tyrosinaemia type I

Definition

Tyrosinaemia type I is an autosomal recessively inherited deficiency of fumarylacetoacetate hydrolase.

Incidence

1:100,000.

Pathogenesis

This enzyme deficiency and the disturbed tyrosine metabolism results in accumulation of toxic metabolites such as succinylacetone (SA), which can be detected in various body fluids (☞ Figure 5.3).

Succinylacetone is a potent inhibitor of δ-aminolaevulinacid-dehydratase, a key enzyme in porphobilinogen synthesis. This explains the porphyria-like symptoms in patients.

Clinical spectrum

The acute form usually presents within the first weeks of life with severe liver failure and coagulation dysfunction. The progressive form manifests as gastrointestinal bleeding, icterus, ascites or hypoglycaemia. The rare chronic form usually presents after the first year of life with hepatopathy, failure to thrive, growth delay and renal tubular dysfunction with Fanconi syndrome. This results in a hypophosphataemic rickets. There may be a progressive course of kidney disease with chronic renal failure. Porphyria-like neurological crises with altered consciousness, peripheral neuropathy and respiratory failure may occur.

Diagnosis

Plasma tyrosine and methionine are usually elevated. In urine, metabolites of tyrosyluria (4-OH-phenylpyruvate and 4-OH-phenyllactate) are present. Diagnosis of tyrosinaemia type I is supported by detection of increased levels of succinylacetone in urine, plasma or dried blood spots. Elevated alkaline phosphatase, increased α-fetoprotein, coagulation dysfunction or mildly elevated liver transaminases are found by routine laboratory work-up. Diagnosis is confirmed by enzyme analysis or mutational analysis.

Treatment

Since NTBC (nitisinone, Orfadin®) was introduced into therapy in the early 1990s, it has been the most important component of the treatment of tyrosinaemia type I. NTBC inhibits the degradation of tyrosine at the level of 4-OH phenylpyruvate dioxygenase, and thus interferes before the formation of toxic metabolites including succinylacetone. NTBC is administered as a sustained therapy at a dose of about 1 mg/kg/day. The therapy is monitored by NTBC level controls and the lack of detection of succinyl acetone. NTBC levels of 40-60 µmol/l are targeted. In addition, a phenylalanine- and tyrosine-restricted diet is necessary.

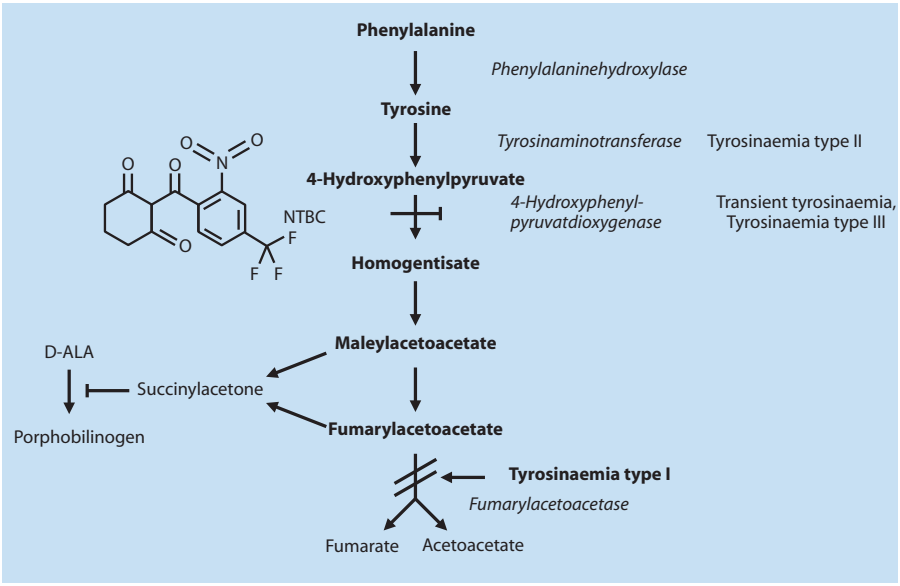


Figure 5.3: Tyrosine metabolism.

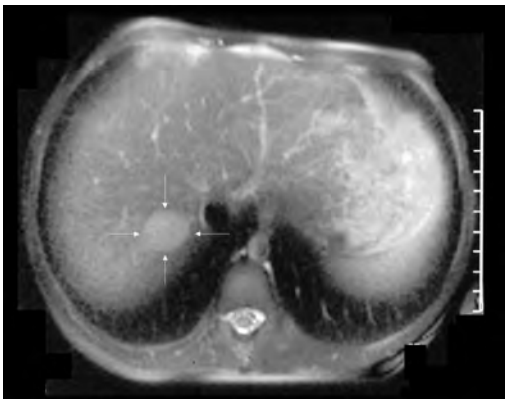


Figure 5.4: A 6-year-old girl with tyrosinaemia type I, untreated at this time. MRI of the liver, T2-signal: 2.5cm round, signal intense region (arrows) in segment 7 of the right lobe. Histology revealed a hepatocellular carcinoma.

Prognosis

With an early start of NTBC, prognosis is very good based on the available data. Therefore, liver transplantation, the former gold-standard of therapy, is not necessary anymore. Late onset of therapy leads to increased risk of hepatocellular carcinoma.

5.4. Disorders of methionine and homocysteine metabolism

Homocysteine is metabolised by two different pathways: remethylation and transsulphuration. Elevated levels of homocysteine can be caused by genetic defects in the enzymes involved in its metabolism or by nutritional deficiencies in cofactors of these enzymes, e.g. folic acid, vitamin B_{12}, and vitamin B_6.

Moderately elevated homocysteine levels up to 30 µmol/l are generally caused by an undersupply with folic acid, vitamin B_6 and/or vitamin B_{12} or by polymorphisms in the *MTHFR* gene. Moderate hyperhomocysteinaemia is considered a minor risk factor for the development of peripheral vascular, cerebrovascular and coronary vascular disease, and is associated with a slightly increased risk of venous thromboembolic events, particularly at a higher age. In homocysteine levels of more than 60 µmol/l, cobalamin metabolism defects must be considered as differential diagnosis to classical homocystinuria or severe MTHFR deficiency. Table 5.5 gives an overview of differential diagnoses in elevated homocysteine levels.

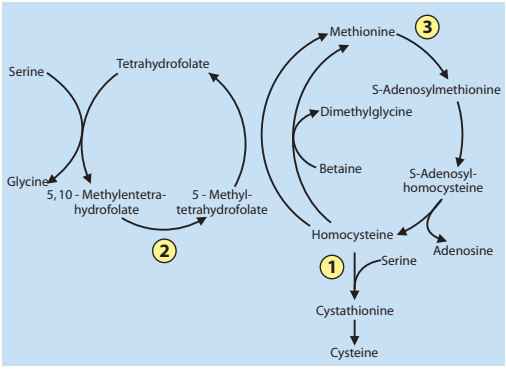


Figure 5.5: Homocysteine and methionine metabolism. 1=Cystathionine-β-synthetase deficiency, 2= MTHFR-deficiency, 3=methionine-S-adenosyltransferase deficiency.

	Homocysteine 15-60 µmol/l	Homocysteine >60 µmol/l
Methionine n/↓	• MTHFR variants • Dietary folate/vitamin B_6/vitamin B_{12} deficiency	• MTHFR deficiency • Cobalamin metabolism defects • Severe vitamin B_{12} deficiency
Methionine ↑	• Classical homocystinuria (CBS deficiency) • Methionine-adenosyl transferase I/III deficiency • S-adenosylhomocysteine hydrolase deficiency • Adenosinekinase deficiency	• Classical homocystinuria (CBS deficiency)

Tab. 5.5: Causes of elevated homocysteine levels.

5.4.1. Classical homocystinuria

Definition

Classical homocystinuria is an autosomal recessive disorder caused by cystathione-β-synthetase (CBS) deficiency.

Pathogenesis

Deficiency of CBS results in impaired degradation of homocysteine leading to an accumulation of homocysteine, methionine, and their S-adenosyl derivatives. At the same time there is a decrease in cysteine. Elevated homocysteine levels in plasma and tissues lead to damage to the eyes, bones, vascular system, and CNS, and alter platelet and endothelial cell function leading to a hypercoagulable state and causing thromboembolic events and premature arteriosclerosis.

Clinical spectrum

Patients are usually asymptomatic at birth. First clinical symptoms such as worsening myopia, lens dislocation, cataracts, osteoporosis and developmental delay/learning disabilities usually develop at school age. Patients often present marfanoid features and scoliosis and are prone to osteoporosis. Patients may suffer from seizures. The risk of thromboembolic events is markedly increased. Most frequently, thrombophlebitis or pulmonary embolism have been observed. This must also be considered if patients require surgery.

Diagnosis

In healthy individuals, plasma homocysteine levels are generally below 15 µmol/l. In patients with classical homocystinuria, plasma levels of homocysteine and methionine are increased. Homocysteine plasma levels are usually massively elevated, sometimes exceedig the upper limit of normal levels about 10-fold.

The cyanide-nitroprusside test in urine is positive in patients with classical homocystinuria.

Treatment

Treatment aims to decrease homocysteine levels as much as possible. About half of the patients with CBS deficiency respond to a treatment with pyridoxine (vitamin B_6). Most of these patients have some residual enzymatic activity. Dosage of pyridoxine is variable and has to be adjusted individually. As pyridoxine treatment can result in secondary folic acid deficiency, supplementation with folic acid is necessary. Patients not responding to pyridoxine are treated with a methionine-reduced and cysteine-rich diet. Betaine, which acts as a methyl donor in homocysteine remethylation resulting in an increased formation of methionine, is also used in long-term therapy.

Prognosis

Prognosis depends on the time therapy is commenced and on the reduction of homocysteine plasla levels that can be achieved in long-term treatment. The target level is <60 µmol/l (<20 µmol/l in the first 2 years of life). Symptoms can be mitigated by early diagnosis and consistent therapy. In late-diagnosed patients, the occurence of thromboembolic complications can be postponed by initiating pyridoxine treatment. Mortality mainly depends on the occurrence of premature thromboembolic complications such as strokes, thromboembolisms and myocardial infarctions.

5.4.2. Methylene tetrahydrofolate reductase (MTHFR) deficiency

Methylene tetrahydrofolate reductase (MTHFR) is necessary for the production of methyl tetrahydrofolate (MTHF). It functions as a co-substrate for the remethylation of homocysteine and methionine. Mutations in the *MTHFR* gene are of different severity.

Pathogenesis

Severe deficiency of MTHFR is the most common cause for inborn folic acid deficiency. In this condition, methylenetetrahydrofolate-bound folic acid cannot be recycled adequately. Deficiency of methyltetrahydrofolic acid results in disturbed conversion of homocysteine to methionine. Most relevant for the clinical outcome is the methionine deficiency in the brain causing severe neurological symptoms. The increased risk for thromboembolism is due to elevated homocysteine plasma levels.

Clinical spectrum

The clinical spectrum is wide. Usually first symptoms are present already during the first year of life, but variation is broad and age of onset varies between the neonatal period and adulthood. Often, patients suffer from severe neurological symptoms such as apnoea, seizures or progressive encephalopathy leading to severe developmental delay. In adulthood, psychiatric problems may be the first manifesting sign. In addition, vascular complications such as thromboembolism are frequently observed.

Severe MTHFR deficiency must be distinguished from frequently occuring *MTHFR* polymorphisms, which can lead to a mild reduction of enzyme activity and to moderately elevated homocysteine levels. Female carriers also carry a risk for early miscarriages.

Diagnosis

Hyperhomocysteinaemia with normal or decreased concentrations of methionine are found. Megaloblastic anaemia is not present. Folic acid levels can be decreased or normal.

Treatment

Betaine is applied therapeutically because betainmethyltransferase converts homocysteine to methionine. It is important to start treatment as early as possible to improve outcome. Treatment is monitored by measurement of methionine and homocysteine levels in plasma. Treatment aims at lowering homocysteine plasma levels below 60 µmol/l. Methionine has to be supplemented. Further therapeutic options include the administration of folic acid or folinic acid, pyridoxine, hydroxycobalamine or riboflavin (vitamin B_2), however, these compounds are less effective than betaine.

Prognosis

In severe forms of MTHFR deficiency, a positive development can only be achieved if treatment is started early.

5.4.3. Sulfite oxidase deficiency and molybdenum cofactor deficiency

Definition

Isolated sulfite oxidase deficiency has to be distinguished from molybdenum cofactor deficiency. Molybdenum cofactor forms the active site of xanthine oxidase and other human molybdoenzymes. Its deficiency leads to a clinical picture which is identical to isolated sulfite oxidase deficiency. In both cases inheritance is autosomal recessive.

Pathogenesis

Sulfite oxidase catalyses the last step of the metabolism of sulfur-containing amino acids. Its deficiency results in decreased sulfate and increased sulfite production. The latter is thought to be one of the main pathogenetic agents of the disease.

Clinical spectrum

Both disorders do not differ in their clinical presentation and typically present with treatment-refractory seizures in early childhood. Children present with severe psychomotor development delay, microcephaly and muscular hypotonia, which later progresses to spasticity. Lens dislocation is often observed in affected patients.

Diagnosis

Urine test strips for sulfite in fresh urine are positive. Increased excretion of taurine and sulfocysteine is found. Analysis of purine metabolites reveals increased xanthine/hypoxanthine in molybdenum cofactor deficiency.

Treatment and prognosis

Prognosis is generally poor, and affected children mostly die early. However, milder courses have also been described. Some patients with molybdenum cofactor deficiency have shown a good response to early therapy with cyclic pyranopterin monophosphate (cPMP), a precursor of the molybdenum cofactor.

5.5. Non-ketotic hyperglycinaemia

Definition

Non-ketotic hyperglycinaemia (NKH) is an autosomal recessively inherited disorder caused by a defect of the glycine-cleavage system. This mitochondrial enzyme complex consists of four proteins (P, T, H and L) and is localised in brain and liver.

Incidence

General incidence is unknown. In Finland it is approximately 1:12,000.

Pathogenesis

The defect results in increased concentrations of glycine in all body fluids, particularly in cerebral spinal fluid. By activation of glutaminergic N-methyl-D-aspartate (NMDA)-receptors, glycine can cause severe convulsions and exocitotoxic effects in the brain.

Clinical spectrum

NKH usually already becomes manifest in newborns (mostly 2nd to 8th day of life) with lethargy, hypotonia, myocloni and apnoea. The typical course of the disease is progression to severe epileptic encephalopathy with convulsions which are barely responsive to any medical treatment. Psychomotor development is usually very limited. Onset may occur after the newborn period in about 20% of patients. In these cases clinical symptoms may be highly variable with non-specific neurological deterioration. In addition, atypical forms and transient forms are also known.

Diagnosis

Diagnosis is based on an increased ratio of CSF glycine to plasma glycine (>0.08, reference limit <0.02). Analysis of organic acids in urine excludes ketotic hyperglycinaemia (organic aciduria) as a cause of increased glycine. An EEG shows a typical "burst–suppression" pattern. The glycine cleavage system can be found in the liver, brain and kidneys, amongst other organs.

Treatment

No satisfactory treatment is available. All therapeutical approaches could not essentially influence the natural course of this disease. Sodium benzoate has been introduced with the idea to decrease plasma glycine by conjugation and excretion, leading to improvement of symptoms. It seems that this particular approach might be able to reduce the number of convulsions in some patients, but has no impact on the clinical outcome. Dextromethorphan is given experimentally to block NMDA receptors. However, even the combination of both drugs has improved the development only in single affected patients. A low-protein diet also has not shown any long-term treatment success in lowering glycine levels.

Prognosis

Many patients with typical neonatal manifestation die during the first days or weeks of life. Often, weaning from mechanical ventilation is difficult or even impossible. Patients surviving the neonatal period often suffer from treatment-refractory convulsions and myoclonia. Only minimal gain of psychomotor development can be expected.

5.6. Urea cycle disorders

Definition

Inborn errors of the urea cycle lead to disturbed detoxification of ammonia (NH_3), which is produced in the catabolism of amino acids (☞ Figure 5.6).

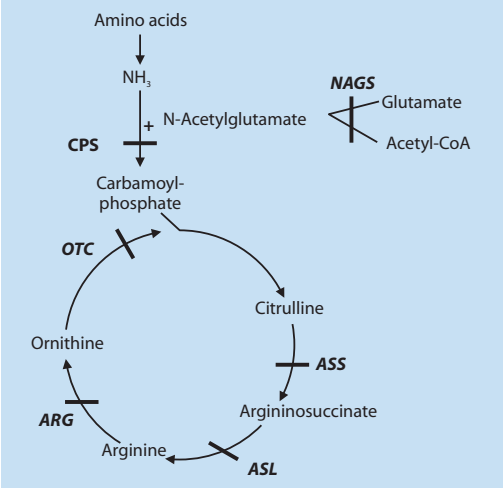


Figure 5.6: Urea cycle. OTC=Ornithine-transcarbamylase, CPS=Carbamoylphosphate synthetase, NAGS=N-acetylglutamate synthetase, ASS=Argininosuccinate synthetase, ASL=Argininosuccinate lyase, ARG=Arginase.

Incidence

The cumulative incidence of urea cycle disorder is 1:8,000. Ornithine transcarbamylase (OTC) deficiency is the most frequent urea cycle defect, whereas NAGS deficiency and arginine deficiency are the rarest.

Pathogenesis

Ammonia is metabolised to carbamoylphosphate by action of carbamoylphosphate synthetase (CPS). CPS first has to be activated by N-acetylglutamate. N-acetylglutamate is produced from glutamate with the help of N-acetylglutamate synthetase (NAGS). The urea cycle itself comprises four enzymatic reactions. These enzymes are ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL) and arginase (ARG).

The mitochondrial ornithine transporter and mitochondrial aspartate transporter (citrine) carry intermediates of the urea cycle between mitochondria and cytosol. Defects of these two transporters cause a similar clinical picture as defects of the enzymes of the urea cycle itself.

Inheritance of OTC deficiency is x-chromosomal recessive. The other enzyme deficiencies follow an autosomal recessive inheritance.

Clinical spectrum

Urea cycle disorders manifest at different ages. Manifestation is most common in the neonatal period. After an uncomplicated pregnancy and birth, affected children present with feeding problems, vomiting, lethargy, irritability and tachypnoea indicative of encephalopathy. Clinical symptoms worsen quickly and progress to coma. Milder forms may manifest during infancy with developmental delay, irritability and behavioural disorders. Further symptoms are failure to thrive, refusal to eat and recurrent vomiting, and frequently hepatopathy with elevated transaminases and possible clotting dysfunction. During infections or other situations triggering protein catabolism, also patients with milder phenotypes may develop encephalopathy, coma, and neurological symptoms. Manifesting signs in adolescence or adulthood are often psychomotor impairment, behavioural disorders or other neurological and psychiatric symptoms. Protein catabolism can induce encephalopathic and potentially life-threatening crises at any age.

Diagnosis

Analysis of plasma amino acids is the primary diagnostic test. In addition to elevated ammonia, an elevation of plasma glutamine is the most sensitive parameter of insufficient urea synthesis and the presence of a urea cycle disorder.

Urea cycle disorders typically present with an accumulation of glutamine and alanine. In the presence of citrullinaemia, arginine succinic acid and arginase deficiency, the diagnosis can be made using the specific amino acid profile. The amino acid pattern is unspecific in the other, more proximal, defects. Urinary excretion of orotic acid is massively increased in OTC deficincy and may be increased in the other urea cycle disorders apart from NAGS and CPS deficiency. The diagnosis is confirmed by molecular genetic analysis. Prenatal diagnosis exists for all defects.

Treatment

An acute hyperammonaemic crisis is a life-threatening condition and requires immediate treatment due to the risk of developing cerebral oedema. De-

Disease	Nomen-clature	Plasma amino acids	Orotic acid in urine
Carbamoylphosphate synthetase deficiency	CPS	Glutamine, alanine ↑ citrulline, arginine ↓	Normal
N-acetylglutamate synthetase deficiency	NAGS	Glutamine, alanine ↑	Normal
Ornithine-transcarbamylase deficiency	OTC	Glutamine, alanine ↑ Citrulline, arginine ↓	Highly increased
Citrullinaemia, ASS deficiency,	ASS or CIT1	Citrulline ↑↑ Arginine ↓	Increased
ASL deficiency	ASL	Citrulline↑ Argininosuccinic acid↑ Arginine ↓	Increased
Hyperargininaemia, arginase deficiency	ARG	Arginine ↓	Increased
Hyperammonaemia-hyperornithinaemia-homocitrullinuria syndrome	HHH	Ornithine ↑↑ (in newborns also normal) (Homocitrulline ↑ in urine)	
Citrullinaemia type II (citrin deficiency)	CIT2	Citrulline ↑↑ Arginine ↓	

Table 5.6: Diagnostic markers in urea cycle disorders and related defects of ammonia detoxification.

tailed information on emergency treatment of hyperammonia is given in Chapter 3.1.

Long-term treatment consists of:

- Reduction of dietary protein intake and supplementation with synthetic amino acid preparations which are rich in essential amino acids.
- Ensuring sufficient energy intake to maintain anabolism.
- Supplementation with arginine or citrulline (not in arginase deficiency)
- Ammonia scavenging drugs (sodium benzoate, sodium phenylbuyrate)
- Carglumic adid/N-acetylglutamate in NAGS deficiency

Table 5.7 gives an overview of the specific drug treatment options for urea cycle disorders and related defects of ammonia detoxification.

Monitoring

Patients are monitored for growth and development. Ammonia and plasma amino acids need to be checked on a regular basis. Plasma ammonia levels should be below 80 µmol/l (136 µg/dl), plasma glutamine levels should not exceed 1000 µmol/l (1700 µg/dl). Arginine plasma levels should be in the high normal range, and essential amino acids should be within the normal range three to four hours after a meal. Monitoring of electrolytes is necessary under treatment with sodium benzoate or sodium phenylbutyrate.

Prognosis

Prognosis depends on the maximum level and duration of hyperammonaemia. Severe neonatal manifestations of OTC, CPS or NAGS deficiency are often lethal.

Distinctive characteristics of individual enzyme deficiencies

▶ Ornithine-transcarbamylase deficiency

OTC deficiency is inherited in an X-linked manner. Males are usually severely affected. Heterozygous females may become symptomatic at any age depending on the degree of X-inactivation (lyonisation). Encephalopathic crises, neurological, neurodegenerative or psychiatric abnormalities may be signs of OTC deficiency and intermittent hyperammonaemia in females. Female relatives of a patient with OTC deficiency should be tested for OTC deficiency by molecular analysis as soon as the mutation of the index patient is delineated.

Enzyme defect	Long-term drug treatment	Dose
CPS	Sodium benzoate	250 mg/kg body weight per day max. 12 g per day
	Sodium phenylbutyrate	<20 kg: ≤250 mg/kg body weight per day >20 kg: 5 g/m² per day max. 12 g per day
	L-Arginine	<20 kg: 100-200 mg/kg body weight per day >20 kg: 2,5-6 g/m² per day max. 6 g per day
	L-Citrulline	100-200 mg/kg body weight per day max. 6 g per day
NAGS	Carglumic acid/N-acetylglutamate	10-100 mg/kg body weight per day
OTC	Sodium benzoate	250 mg/kg body weight per day max. 12 g per day
	Sodium-phenylbutyrate	<20 kg: ≤250 mg/kg body weight per day >20 kg: 5 g/m² per day max. 12 g per day
	L-Arginine	<20 kg: 100-200 mg/kg body weight per day >20 kg: 2,5-6 g/m² per day max. 6 g per day
	L-Citrulline	100-200 mg/kg body weight per day max. 6 g per day
ASS	Sodium benzoate	250 mg/kg body weight per day max. 12 g per day
	Sodium phenylbutyrate	<20 kg: ≤250 mg/kg body weight per day >20 kg: 5 g/m² per day max. 12 g per day
	L-Arginine	<20 kg: 100-300 mg/kg body weight per day >20 kg: 2,5-6 g/m² per day max. 6 g per day
ASL	Sodiumbenzoate	250 mg/kg body weight per day max. 12 g per day
	L-Arginine	<20 kg: 100-300 mg/kg body weight per day >20 kg: 2,5-6 g/m² per day max. 6 g per day
ARG	Sodium benzoate	250 mg/kg body weight per day max. 12 g per day
	Sodium phenylbutyrate	<20 kg: ≤250 mg/kg body weight per day >20 kg: 5 g/m² per day max. 12 g per day
HHH	Sodium benzoate	250 mg/kg body weight per day max. 12 g per day
	Sodium phenylbutyrate	<20 kg: ≤250 mg/kg body weight per day >20 kg: 5 g/m² per day max. 12 g per day
	L-Arginine	<20 kg: 100-200 mg/kg body weight per day >20 kg: 2,5-6 g/m² per day max. 6 g per day
	L-Citrulline	100-200 mg/kg body weight per day max. 6 g per day

Tab. 5.7: Long-term drug treatment of urea cycle disorders and related defects of ammonia detoxification.

▶ Hyperargininaemia

Patients with the extremely rare arginase deficiency develop progressive spastic diplegia, which initially is suggestive of cerebral palsy. In the further course of the disease, seizures, ataxia and dystonia are observed. Severe hyperammonaemia occurs less frequently than in the other urea cycle defects, however, moderate hyperammonaemia and acute encephalopathy may occur.

▶ HHH syndrome (hyperammonaemia, hyperornithinaemia, homocitrullinuria)

HHH syndrome is due to an impaired transport of ornithine between cytoplasm and mitochondria. Clinical symptoms comprise encephalopathy and a coagulation disorder.

▶ Citrullinaemia type II

Citrullinaemia type II is an autosomal recessive disease mainly occuring in the Japanese population. Deficiency of the citrin transporter causes transient neonatal cholestasis with hepatic dysfunction of varying severity in the newborn. Adults present with with recurrent episodes of hyperammonaemia with neuropsychiatric symptoms and can develop liver cirrhosis. As opposed to other urea cycle disorders, a high-protein diet with reduced carbohydrate intake and avoidance of galactose is indicated, a form of nutrition that most patients intuitively prefer.

5.7. Organic acidurias

Organic acidurias are characterised by disturbances in the intermediary metabolism of the branched-chain amino acids with accumulation of characteristic carbonic acids. Three types of clinical manifestation can be distinguished:

- neonatal form
- chronic-intermittent form
- chronic-progressive form

Diagnosis is based on the excretion of characteristic organic acids in the urine or by the typical pattern of carnitine compounds in the acylcarnitine profile. Diagnosis should be confirmed by enzyme analysis or mutational analysis of the corresponding genes.

Some examples of the most important and most frequent disorders of this large group of metabolic diseases will be described in more detail in the following sections.

5.7.1. Propionic aciduria

Definition

Propionic aciduria (PA) is caused by an autosomal recessively inherited deficiency of propionyl-CoA carboxylase (☞ Figure 5.2).

Pathogenesis

Accumulation of propionyl-CoA causes inhibition of different metabolic pathways, such as pyruvate dehydrogenase complex, N-acetyl-glutamate synthetase (NAGS) or the glycine-cleavage system.

Incidence

Incidence is approximately 1:100,000.

Clinical spectrum

Most patients develop clinical symptoms within the first week of life. At this time, a state of catabolism dominates. The secondary inhibition of the urea cycle causes hyperammonaemia which may lead to cerebral oedema and encephalopathy. Affected newborns manifest with vomiting, lethargy, and coma. Next to hyperammonaemia, metabolic acidosis, ketosis and elevated lactate are usually found. In addition, the following laboratory abnormalities can be present: hypoglycaemia, neutropenia, thrombopenia or pancytopenia. Another typical complication of PA is the development of acute pancreatitis.

Diagnosis

The acylcarnitine profile reveals increased levels of propionylcarnitine. The analysis of plasma amino acids shows elevated glycine. The analysis of organic acids in the urine shows increased urinary 3-OH-propionic acid, propionylglycine, methylcitrate and tiglylglycine. Diagnosis is confirmed by enzyme analysis in fibroblasts.

Treatment

The aim of emergency treatment is to eliminate toxic metabolites as soon as possible. Primary target is the treatment of hyperammonaemia. If the ammonia concentration exceeds >400 µmol/l,

haemodialysis or haemofiltration have to be considered. In the scenario of an emergency situation an immediate stop in protein intake is necessary. In addition, high glucose infusion and insulin administration are important (☞ Hyperammonaemia, Chapter 3.1). Enhanced diuresis and intravenous carnitine application (100 mg/kg per day) are additional therapeutical approaches.

Besides the maintenance of a sufficient carnitine intake, a life-long low-protein diet is needed. Protein intake is calculated on the basis of the minimum age-related requirement. In some patients the intake of natural protein is very low so that an amino acid mixture free of isoleucine, methionine, threonine and valine has to be introduced. Caloric intake must be adequate. Fasting must be avoided. Most patients need gastric tube feeding to assure adequate nutrition. In the first year of life patients tend to suffer from recurrent episodes of metabolic decompensation, starting with vomiting. For long-lasting gastric tube feeding a percutaneous enterogastrostomy may be reasonable. Metronidazole and/or colistin may be temporarily administered to reduce the production of propionate by the intestinal flora.

For intercurrent diseases accompanied by fever, vomiting, diarrhoea or refusal of nutrition it is important to avoid catabolism. Oral feeding of maltodextrin solution will facilitate intake of additional calories. Recurrent vomiting or worsening of the clinical condition requires admission to hospital and i.v. treatment. In relation to the clinical condition, protein intake has to be reduced or stopped for a short-term period.

Prognosis

Psychomotor development mainly depends on duration and extent of initial hyperammonaemia. Patients with neonatal manifestation are often severely disabled. Intellectual disability and motor development delay with extrapyramidal movement disorder are often present. Therefore, special attention should be given to early intervention in these patients.

5.7.2. Methylmalonic aciduria

Definition

Methylmalonic aciduria (MMA) is similar to PA in many different aspects. The defect is localised one step further downstream in the metabolism of branched-chain amino acids, caused by a deficiency of methylmalonyl-CoA mutase (MCM) (☞ Figure 5.3). In addition to the primary deficiency of this enzyme, the loss of the co-factor vitamin B_{12} (cobalamine) leads to variant forms of MMA. The inheritance pattern of the enzyme deficiency is autosomal recessive.

Incidence

Frequency of MMA is about 1:50,000.

Pathogenesis

Enzyme deficiency causes accumulation of methylmalonyl-CoA leading to increased concentrations of methylmalonic acid. Secondary suppression of propionyl-CoA carboxylase activity results in elevated levels of propionyl-CoA metabolites.

Clinical spectrum

Clinical symptoms in neonates are similar to those described in patients with PA (☞ Chapter 5.7.1). Hyperammonaemic coma and secondary complications are leading symptoms. MMA can lead to metabolic decompensation, e.g. in cases of infections, high protein intake or catabolism.

Diagnosis

Diagnosis is confirmed by an abnormal acylcarnitine profile (increased propionylcarnitine) and very high excretion of methylmalonic acid in the urine. Subsequently, excretion of methylmalonic acid is re-evaluated after parenteral treatment with vitamin B_{12} to identify vitamin B_{12}-responsive forms. Confirmation of diagnosis and determination of subforms (Mut^0: no enzyme activity or Mut^-: detectable enzyme activity) can be achieved in cultured fibroblasts.

Treatment

Emergency and long-term treatment are carried out in analogy to propionic aciduria (☞ Chapter 5.7.1). Next to carnitine treatment, a diet with reduction of natural protein is introduced to the patient. To avoid protein deficiency a special amino acid mixture (without isoleucine, valine, methionine and threonine) is frequently added to this diet. Patients responding to a high dose of vitamin B_{12} are treated with vitamin B_{12} injections (e.g. 1-2mg i.m./week). In these cases, a higher intake of protein can usually be tolerated.

Prognosis

In MMA patients psychomotor developmental delay is usually less severe than in patients with propionic aciduria. Patients may be completely normal or mildly intellectually disabled under adequate treatment. However, encephalopathic crises have been also observed in patients with MMA resulting in severe irreversible neurological damage (intellectual disability, extrapyramidal movement disorder). High urinary methylmalonic acid clearance may lead to chronic deterioration of renal function. This may lead to end-stage renal failure at the end of the second decade. For the reliable assessment of the renal function, only the glomerular filtration rate is suitable in the presence of this disease. Patients with a vitamin B_{12}-responsive form have a much better prognosis than patients with a vitamin B_{12}-unresponsive form.

5.7.3. Isovaleric aciduria

Definition

The underlying cause of isovaleric aciduria (IVA) is an autosomal-recessively inherited deficiency of isovaleryl-CoA-dehydrogenase.

Incidence

1:100,000 in Germany.

Pathogenesis

The enzyme deficiency leads to accumulation of isovaleryl-CoA derivates such as the toxic isovaleric acid.

Clinical spectrum

Patients with the acute neonatal form of IVA present with encephalopathy including metabolic acidosis and hyperammonia on the second or third day of life. The newborns may develop the typical smell of "sweaty feet". In the chronic intermittent form, onset occurs later in childhood with repeated episodes of vomiting, lethargy and even coma. There are also individuals with a mild, possibly asymptomatic manifestation of the condition, who only became apparent after the introduction of newborn screening for IVA and have lower metabolite accumulations.

Diagnosis

IVA belongs to the diseases diagnosed by neonatal screening in Germany. The acylcarnitine profile shows increased concentrations of isovalerylcarnitine (C5) in the blood. Analysis of organic acids in urine shows an increased excretion of isovalerylglycine and 3-OH-isovaleric acid. Mutation analysis of the *IVD* gene may be performed if necessary. The biochemically mild form of IVA is often associated with the *IVD* gene mutation c.932C>T (p.A282V).

Treatment

Main principle of treatment is the significant reduction of toxic compounds. This can be achieved by reduction of natural protein intake and substitution of L-carnitine (50-100 mg/kg per day). Alternatively or in some cases additionally, L-glycine can be administered. As a result of the high affinity of isovaleryl-CoA to glycine-N-acylase, treatment with glycine (150-300 mg/kg per day) leads to the formation of N-isovalerylglycine instead of toxic isovaleric acid. Catabolic states should be avoided. In the biochemically mild form of IVA, no dietary therapy is recommended, but the administration of carnitine is initiated.

Prognosis

Prognosis is usually good in individuals receiving early and adequate treatment in order to avoid metabolic crises.

5.7.4. Glutaric aciduria type I

Definition

Glutaric aciduria type I (GA-I) is caused by impaired degradation of lysine, hydroxylysine and tryptophan due to a deficiency of glutaryl-CoA dehydrogenase.

Incidence

Incidence is estimated at about 1:130,000.

Pathogenesis

There is evidence that organic acids (glutaric acid or glutaryl-CoA and/or 3-hydroxyglutaric acid) may be involved in the neuropathogenesis, and a markedly increased cerebral accumulation of these metabolites is found. However, different mechanisms involved in this process have been discussed (e.g. excitotoxicity, mitochondrial dysfunction, oxidative stress, vasculopathy, disruption of the blood–brain barrier as well as cerebral *de novo* synthesis and accumulation of dicarboxylic acids).

Clinical spectrum

In untreated patients a metabolic crisis often occurs during the first two years of life (median age of first crisis: 9 months), usually during catabolic states of febrile illnesses. This crisis may lead to severe neurological deterioration. Subsequent cerebral imaging often demonstrates variable damage of the basal ganglia. Affected patients show a dystonic-dyskinetic movement pattern and pronounced hypotonia of the trunk. In addition, a severe loss of motor developmental milestones is found after such a crisis. Neurological problems such as seizures might occur.

Mental impairment is often less severe than expected from the first impression. Loss of oral motor function often compromises verbal communication. Frequently, oral food intake and swallowing is impaired and patients need continuous tube feeding.

Prior to an encephalopathic crisis patients may present with macrocephaly (found in 70-80% of all patients) or a rapid increase of the head circumference between 3 and 6 months of age and mild clinical symptoms. Neuroradiological evaluation may demonstrate fronto-temporal atrophy in many symptomatic patients, but also in asymptomatic individuals with GA-I (☞ Figure 5.7).

Apart from this classical course, rarely milder types of GA-I have been described:

- Slow neurological deterioration without encephalopathic crisis
- Neurological late onset in adults with leucoencephalopathy
- Neonatal manifestation with non-specific clinical deterioration
- Presumptive asymptomatic course

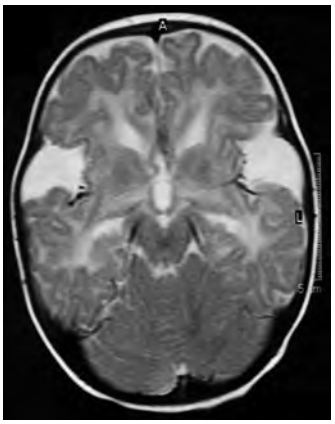


Figure 5.7: 13-month-old girl with glutaric aciduria type I. MRI of the head, T2-sequences: symmetrical enlargement of frontotemporal CSF spaces, large sylvian fissures and hyperintensity of the white matter and subcortex.

Diagnosis

GA-I can be diagnosed by newborn screening. Diagnosis results from detection of increased glutarylcarnitine (C5DC) in dried blood spots. It is necessary to calculate different glutarylcarnitine ratios. Diagnosis is supported by the presence of 3-OH-glutaric acid in urine (stable isotope dilution!). Diagnostic difficulties may occur in so-called "low excreters". Some affected children have not been identified by selective metabolic screening due to an absence of 3-OH-glutaric acid in the urine. Enzymatic investigations in cultured fibroblasts or lymphocytes and mutation analysis of the *GCDH* gene are therefore recommended to confirm the diagnosis.

Treatment

Oral carnitine intake (100 mg/kg body weight per day; from age 6 years 50 mg/kg body weight per day) and dietary lysine restriction are particularly important for early diagnosed, neurologically asymptomatic patients. Lysine restriction should be maintained in presymptomatic individuals at least until 6 years of life. Later in life, excessive protein intake has to be avoided and food with low lysine content should be consumed. In contrast, the therapeutic benefit of dietetic treatment in neurologically affected patients is limited. Carnitine supplementation may have a positive effect on the degree of disability and survival and should be maintained for life. Riboflavine in general has no significant effect on the natural course of the disease. However, in single individuals a positive biochemical effect might still be verified.

The prevention of any encephalopathic crisis is crucial, in particular during the first 6 years of life. This is essential for all asymptomatic patients diagnosed by newborn screening programmes. Since life-threatening crises usually occur during periods of catabolism like febrile illness, surgery or vaccinations, the highest precaution is required in these situations. Parents should have an emergency plan, which gives precise instructions as to when a physician is to be consulted and what measures need to be taken to avoid a crisis. At an early stage, sufficient calorie intake should be ensured by frequent meals and administration of maltodextrin. If a catabolic state cannot be reliably avoided, hospital admission and administration of intravenous glucose or maltodextrin via a gastric tube are carried out.

▶ Management of movement disorders

As in almost all secondary dystonias, the therapeutic benefit of pharmacotherapy may only be satisfactory in individual cases. The use of baclofen and diazepam as monotherapy or as a combination therapy, and of trihexyphenidyl is common. Intrathecally administrated baclofen can be used in severe dystonia. The use of botulinum toxin or other medication may also be useful in individual cases.

Prognosis

With early diagnosis and consequent therapy, encephalopathic crises can usually be avoided, which can lead to age-appropriate mental and motor development. The long-term prognosis with regard to the development of milder symptoms of patients diagnosed by neonatal screening is still to be determined prospectively.

Life expectancy is significantly reduced after the occurrence of an encephalopathic crisis (approximately 50% survival probability after 25 years). Loss of important physiological functions (e.g., active food intake, mobility) is prognostically unfavourable.

5.8. Disorders of biotin metabolism

Incidence

Biotinidase deficiency: about 1:30,000.

Pathogenesis

Biotin is a cofactor of four different carboxylases. Multiple carboxylase (MC) deficiency occurs:

- In rare cases of acquired biotin deficiency
- In cases of biotinidase deficiency resulting in impaired recycling of endogenous biotin and impaired release of alimentary biotin from the protein binding
- In cases of holocarboxylase synthetase (HCS) deficiency. HCS catalyses the conversion of inactive apocarboxylases into active holocarboxylases

The four carboxylases comprise: acetyl-CoA carboxylase (ACC), pyruvate carboxylase (PC), propionyl-CoA carboxylase (PCC) and 3-methylcrotonyl-CoA carboxylase (MCC) (☞ Figure 5.8). ACC catalyses the conversion of acetyl-CoA into malonyl-CoA and is important for fatty acid synthesis. Pyruvate carboxylase is a key enzyme of gluconeogenesis. PCC and MCC play an important role in amino acid catabolism. Deficiency of these enzymes results in a number of biochemical and clinical symptoms.

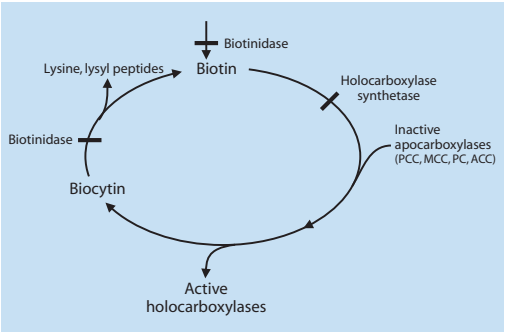


Figure 5.8: The biotin cycle.

Clinical spectrum

Clinical symptoms in multiple carboxylase deficiency are highly variable. Characteristic features are: metabolic acidosis, neurological symptoms such as muscular hypotonia, epileptic seizures, ataxia and lethargy, dermatological symptoms such as alopecia and rash and impaired immunological functions. While the early-onset phenotype of holocarboxylase synthetase deficiency presents with such a variety of symptoms within the first hours and days of life, biotinidase deficiency is more difficult to diagnose clinically. Neurological symptoms usually present first, however, the full picture of biotinidase deficiency can only be identified at 7-8 weeks of life. Delayed diagnosis results in psychomotor impairment. Clinically, later-onset holocarboxylase synthetase deficiency cannot be distinguished from biotinidase deficiency. Episodes of acute clinical deterioration are mostly induced by infections.

Diagnosis

Diagnostic biochemical markers in blood are increased lactate, increased ammonia and increased alanine. Organic acid analysis in urine reveals increased excretion of lactate, 3-OH-isovaleric acid, methylcrotonylglycine and methylcitrate. Biotinidase deficiency is confirmed by enzyme analysis in dried blood spots or plasma. Biotinidase deficiency is a target disease of newborn screening: severe biotinidase deficiency is suspected with residual enzyme activity is <10%; when a residual activity is 10-30%, partial biotinidase deficiency is suspected. In cases of suspected holocarboxylase synthetase deficiency, the diagnosis can be confirmed by measuring enzyme activity in lymphocytes or fibroblasts.

Treatment

Both enzyme defects are successfully treated with oral biotin in pharmacological doses. In biotinidase deficiency, the daily dose is 5-10 mg. Supplementation with biotin in partial biotinidase deficiency is controversial, however, it has been shown to have positive effects in several studies. In holocarboxylase synthetase deficiency, the biotin dose has to be adjusted individually and may be 10-20 (-40) mg per day. Protein restriction is generally not necessary, however, there are severe forms of HCS deficiency that clearly benefit from a protein-restricted diet. Patients suffering from acute metabolic decompensation (e.g. during infections) require, in addition to supplementation with biotin, an emergency regimen according to the emergency treatment in disorders of organic acids.

Monitoring

In case of biotin responsiveness, biochemical disease markers are all normalised.

Prognosis

Prognosis is excellent if treatment starts early and there is a good response to biotin. If biotin supplementation is adequate, there are no clinical and biochemical abnormalities. However, if the therapy starts too late, irreversible symptoms may occur, e.g. loss of vision or hearing.

5.9. Mitochondrial disorders

Definition

Classical mitochondriopathies are primary disorders of the pyruvate oxidation pathway. These include in particular biochemical defects in the respiratory chain, the oxidative phosphorylation system (OXPHOS) or the pyruvate dehydrogenase complex. There are also disorders in the area of mitochondrial cofactor metabolism (e.g., primary coenzyme Q_{10} biosynthesis defects, thiamine metabolism disorders). These must be differentiated from so-called secondary mitochondrial diseases in which, e.g., toxic metabolites lead to an indirect disturbance of OXPHOS function (☞ Figure 5.9).

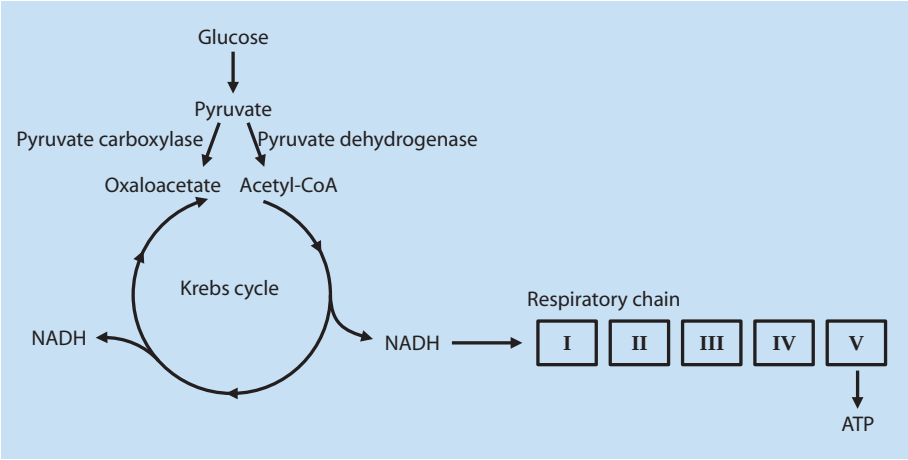


Figure 5.9: Pyruvate oxidation, tricarboxylic acid cycle and respiratory chain.

Various definitions are used for this group of diseases. The often used term "mitochondrial encephalomyopathy" suggests that the CNS and the skeletal muscle are frequently affected. Overall, disturbances in mitochondrial energy metabolism can strike almost any organ system. Terms such as "respiratory chain defects" and "OXPHOS diseases" are also used synonymously.

Frequency

Minimum prevalence of about 1-1.5:10,000.

Pathogenesis

The causes of cell and tissue damage in mitochondrial disorders are manifold and also vary depending on the underlying genetic defect. The main factors involved are reduced mitochondrial ATP production, oxidative stress, depolarisation of the mitochondrial membrane potential and disruption of cellular calcium homeostasis.

Clinical spectrum

Patients with mitochondrial disorders present with various and often non-specific clinical features. Functional impairment is mainly observed in organs with high energy requirement such as the brain (i.e. delayed cognitive/motor development, lethargy, ataxia, tetraspasticity, dystonia, epilepsy), skeletal muscles (muscular hypotonia, exercise-induced muscle weakness, ptosis), heart (cardiomyopathy) and eye (retinitis pigmentosa, optic atrophy). The clinical spectrum of mitochondriopathies ranges from pre- and neonatal diseases with a rapidly fatal course to manifestations in the late adult age, presenting, e.g., as muscle weakness or eye motility disorders. Some of the disorders can be classified as so-called mitochondrial syndromes by a characteristic constellation of symptoms and findings (☞ Table 5.8).

Diagnosis

There are no clinical features which are specific for classical mitochondriopathy. However, certain details of a patient history can raise the suspicion of mitochondriopathy, for example, signs of so-called regression or loss of already aquired abilities. In addition, episodic clinical deterioration, e.g. triggered by infection, may suggest a mitochondriopathy. Also important is the complete family history (consanguinity of the parents, previous miscarriages, etc.).

Baseline investigations

Baseline investigations are primarily performed to rule out differential diagnoses. Most laboratory findings in mitochondrial diseases are unspecific. For example, chronic lactate acidaemia and/or acute lactate acidosis or a lactate elevation in the cerebrospinal fluid may be suggestive. Basic laboratory testing should include the following parameters:

- **Blood:** Blood count, liver transaminases, retention parameters, electrolytes, glucose, creatine kinase, lactate, pyruvate, amino acids (alanine), acid–base status, acylcarnitines, CDG tests

Syndrome	Abbr.	Disease-specific symptoms	Diagnostic approach	Inheritance
Alpers-Huttenlocher syndrome	Alpers	Fast progressing neurodegenerative disorder with onset in early infancy, epilepsy, impaired liver function, microcephaly, cortical atrophy	Candidate gene analysis (*POLG*)	Autosomal recessive
Barth syndrome	Barth	Dilating cardiomyopathy, recurrent infections, failure to thrive, granulopenia, 3-methylglutaconic aciduria (type II)	Candidate gene analysis (*TAZ*)	X-chromosomal recessive
Chronic-progressive external ophthalmoplegia	CPEO	Ptosis, progressive external ophthalmoplegia	mtDNA molecular analysis (deletions), in case of multiple deletions often nuclear genes involved	Sporadic, autosomal-dominant
mtDNA-depletion syndrome	(Depletion syndrome)	Variable (myopathy; hepatocerebral syndrome)	Quantification of mtDNA in affected tissues, based on these results molecular analysis	Autosomal recessive
Kearns-Sayre syndrome	KSS	Ptosis, progressive external ophthalmoplegia, ataxia, retinitis pigmentosa, conduction defects (ECG), cardiomyopathy, basal ganglia calcifications, signal intensities in white matter region, elevated CSF protein	mtDNA molecular analysis (deletions)	Sporadic
Leigh syndrome, DD: Leigh-like syndrome	Leigh	Neurodegenerative disorder with onset in early infancy, ataxia, brain stem symptoms, specific MRI findings	Candidate gene analysis (however already >75 different genes known); Possibly exom sequencing	Autosomal recessive, maternal, X-chromosomal recessive
Leber's hereditary opticus atrophy	LHON	Painless loss of vision, optic nerve atrophy	mtDNA molecular analysis (point mutations in complex I-gens - *MTND1, MTND6, MTND4*)	Maternal/ sporadic
Mitochondrial encephalomyopathy with lactic acidosis and "stroke-like" episodes	MELAS	Onset generally in 2nd decade, migraines, stroke-like episodes (often hemianopsy), microsomia, stroke-like lesions on MRI	mtDNA molecular analysis (point mutations e.g. in *MTTL1, MTND6, MTTQ*)	Mostly paternal, rarely sporadic
Mitochondrial neurogastrointestinal encephalomyopathy	MNGIE	Myopathy, episodes of gastrointestinal pseudoobstruction, neuropathy, often ptosis and CPEO, typical MRI changes, RRF possible, multiple deletions or depletion of mtDNA	Biochemical testing: Thymidine phosphorylase activity, blood and urine thymidine; molecular analysis *ECGF1* (22q13.32-qter)	Autosomal recessive
Neuropathy, Ataxia and Retinitis pigmentosa	NARP	Ataxia, loss of vision, retinitis pigmentosa, neuropathy	mtDNA molecular analyis (point mutation T8993G/C in *MTATP6*)	Maternal/ sporadic
Pearson-Marrow-Pancreas syndrome	Pearson	Anaemia, malabsorption, microsomia, exocrine pancreas insufficiency, refractory sideroblastic anaemia, later development of KSS possible	mtDNA molecular analysis (deletions)	Sporadic

Table 5.8: A selection of mitochondrial syndromes.

- **Urine:** Organic acids
- **CSF:** Lactate, protein, glucose, alanine, cell count/differentiation

Biochemical investigations

A biochemical diagnosis in mitochondrial diseases is usually performed via muscle and/or skin biopsies. However, other tissues (e.g., liver or heart muscle) can also be examined. The biochemical analysis of fresh muscle tissue as a gold standard applies in principle. Alternatively, shock-frozen tissue can also be examined, but the information content will be reduced. In the analysis of a fresh muscle biopsy many factors have to be considered (transport conditions, transport time, etc.). The amount of tissue is critical (e.g., difficult in small neonates or infants). The biopsy has to be carried out in general anaesthesia (local anaesthetics influence the measurements). Skin biopsies are much simpler to perform (on an outpatient basis) and living tissue is obtained (cells can be cultivated and frozen, advantages for scientific analyses, etc.). However, many OXPHOS defects do not show up in fibroblasts, so that mitochondrial disease is by no means excluded in the case of an inconspicuous finding.

Genetic investigations

The exact diagnosis of a mitochondriopathy is made by molecular genetic testing. In classical mitochondrial syndromes the disorder can usually be clarified by means of candidate gene analysis. However, many children present with rather unspecific clinical symptoms and a large number of potentially affected genes need to be analysed. In this context, exome or genome sequencing has gained importance in recent years.

In mitochondriopathies the so-called bigenomic organisation has to be considered. This means that proteins of the OXPHOS system are partly encoded by the nuclear DNA as well as by the mitochondrial DNA (mtDNA). This makes genetic testing complex. This can particularly complicate prenatal testing, since the so-called heteroplasmic degree of the mutations (i.e., the ratio of normal mtDNA to mutated mtDNA) can vary greatly in a tissue-specific manner

In addition to classical genetic prenatal testing with a known mutation, the possibility of biochemical prenatal testing of chorion cells also exists theoretically. However, this is only possible in specific biochemical OXPHOS defects and has some uncertainties.

Treatment

Treatment options in mitochondrial disorders are limited. Only a few defects are accessible to specific therapy. These include, in particular, primary coenzyme Q_{10} biosynthesis defects, disorders in thiamine metabolism (e.g., biotin-thiamine-responsive basal ganglia disease) and *ACAD9* mutations (riboflavin).

Symptomatic therapy is non-specific and, as in other neurodegenerative diseases, the patient has to be treated by a skilled multidisciplinary team in a neuropaediatric and/or metabolic centre. Symptomatic therapy comprises:

- Correction of acidosis(e.g., by means of sodium bicarbonate buffering)
- Treatment of seizures (anticonvulsive treatment), of stroke-like episodes (L-arginine, corticosteroids), of spasticity (botulinum toxin), of dystonia (L-dopa and others) and adequate physiotherapy, occupational therapy, speech therapy, etc.
- Sufficient intake of calories; if necessary feeding via percutaneous gastrostoma
- Mitigation of stressful factors (e.g., good perioperative management in interventions, early infusion therapy in case of vomiting or diarrhoea, treatment of infections)
- Avoidance of potentially toxic substances (e.g. valproic acid, tetracycline)

Other treatment measures try to affect the intermediary metabolism, such as stimulation of enzymes by cofactors, application of electron transporters or antioxidative agents, reduction of toxic metabolites, antioxidative membrane protection, provision of sufficient energy, supplementation of minerals and vitamins in case of secondary deficiencies, and a ketogenic diet (e.g. in PDH deficiency). Substances with evidence of positive effects are: Coenzyme Q_{10}, idebenone, thiamine, ketogenic diet, riboflavine, L-carnitine, creatine and aerobic physical exercise.

Prognosis

The prognosis is generally very variable. Many defects are associated with neurological impairment. Many of the early-onset mitochondriopathies have a poor prognosis. Detailed counselling of the family is usually only possible with knowledge of the genetic defect. In addition to the above-mentioned "treatable mitochondrial diseases", it is important to note that in some defects mitochondrial function may stabilise or even normalise (so-called "reversible mitochondrial diseases", for example mutations in *TRMU* or *EARS2*).

5.10. Disorders of the carnitine cycle, fatty acid oxidation and ketone body metabolism

Biochemistry

Mitochondrial fatty acid oxidation is used to generate energy from fats. During fasting or physical exertion, the long-chain fatty acids stored in adipose tissue as triglycerides are mobilised, transported to the liver, and then transported into the mitochondria of the liver cells via a carnitine-mediated shuttle system. Inside the mitochondria fatty acids are successively shortened with each oxidation cycle (☞ Figure 5.10). At the end of each cycle consisting of four enzyme steps, acetyl-CoA is cleaved off, which is then introduced into the citric acid cycle or is available for ketone body formation. Depending on the length of the fatty acid to be oxidised (long/medium/short chain), different enzymes are active. In fatty acid oxidation disorders (☞ Section 5.10.3) the energy production from fatty acids is disturbed, so that hypoketotic hypoglycaemias may occur, particularly in periods of longer fasting, in the context of infections or during severe physical stress. Toxic intermediates from the degradation of long-chain fatty acids can also lead to lactic acidosis, myopathy, cardiomyopathy and Reye-like hepatopathy. Defects of the carnitine cycle (☞ Section 5.10.2) are associated with a similar clinical picture because intramitochondrial fatty acid oxidation is impaired.

The hydrogen obtained by the dehydrogenases during fatty acid oxidation is transferred to the respiratory chain for energy production. This process is disrupted in multiple acyl-CoA dehydrogenase (MAD) deficiency (☞ Section 5.10.4). The disorder presents similarly to fatty acid oxidation deficiencies. The severe neonatal developmental form is often lethal during the first weeks of life.

Ketone bodies are synthesised in the liver in two successive enzyme steps from acetyl-CoA and are a source of energy for extrahepatic tissues, especially during fasting. Similar to fatty acid oxidation disorders, defects of ketogenesis (☞ Section 5.10.5) lead to acute hypoketotic hypoglycaemias. The disturbed utilisation of ketone bodies is due to a deficiency of ketolytic enzymes (☞ Table 5.11 + 5.12). This results in severe ketoacidosis and hyperketotic hypoglycaemia.

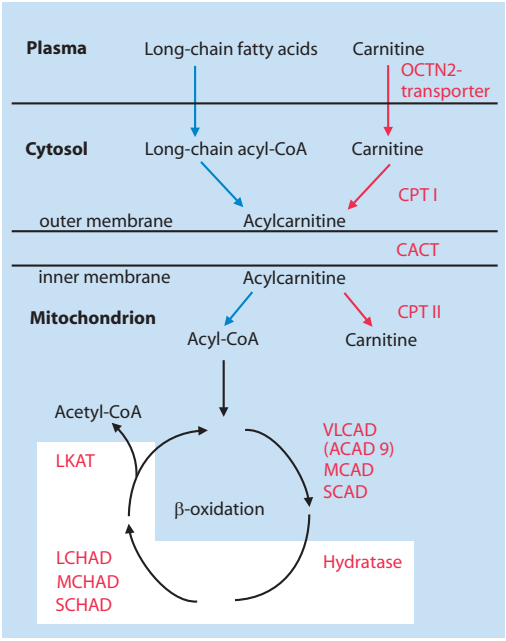


Figure 5.10: Carnitine-mediated transport of long-chain fatty acids into mitochondria and mitochondrial β-oxidation.
Long chain fatty acids are bound to carnitine and pass through the mitochondrial membrane as acylcarnitines. The transport of free carnitine into the cells and the carnitine-mediated transport of long-chain fatty acids into the mitochondria is mediated by various enzymes and transporters (red). The enzymes of the β-oxidation cycle (red) have different substrate specificity depending on the length of the fatty acids to be oxidised. The last three enzymes of the four-stage β-oxidation cycle form the mitochondrial trifunctional protein (TFP) complex (white).
OCTN2 = organic cation carnitine transporter 2; CPTI = carnitine palmitoyl transferase I; CACT = carnitine/

acylcarnitine translocase; CPTII = carnitine palmitoyl transferase II; VLCAD = (very) long-chain acyl-CoA dehydrogenase; ACAD9 = acyl-CoA dehydrogenase 9; MCAD = medium-chain acyl-CoA dehydrogenase; SCAD = short-chain acyl-CoA dehydrogenase; LCHAD = Long-chain hydroxyacyl-CoA dehydrogenase; MCHAD = Medium-chain hydroxyacyl-CoA dehydrogenase; SCHAD = short-chain hydroxyacyl-CoA dehydrogenase; LKAT = Long-chain ketoacyl-CoA thiolase.

5.10.1. Carnitine transporter defect (organic cation carnitine transporter 2 defect, OCTN2, primary carnitine deficiency)

Pathogenesis

In the autosomal recessive carnitine transporter defect, the transport of free carnitine across the plasma membrane into the cells is disrupted, leading to a primary carnitine deficiency through the loss of free carnitine in the urine.

Clinical spectrum

The clinical spectrum is wide. Hypoketotic hypoglycaemias, cardiac problems (cardiomyopathy, arrhythmias, acute cardiac failure), muscular complaints, severe rhabdomyolysis and Reye-like symptoms may occur. Severe neonatal presentations are rare. Also, asymptomatic subjects have been reported who were coincidentally diagnosed (e.g., mothers of newborns who presented with reduced free carnitine in the neonatal screening blood spot).

Diagnosis

Total and free carnitine in the blood are markedly reduced due to increased excretion of carnitine in the urine (decreased fractional tubular reabsorption) (☞ Tab. 5.11).

Treatment

☞ Table 5.12.

Monitoring

The carnitine dose is adjusted on the basis of the levels of free carnitine in the plasma. The levels should be within the normal range.

Prognosis

With adequate carnitine treatment, the prognosis is good, and a coexisting cardiomyopathy may recover.

5.10.2. Carnitine cycle disorders

5.10.2.1. Carnitine palmitoyltransferase 1 (CPT 1) deficiency

Pathogenesis

In the autosomal recessive carnitine palmitoyltransferase 1 (CPT1) deficiency, the carnitine-dependent transport of long-chain fatty acids into the mitochondria is disturbed because the necessary binding to carnitine cannot take place.

Clinical spectrum

Fasting-induced crises occur frequently in the first years of life, and often occur in the neonatal period. Hypoketotic hypoglycaemia, pronounced hepatopathy and possible Reye-like syndrome are observed. There is typically no involvement of cardiac or skeletal muscle. In addition, renal tubular acidosis can develop.

Diagnosis

Free carnitine in the blood is usually increased and long-chain acylcarnitins are low (☞ Tab. 5.11). CPT 1 deficiency is a target disease of expanded newborn screening in Germany. The diagnosis should be confirmed by enzyme analysis or molecular genetic testing.

Treatment

☞ Table 5.12.

Monitoring

Metabolic derangement, prolonged fasting or poor long-term metabolic control are accompanied by elevated liver transaminases.

Prognosis

In the event of an early diagnosis, crisis-triggering situations can frequently be avoided and a favourable outcome can be achieved. Nevertheless, crises cannot always be prevented.

5.10.2.2. Carnitine/acylcarnitine translocase (CACT) deficiency

Pathogenesis

This autosomal recessive defect of the carnitine cycle relates to the transport protein for the transfer of long-chain fatty acids as long-chain acylcarnitines into the mitochondria.

Clinical spectrum

Frequently symptoms such as cardiomyopathy and life-threatening cardiac arrhythmias arise in the neonatal period or in infancy. Myopathy and hepatic dysfunction may also occur. Fasting may induce hypoketotic hypoglycaemia.

Diagnosis

There is an increase in long-chain acylcarnitines in the blood. Free carnitine can be secondarily reduced (☞ Tab. 5.11). CACT deficiency is a target disease of newborn screening in Germany. The diagnosis should be confirmed by enzyme analysis or molecular genetic testing.

Treatment

☞ Table 5.12.

Monitoring

For treatment monitoring, creatine kinase, transaminases, free carnitine and acylcarnitines are measured. On a fat-modified diet, the measurement of the essential fatty acids and fat-soluble vitamins is recommended. Cardiac follow-up should be performed regularly.

Prognosis

The mortality of the severe, early-onset form of CACT deficiency is high. Even with consequent therapy, severe courses cannot be avoided.

5.10.2.3. Carnitine palmitoyltransferase 2 (CPT 2) deficiency

Pathogenesis

In the autosomal-recessively inherited CPT2 deficiency, acylcarnitines cannot be cleaved into acyl-CoA and carnitine in the mitochondria, so that the activated fatty acids cannot enter β-oxidation.

Clinical spectrum

The severe form with onset in the neonatal period and early childhood is accompanied by cardiomyopathy, liver dysfunction, hypoketotic hypoglycaemia and life-threatening coma. Concomitant kidney and brain malformations are frequently observed. The milder form with onset during adolescence or adulthood presents with myopathy and episodic rhabdomyolysis induced by physical exercise or illness.

Diagnosis

Reduced free carnitine and elevated long chain acylcarnitines are found in the blood (☞ Tab. 5.11). CPT 2 deficiency is a target disease of newborn screening in Germany. The diagnosis should be confirmed by enzyme analysis or molecular genetic testing.

Treatment

☞ Table 5.12.

Monitoring

The effect of treatment can be monitored by creatine kinase, liver transaminases, free carnitine and acylcarnitines. On a fat-modified diet, the measurement of the essential fatty acids and fat-soluble vitamins is recommended. Cardiac follow-up should be performed regularly.

Prognosis

The severe, early onset phenotype of CPT 2 deficiency has a poor prognosis and is often lethal.

5.10.3. Disorders of β-oxidation of fatty acids

5.10.3.1. Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency

Prevalence

Approximately 1: 80,000.

Pathogenesis

In the autosomal-recessively inherited VLCAD deficiency, the first step of β-oxidation is affected. It is catalysed by different acyl-CoA dehydrogenases depending on the chain length of the fatty acids.

Since long-chain fatty acids with a chain length between 14 and 20 C atoms cannot be degraded due to VLCAD deficiency, a severe energy deficit ensues, as well as an accumulation of acyl-CoA esters and their derivatives produced before the defective enzyme step. In addition, the production of ketone bodies, which serve as energy supply during longer periods of fasting, is defective.

Clinical spectrum

VLCAD deficiency can be classified clinically into three forms which are differentiated by the severity of clinical symptoms and age of onset (☞ Table 5.9).

Diagnosis

VLCAD deficiency is a target disease of newborn screening in Germany (☞ Tab. 5.11). For confirmation, the following is recommended: analysis of an acylcarnitine profile in dried blood or plasma, measurement of VLCAD activity in lymphocytes or fibroblasts, and mutation analysis of the *ACADVL* gene.

Treatment

☞ Table 5.12.

Monitoring

The effect of treatment can be monitored by creatine kinase, liver transaminases, free carnitine and acylcarnitines in the blood. On a fat-modified diet, a measurement of the essential fatty acids and fat-soluble vitamins is recommended. Cardiac follow-up should be performed regularly.

Prognosis

In the case of presymptomatic diagnosis before the occurrence of a metabolic crisis and prophylactic measures in the context of catabolic conditions, derangements can be largely avoided and a favourable course can be achieved. However, all phenotypes can develop rhabdomyolyses and myopathic symptoms. The myopathic symptoms can respond well to MCT supplementation. The long-term prognosis depends on heart muscle involvement.

5.10.3.2. Mitochondrial trifunctional protein (mTFP) deficiency, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency, long-chain 3-ketoacyl-CoA thiolase (LKAT) deficiency

LCHAD deficiency occurs either isolated or combined as a generalised defect of the mitochondrial trifunctional protein (mTFP). In the case of mTFP deficiency, the activity of three enzymes is impaired: LCHAD, LKAT and long chain enoyl-CoA hydratase (LCEH).

Incidence

1:170,000.

Pathogenesis

The autosomal-recessively inherited LCHAD/mTFP deficiency leads to a significant impairment of the oxidation of long-chain fatty acids from the diet and body fat due to functional limitations of one or more enzymes of the mTFP. This results in considerable energy deficiency in energy-dependent organs, including the heart muscle, skeletal muscle and the liver. In addition, hydroxyacyl-CoA esters and the resulting derivatives produced before the defective enzyme step accumulate,

Phenotype	Main symptoms	Minor symptoms	Age of onset
Severe–infantile	Cardiomyopathy, pericardial effusion, arrhythmias, catabolism-induced Reye syndrome-like symptoms	Muscular hypotonia, hepatomegaly, hypoketotic hypoglycaemia	First months of life
Intermediate	Hypoketotic hypoglycaemia, hepatomegaly	Muscular hypotonia	First years of life
Mild–adult	Myopathy, episodic rhabdomyolysis, excercise intolerance	Hypoketotic hypoglycaemia	Adolescence and adulthood

Table 5.9: Phenotypes of VLCAD deficiency.

Phenotype	Main symptoms	Minor symptoms	Age of onset
Severe–infantile	Cardiomyopathy (possibly progressive), arrhythmias, lactic acidosis, hypoketotic hypoglycaemia, catabolism-induced Reye syndrome-like symptoms	Muscular hypotonia	Neonatal period
Intermediate	Hypoketotic hypoglycaemia, catabolism-induced Reye syndrome-like symptoms	Muscular hypotonia	First months of life
Mild–adult	Myopathy, episodic rhabdomyolysis, excercise intolerance	Hypoketotic hypoglycaemia, cardiomyopathy	Later childhood, adolescence and adulthood

Table 5.10: Phenotypes of TFP/LCHAD deficiency.

which can have toxic effects on cell membranes of the muscle and the brain. Also the production of ketone bodies, which serve as energy supply during longer periods of fasting, is disrupted.

Clinical spectrum

LCHAD/mTFP deficiency can be classified into three forms that are differentiated by the severity of clinical symptoms and age of onset (☞ Table 5.10). Clinically, mTFP deficiency and LCHAD deficiency are not distinguishable. Heterozygous mothers of affected fetuses have an increased risk of developing acute hepatic steatosis in pregnancy and HELLP syndrome.

Diagnosis

LCHAD/mTFP deficiency is a target disease of newborn screening in Germany (☞ Tab. 5.11). For confirmation, the following is recommended: analysis of the acylcarnitine profile in dried blood or plasma, measurement of LCHAD activity in lymphocytes or fibroblasts, mutation analysis of the *HADHA* gene or *HADHB* gene. Homozygosity for the prevalent *HADHA* mutation c.1528G>C (p.E510Q) confirms isolated LCHAD deficiency.

Treatment

☞ Table 5.12.

Monitoring

The effect of treatment can be monitored by creatine kinase, liver transaminases, free carnitine and acylcarnitines in the blood. On a fat-modified diet, the measurement of the essential fatty acids and fat-soluble vitamins is recommended. Cardiac follow-up should be performed regularly.

Prognosis

Newborns with severe, early-onset forms of TFP deficiency are often acutely ill in the first days of life and can rapidly develop fatal cardiomyopathy. In all forms, episodic rhabdomyolyses and myopathic symptoms may occur. In contrast to other fatty acid oxidation disorders, independent of the form, long-term complications often result in retinopathy and peripheral neuropathy which are not yet modifiable using the available therapeutic measures. The long-term prognosis depends on heart muscle involvement.

5.10.3.3. Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency

Prevalence

1:10,000.

Pathogenesis

The autosomal-recessively inherited MCAD deficiency is the most common disorder of mitochondrial β-oxidation, which leads to the inability to break down long-chain fatty acids from the diet and adipose tissue to chain lengths under 6 to 12 C atoms. In addition to an energy shortage, accumulation of medium-chain acyl-CoA esters and their derivatives produced before the defective enzyme step occur. Also, the production of ketone bodies, which serve as energy supply during longer periods of fasting, is disrupted.

Clinical spectrum

Without presymptomatic diagnosis, MCAD deficiency manifests during longer periods of fasting, infections or surgery as acute metabolic crises, which may be associated with hypoketotic hypoglycaemia, lethargy, convulsions, unconsciousness, coma and death. In individual cases, life-threatening crises may occur even in the neonatal period. If severe crises are survived, residual neurological symptoms often persist. After diagnosis thanks to newborn screening, children develop normally on prophylactic therapy, and no clinical symptoms, especially no (cardio)myopathic signs, are to be expected.

	Pathological metabolites
OCTN2	Free carnitine (B) ↓, total carnitine (B) ↓, acylcarnitines (B) n–↓, free carnitine (U) n–↑, fractional tubular carnitine reabsorption ↓
Carnitine cycle disorders	
CPT1	Free carnitine (B) n–↑, total carnitine (B) n–↑, long-chain acylcarnitines (C16; C18; C18:1) (B) n–↓, ratio C0/(C16+C18) (B) ↑
CACT	Free carnitine (B) ↓, total carnitine (B) ↓, long-chain acylcarnitines (C16; C18; C18:1) (B) ↑
CPT2	Free carnitine (B) ↓, total carnitine (B) ↓, long-chain acylcarnitines (C16; C16:1; C18; C18:1; C18:2) (B) ↑, ratio (C16+ C18:1)/C2 (B) ↑
Disorders of β-oxidation of fatty acids	
VLCAD	C14:1(B) ↑, poss. C14:2, C16:1, C18:1 (B) ↑, ratio C14:1/C4 (B) ↑, free carnitine (B) n–↓, dicarboxylic acids (U) ↑, CK, transaminases (B) ↑
TFP, LCHAD, LKAT	C14-OH, C16-OH, C18-OH, C18:1-OH (B) ↑, free carnitine (B) n–↓, dicarboxylic acids (U) ↑, CK, transaminases (B) ↑, poss. lactate (B) ↑
MCAD	C6, C8, C10, C10:1 (B) ↑, ratio C8/C6, C8/C10, C8/C12 (B) ↑, free carnitine (B) n–↓
Disorders of the electron transfer	
MAD	All acylcarnitines (C4 – C18) (B) ↑, free carnitine (B) n –↓, lactate, ethylmalonic acid, glutaric acid, 2-hydroxy-glutaric acid, dicarboxylic acids (U) ↑, lactate, CK, transaminases and γ-GT (B) ↑
Defects of ketone body metabolism	
HMG-CoA Synthase	Dicarboxylic acids (U) after fasting ↑↑↑, poss. C2 (B) ↑, otherwise normal, ratio free fatty acids / total ketone bodies >2.5
HMG-CoA Lyase	Typical metabolite profile with leucine metabolites: 3-hydroxyisovalerate, 3-methylglutaconate, 3-hydroxy-3-methylglutarate and 3-methylcrotonylglycine (U) ↑, C5-OH, C6-DC (B) ↑, ratio free fatty acids / total ketone bodies >2.5
SCOT	Ketone bodies (D-3-hydroxybutyrate) (B, U) ↑, also postprandial ↑, excessively after fasting ↑ ↑ ↑, ratio free fatty acids / total ketone bodies <0.3
MAT	Ketone bodies (D-3-hydroxybutyrate) (B, U) ↑, (lactic-) acidosis (B), NH_3 (B) n–↑, tiglylcarnitine, 2-methyl-3-hydroxybutyrylcarnitine (B) ↑, tiglylglycine, 2-methyl-3-hydroxybutyrate, 2-methylacetoacetate (U) ↑, ratio free fatty acids / total ketone bodies <0.3
MCTI	During crisis ketone bodies (3-hydroxybutyrate and acetoacetate) (B, U) ↑↑↑, outside of crisis normal

Table 5.11: Diagnostically relevant metabolites in defects of the carnitine cycle, fatty acid oxidation, ketogenesis and ketolysis. B=Blood; U=Urine.

Diagnosis

MCAD deficiency is diagnosed by expanded newborn screening in Germany (☞ Table 5.11). For confirmation, the following is recommended: analysis of the acylcarnitine profile in dried blood or plasma, measurement of acylglycines in the urine, mutation analysis of the *ACADM* gene. The mutation c.985A>G (p.K304E) occurs most frequently.

Treatment

☞ Table 5.12.

Monitoring

A secondary lowering of free carnitine in the blood can occur, but the necessity of a low-dose supplementation with carnitine is critically discussed.

Prognosis

If the diagnosis is made before the occurrence of a metabolic crisis and prophylactic measures are applied during catabolic situations, decompensations can generally be avoided and a completely normal course can be achieved.

	Acute therapy	Long-term therapy
OCTN2	L-carnitine i.v. (100-300 mg/kg × day), glucose i.v.	L-carnitine p.o. (100-300 mg/kg × day), normal diet with regular meals to avoid catabolism
Defects of carnitine cycle		
CPT1	Glucose i.v. (<3 y: 10-12 mg/kg × min; 3-10 y: 8-10 mg/kg × min; >10 y: 5-8 mg/kg × min); oral or enteral glucose polymers, oral or enteral MCT; **no** carnitine	Normal diet with regular meals to avoid catabolism, possibly MCT supplementation, **no** general carnitine supplementation
CACT	Glucose i.v. (<3 y: 10-12 mg/kg × min; 3-10 y: 8-10 mg/kg × min; >10 y: 5-8 mg/kg × min); oral or enteral glucose polymers, oral or enteral MCT (or i.v., pure MCT fat generally not available as i.v. preparation); **no** carnitine	Fat-modified diet using MCT fats, regular meals to avoid catabolism, **no** general carnitine supplementation
CPT2	Glucose i.v. (<3 y: 10-12 mg/kg × min; 3-10 y: 8-10 mg/kg × min; >10 y: 5-8 mg/kg × min); oral or enteral glucose polymers, oral or enteral MCT; **no** carnitine	***Severe Phenotypes:*** Regular meals to avoid catabolism, carbohydrate-rich diet (65-75% of the daily energy requirement), fat restriction by using MCT fats and substitution of essential fatty acids (10-15% of the daily energy requirement as MCT fat, 10% as LCT fat, 4% essential fatty acids), after the first year of life glucose polymers at night, no general carnitine supplementation ***Myopathic Phenotypes:*** Fat-reduced or normal diet with regular meals, if necessary MCT supplementation in case of physical activity, no general carnitine supplementation Therapy trials with bezafibrate and triheptanoin (anaplerotically effective odd-numbered C7 fatty acid)
Defects of β-oxidation of fatty acids		
MCAD	Glucose i.v. (<3 y: 10-12 mg/kg × min; 3-10 y: 8-10 mg/kg × min; >10 y: 5-8 mg/kg × min); oral or enteral glucose polymers, no MCT; no general carnitine supplementation (poss. low-dose in deficiency)	Avoidance of long fasting periods, regular meals

VLCAD, TFP, LCHAD, thiolase	Glucose i.v. (<3 y: 10-12 mg/kg × min; 3-10 y: 8-10 mg/kg × min; >10 y: 5-8 mg/kg × min); oral or enteral glucose polymers, oral or enteral MCT (or i.v., pure MCT fat generally not available as i.v. preparation); **no** carnitine	***Severe Phenotypes:*** Regular meals to avoid catabolism, carbohydrate-rich diet (65-75% of the daily energy requirement), fat restriction by using MCT fats and substitution of essential fatty acids (10-15% of the daily energy requirement as MCT fat, 10% energy consumption as LCT fat, 4% essential fatty acids), after the first year of life glucose polymers at night, possibly continuous gastric tube feeding at night necessary, no general carnitine supplementation ***Myopathic Phenotypes:*** Fat-reduced or normal diet with regular meals (except for LCHAD/mTFP deficiency: always strict fat restriction!), Possibly MCT supplementation in case of physical activity, no general carnitine supplementation ***In the case of LCHAD/mTFP defects***, additional: docosahexaenoic acid (200-400 mg/kg/d) ***Exception:*** Asymptomatic neonates with VLCAD deficiency: e.g. 50% breast milk - 50% MCT Formula; on the absence of symptoms fat reduction to 30-40% of the daily energy requirement, of which 10-15% as MCT fat, regular meals
Disorders of the electron transfer		
MAD	Glucose i.v. (<3 y: 10-12 mg/kg × min; 3-10 y: 8-10 mg/kg × min; >10 y: 5-8 mg/kg × min); oral or enteral glucose polymers, L-carnitine i.v. (100 mg/kg × d), riboflavin (vitamin B_2) (100-300 mg × d), poss. D, L-3-hydroxybutyrate (in severe cardiomyopathy)	Regular meals to avoid catabolism, fat and protein-restrictive diet Carbohydrates: 65-75%, fat: 20-25%, protein: 8-10% of the daily energy requirement Riboflavin (100-300 mg × d) and normal diet in riboflavin-responsive forms Carnitine p.o. (100 mg/kg × d), optionally D, L-3-hydroxybutyrate
Defects of ketogenesis		
HMG-CoA synthase	Glucose i.v. (5-8 mg/kg × min)	Regular meals to avoid catabolism, normal diet
HMG-CoA lyase	Glucose i.v. (5-8 mg/kg × min), in case of acidosis (pH<7.20) buffer with $NaHCO_3$, carnitine (100 mg/kg × d)	Regular meals to avoid catabolism, fat- and protein-reduced diet Carbohydrates: 65-75%, fat: 20-25%, protein: 8-10% of the daily energy requirement Carnitine p.o. 100 mg/kg × d
Defects of ketolysis		
SCOT	Glucose i.v. (5-8 mg/kg × min), in case of acidosis (pH<7.20) buffer with $NaHCO_3$	Regular meals to avoid catabolism, avoid excessive fat supply, possibly mild protein restriction
MAT	Glucose i.v. (5-8 mg/kg × min), in case of acidosis (pH<7.20) buffer with $NaHCO_3$, poss. carnitine	Regular meals to avoid catabolism, avoid excessive fat supply, possibly mild protein restriction, possibly carnitine
MCT1	Glucose i.v. (5-8 mg/kg × min), in case of acidosis (pH<7.20) buffer with $NaHCO_3$	Regular meals to avoid catabolism

Tab. 5.12: Treatment of defects of the carnitine cycle, fatty acid oxidation, ketogenesis and ketolysis. LCT=long-chain triglycerides, MCT=medium-chain triglycerides, y=years.

5.10.3.4. Short-chain acyl-CoA dehydrogenase (SCAD) deficiency

Pathogenesis

In the autosomal-recessively inherited SCAD deficiency, the degradation of fatty acids is impaired in the range of short-chain length.

Clinical spectrum

Various (especially neurological) symptoms have been associated with SCAD deficiency in the literature. However, since presymptomatically diagnosed individuals appear to remain asymptomatic in the course of the disease, the clinicopathological relevance of the disorder is unclear (presumably "non-disease").

Diagnosis

SCAD deficiency (biochemical elevation of C4 carnitine in blood and ethylmalonic aciduria) is not a target disease of neonatal screening in Germany.

5.10.4. Multiple acyl-CoA dehydrogenase (MAD) deficiency (or electron transfer defect, ETF/ETF-DH, or glutaric aciduria type II)

Pathogenesis

The autosomal-recessively inherited MAD deficiency is due to an electron transport disorder based on a defect of the electron transfer flavoprotein (ETF) or the ETF cytochrome Q oxidoreductase (ETF-QO). This leads to a disturbance in the transfer of the hydrogen produced by certain dehydrogenases to the respiratory chain for energy production. Apart from the acyl-CoA dehydrogenases used in β-oxidation of fatty acids (VLCAD, MCAD, SCAD), dehydrogenases used in the degradation of various amino acids (valine, leucine, isoleucine, tryptophan, lysine) are also functionally impaired.

Clinical spectrum

The clinical spectrum is wide. Patients who are severely affected present with hypoglycaemia, hyperammonia, metabolic acidosis, muscular hypotonia and hepatomegaly in the first days of life. This form may be associated with or without organ malformation (such as renal cysts, cerebral malformations) and facial dysmorphism, and is usually fatal within the neonatal period. Milder forms can manifest at any age from infancy to adulthood, and are often associated with hypoglycaemia, liver dysfunction and Reye-like symptoms as well as muscle weakness, rhabdomyolysis and cardiomyopathy. In addition, there are myopathic forms with the appearance of muscle weakness during youth or adult age. Patients with mild forms often respond to riboflavin supplementation.

Diagnosis

The diagnosis is made on the metabolic level by means of analysis of the acylcarnitine profile in dried blood or plasma and of organic acids in the urine (☞ Tab. 5.11) and confirmed by enzymatic and/or molecular genetic analysis.

Treatment

☞ Table 5.12.

Prognosis

The prognosis is dependent on the severity of the symptoms. In case of neonatal onset, a fatal outcome during the first weeks of life is frequent. The riboflavin-responsive form has a good prognosis.

5.10.5. Defects of ketone body metabolism

5.10.5.1. 3-Hydroxy-3-methylglutaryl-CoA (HMG-CoA) synthase deficiency

Pathogenesis

In the autosomal-recessively inherited HMG-CoA synthase defect, the production of ketone bodies from acetoacetyl-CoA is impaired.

Clinical spectrum

In the context of longer periods of fasting and/or infections or surgery, infants or toddlers present with hypoketotic hypoglycaemia, hepatomegaly and lethargy possibly resulting in coma.

Diagnosis

In fasting urine, a clear dicarboxylic aciduria without ketonuria is indicative of the disorder (☞ Tab. 5.11). Sometimes an increase in acetyl (C2) carnitine in dried blood or plasma is detectable. However, normal metabolic findings may occur outside of fasting intervals. A molecular genetic analysis of the *HMGCS2* gene is required.

Treatment

☞ Table 5.12.

Prognosis

Prognosis is excellent if prolonged fasting is avoided.

5.10.5.2. 3-Hydroxy-3-methylglutaryl-CoA (HMG-CoA) lyase deficiency

Pathogenesis

In autosomal-recessively inherited HMG-CoA-lyase deficiency the production of the ketone body acetoacetate from 3-HMG-CoA is disturbed. At the same time, this enzymatic reaction is the last step in the degradation pathway of the ketogenic, branched-chain amino acid leucine.

Clinical spectrum

In the context of longer periods of fasting and/or infections or surgery, neonates or infants often present with acute hypoketotic hypoglycaemia, metabolic acidosis, hepatopathy and Reye-like symptoms.

Diagnosis

By analysing the organic acids in the urine and the acylcarnitins in dried blood or plasma, the diagnosis can be made by means of the specific metabolite profile (☞ Table 5.11). The molecular genetic analysis of the *HMGCL* gene confirms the diagnosis.

Treatment

☞ Table 5.12.

Prognosis

If residual symptoms and other metabolic crises can be avoided, the prognosis is favourable. The metabolic disorder can, however, be fatal at initial manifestation.

5.11. Disturbances of carbohydrate metabolism

Basically, carbohydrates have two major functions:

- They deliver energy to the body.
- They serve as construction material in each body cell.

Hence, disturbances of carbohydrate metabolism may affect both energy metabolism or structure and function of cells.

5.11.1. Classical galactosaemia

Definition

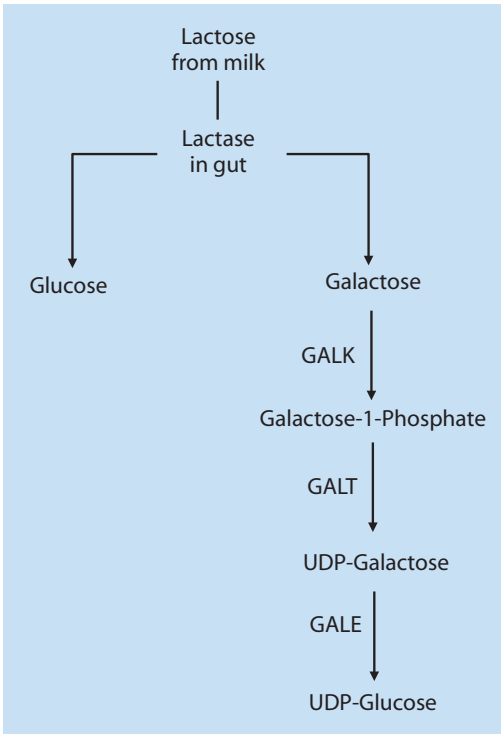
Classical galactosaemia is an inherited disorder affecting the degradation of the disaccharide galactose. It is caused by the autosomal-recessively inherited deficiency of galactose-1-phosphate uridyltransferase (GALT).

Incidence

Incidence in populations of Caucasian origin is about 1:70,000.

Pathogenesis

GALT catalyses the second step in the metabolism of galactose to glucose, which is the conversion of galactose-1-phosphate into UDP-galactose. Hence, in GALT deficiency galactose-1-phosphate accumulates in cells. This potentially hepatotoxic substance is converted to galactitol via an alternative metabolic pathway, which in turn can be secreted with the urine (☞ Figure 5.11a+b).



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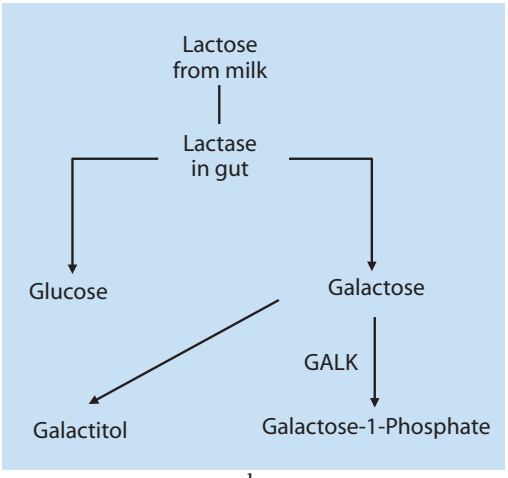

b

Figure 5.11a+b: **a**) Galactose metabolism in healthy individuals; **b**) galactose metabolism in patients with classical galactosaemia. GALK=galactokinase, GALT= galactose1-phosphate-uridyltransferase, GALE=UDP-galactose-epimerase.

Clinical spectrum

Affected children are not symptomatic at birth. Within a few days after starting of feeding (mother's milk or milk-based formula), patients develop symptoms of hepatopathy including jaundice, coagulation disturbances and vomiting. Lethargy and the development of cataract are major clinical manifestations. Untreated patients also have an increased risk for *E. coli* sepsis. However, also without this complication the course in untreated patients is fatal in most cases.

A considerable number of children with early and sufficiently treated GALT deficiency show disturbed speech development. Approximately 80% of female patients develop hypergonadotropic hypogonadism, and pregnancies in women with classical galactosaemia are uncommon. To what extent male patients also show endocrinological alterations is unclear so far.

Diagnosis

Each child with sucking weakness and signs of liver dysfunction with jaundice during the first days of life must be investigated for GALT deficiency. In Germany, the putative diagnosis in most cases arises from newborn screening. Confirmation of this suspicion is carried out by determination of residual GALT activity and/or detection of a pathogenic mutation. In Caucasians, frequent mutations are p.Q188R and p.K285N, but there exists no genotype-phenotype correlation.

Differential diagnosis is the so called Duarte-2-variant. Affected children may also become conspicuous in newborn screening, but compound heterozygous subjects (classical galactosaemia/ Duarte) usually have a residual GALT activity of approximately 25%. As far as it is known today, this seems enough to ensure a regular galactose metabolism, and within weeks or sometimes months, galactose metabolites return to values of biochemically healthy subjects from which these individuals clinically cannot be told apart.

Treatment

As soon as suspicion of classical galactosaemia arises, feeding of mother's milk or regular formula has to be discontinued immediately. Feeding can be carried out by using formula based on lactose-

free soy milk. Once the lactose-free, galactose-restricted diet is instituted, it has to be continued throughout life, which requires intensive nutritional training of the parents, especially with the introduction of solid foods.

Monitoring

Galactose-1-phosphate in red blood cells is used as a monitoring parameter. However, this metabolite shows a high intra-individual variability and increases only after considerable violations of the diet and/or in liver function disturbances.

Prognosis

Overall, the prognosis is good despite the sometimes threatening manifestation in the newborn period. Hepatopathy and cataract are usually completely reversible. Speech development can be supported by speech therapy and is normally no longer a problem in school-aged children. Regardless of sex and the quality and commencement of the diet, there may be oromotor or generalised dyspraxia, ataxia, tremor and osteoporosis. In females ovarian dysfunction and disturbed puberty may occur. Oftentimes intellectual performance remains below average. However, most patients can attend a regular school and find work.

5.11.2. Hereditary fructose intolerance (HFI)

Definition

Hereditary fructose intolerance (HFI) is caused by deficiency of the enzyme fructoaldolase B, which is needed for cleavage of fructose-1-phosphate and fructose-1,6-biphosphate.

Incidence

Incidence in Europe is about 1:20,000.

Pathogenesis

In healthy individuals, 1 mol of fructose delivers 1 mol of ATP. In HFI, hepatotoxic fructose-1-phosphate accumulates, leading to reduction of intracellular ATP. Moreover, fructose-1-phosphate inhibits enzymes necessary for glycolysis, which may also lead to hypoglycaemia. The alternative metabolic degradation of fructose into fructose-6-phosphate takes place in only very little amounts.

Clinical spectrum

Symptoms of HFI typically manifest after introduction of fructose or saccharose or rather the foods containing these sugars, i.e. the introduction of solid foods. Severity of symptoms depend on the child's age (the younger, the more severe) and on the amounts of fructose and/or saccharose in the diet. In some cases, nutrients containing these sugars are avoided by the children even before diagnosis. Occasionally, there are reports on older patients suffering from "sugar allergy" where diagnosis of HFI has been found in adulthood. Table 5.13 summarises the clinical symptoms.

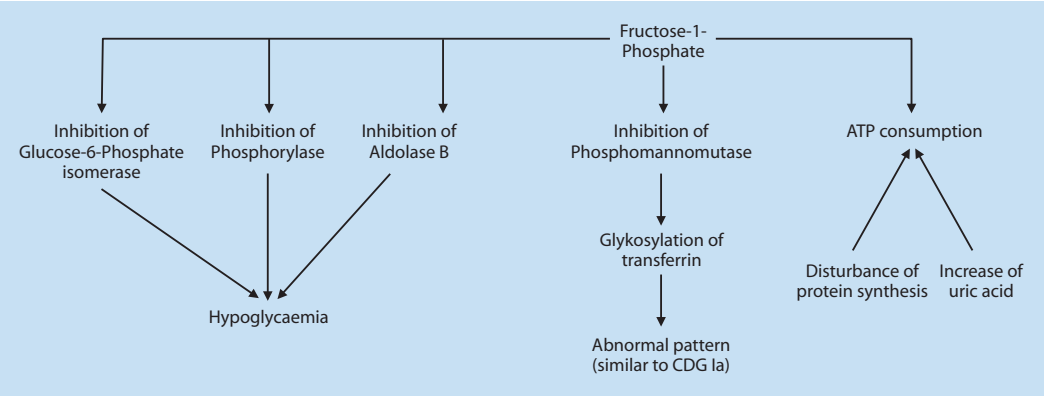

Figure 5.12: Overview on the consequences of fructose-1-phosphate accumulation.

Acute symptoms	Chronic symptoms
• Sweating, tremor, nausea • Dizziness, vomiting • Apathy, lethargy, rarely coma • Coagulation disturbance • Seizures	• Refusal of food intake, diarrhoea, failure to thrive, rarely dwarfism • Agitation, screaming • Fatigue, sleepiness, apathy • Hepatomegaly with jaundice, steatosis and fibrosis, coagulation disturbances; oedema, ascites • Renal-tubular damage

Table 5.13: Symptoms of hereditary fructose intolerance.

Diagnosis

Indicative of HFI is the characteristic onset of symptoms after introduction of solid foods. Hence, in non-specific failure to thrive, a detailed history of nutrition including introduction of new nutrients is a mainstay in diagnosis. Older patients report a distinct aversion to fructose-containing foods. In addition, hypoglycaemia may be indicative for HFI. Liver function disturbances are frequently observed in clinical chemistry. First, a molecular genetic analysis should be attempted, since three mutations occur frequently (p.A150P>50%, p.A175D and p.N335K with 94% of the HFI alleles in European and approximately 68% in North American patients). To determine the residual activity of aldolase B a biopsy either from liver or small intestine tissue is needed (only if the mutation analysis is without result). Activities <15% confirm the diagnosis of HFI. A fructose loading test is no longer recommended.

Treatment

Treatment consists of teh elimination of fructose from the diet. On this diet clinical symptoms and laboratory alterations resolve promptly. However, drugs containing fructose or saccharose as adjuvants have to be taken with caution. In addition, vitamin C should be adequately supplemented because of the avoidance of fruits.

Monitoring

During childhood, growth and liver function should be monitored regularly, since there is no specific biomarker for monitoring the course and severity of the disease.

Prognosis

The overall prognosis of HFI is good if the diet restrictions are adhered to. Typically, patients have no caries throughout their life. With increasing age, the tolerance to fructose increases slightly. Children are allowed to consume up to 1 g of fructose per day, and adults up to 2.5 g, respectively. Alterations of liver structure seen in light microscopy may persist lifelong. However, their clinical relevance is unclear so far. It may be necessary to repeat dietary advice in adolescence to ensure adherence to the diet.

5.11.3. Glycogen storage diseases (GSD)

5.11.3.1. Glycogenosis I (GSD I, von Gierke's disease)

Definition

Glycogenosis Ia is caused by an autosomal-recessively inherited deficiency of glucose-6-phosphatase.

Incidence

Approximately 1:100,000.

Pathogenesis

Glucose-6-phosphatase consists of a catalytic subunit and a transport unit which is located in the cell membrane. A disturbance of the catalytic subunit leads to GSD I a, whereas disturbances of the transport unit are the cause of glycogenosis I non-a. As a consequence of the disturbed activity of glucose-6-phosphatase, glucose is not or insufficiently released from glycogen and/or gluconeogenetic amino acids. During longer fasting periods or during otherwise caused catabolic episodes, hypoglycaemia may occur with increased lactate levels and lactic acidosis. The downregulated cleavage of gluconeogenetic amino acids and their permanent mobilisation in hypoglycaemia leads to an increase of uric acid and may result in gout. Free fatty acids

Glycogenosis		Enzymatic defect	Confirmation of diagnosis
Type	Name		
0		Glycogen synthase	Enzymatic analysis in liver biopsy, mutation analysis
I	van Gierke	• I a: glucose-6-phosphate-dehydrogenase • I non-a: i.e. glucose-6-phosphate-translocase	Mutation analysis, (enzymatic analysis)
II	Pompe	Acid 1,4-phosphatase	Enzymatic analysis in muscle tissue or fibroblasts
III	Cori-Forbes	Debranching enzyme	Enzymatic analysis in red blood cells, mutation analysis
IV	Andersen	Branching enzyme	Enzymatic analysis in liver or muscle tissue, fibroblasts or leucocytes, mutation analysis
V	McArdle	Muscle phosphorylase	Enzymatic analysis in muscle tissue
VI	Hers	Liver phosphorylase	Enzymatic analysis in red blood cells, leucocytes, liver and muscle tissue
VII	Tauri	Muscle phosphofructokinase	Enzymatic analysis in muscle tissue
IX		Phosphorylase kinase	Enzymatic analysis in affected tissue

Table 5.14: Overview on glycogenoses.

are then needed for energy generation, which leads to an increase in triglycerides with the risk of pancreatitis. Finally, carbohydrates which are not immediately used are stored as glycogen in the liver where they cause hepatomegaly.

Clinical spectrum

Acute symptoms are hypoglycaemia, seizures and loss of consciousness. Untreated patients or those with poor metabolic control suffer more frequently from dwarfism and reduced bone density. Progressive kidney dysfunction, impaired platelet function and gout are other clinical manifestations. Moreover, patients may develop a liver adenoma with an increased risk of malignant degeneration. In patients with glycogenosis type I non-a there is also a deficiency and functional impairment of neutrophil granulocytes of varying degree. Often patients suffer from recurrent infections of the upper airways, the gastrointestinal tract or skin. Another characteristic manifestation of neutropenia are (peri-)oral aphtous ulcerations, and a considerable number of patients with GSD I non-a may develop gastrointestinal complaints which resemble Crohn's disease and are therefore called "Crohn's-like bowel disease".

Diagnosis

The tentative diagnosis of GSD I usually is the result of the clinical picture, but it is also possible that altered laboratory parameters (lactic acidosis, hypertriglyceridaemia, increased uric acid) raise suspicion. Glucose loading tests show a decrease of lactate in the serum. Administration of glucagon does not lead to an increase of blood glucose levels. Confirmatory diagnosis is carried out by mutation analysis, and today liver biopsies are usually not needed for diagnostic workup.

Treatment

In principal, treatment consists of an energy-balanced diet. Optimally, exactly as much energy is supplied as the body needs for the respective activity level. The fasting times should not be too long and the carbohydrate intake must be adjusted according to age. Frequent meals (every 2-3 h at infant and toddler age, 4-6 h at school age) with slowly absorbed carbohydrates (maltodextrin, starch) are necessary. The intake of fructose and lactose/galactose should be minimised, and saccharose should be avoided. Exchange tables for vegetables, fruit and dairy products are available

for this purpose. In order to avoid deficiencies, supplementation with vitamins, minerals and trace elements is usually required. Also, the blood glucose level during the night must be kept as stable as possible. In the first years of life, this can best be achieved by night-time tube feeding with carbohydrate-containing food (or maltodextrin solution), and in older children the nightly intake of slowly digestible carbohydrates (e.g., uncooked cornstarch). Pathologically elevated uric acid levels may require drug treatment. Patients with glycogenosis I non-a should be given antibiotic treatment early because of neutropenia in infections. Furthermore, the indication for the administration of filgrastim (G-CSF, Neupogen®) must be checked.

▶ Emergency treatment

In case of refusal of food intake or vomiting, hypoglycaemia has to be avoided by early administration of maltodextrin (orally) or glucose (intravenously) in age appropriate amounts (☞ Table 5.15).

Age	Recommended amount of maltodextrin
Infancy	6.0 mg/kg body weight/min
School age	4.0 mg/kg body weight/min
Adulthood	2.5 mg/kg body weight/min

Table 5.15: Recommended amount of maltodextrin in cases of hypoglycaemia in GSD I.

Monitoring

The dietary therapy should be checked at least initially by regular blood glucose tests before meals. In a stable metabolic situation such measurements are rarely necessary. For further evaluation of the metabolism, lactate excretion (based on creatinine) can be measured in urine specimens collected separately during the day and the night. At the latest from the second decade of life regular ultrasound needs to be performed to detect a possible liver adenoma. At the same time, the renal function should be checked, especially with regard to tubular damage. In girls the development of polycystic ovaries is observed.

Prognosis

Patients with good compliance to the recommended treatment usually show normal growth and normal development, and the risk for long-term complications is reduced.

5.11.3.2. Glycogenosis III (GSD III, Cori/Forbes disease)

Definition

Glycogenosis III is caused by deficiency of the debranching-enzyme (amylo-1,6-glucosidase).

Pathogenesis

The enzyme is responsible for the cleavage of glucose from glycogen and is expressed in liver and muscle. The inheritance is autosomal-recessive.

Incidence

Approximately 1:100,000.

Clinical spectrum

According to the expression of the debranching-enzyme in liver and muscle cells, two different forms of GSD III can be distinguished, a mixed myopathic-hepatic and a purely hepatic variant.

- Myopathic-hepatic form (GSD III a; approximately ¾ of the patients): during infancy children often show muscular hypotonia, however, muscle tone may improve with age. In other patients onset of disease is in adult age. Muscle affection leads to increased concentrations of creatine kinase.
- Hepatic Form (GSD III b; approximately ¼ of the patients): early after birth affected children show massive hepatosplenomegaly and a distended abdomen. Similar to GSD I, they may develop a so-called "doll's face". In prolonged fasting periods or reduced food intake during intercurrent illnesses hypoglycaemia may occur. With increasing age, liver size decreases reaching normal values in puberty. In addition, with increasing age, liver enzymes also return to normal levels, and hypoglycaemia becomes a rare phenomenon. Nevertheless, there is still an increased risk for hepatic adenoma and nodular fibrosis of the liver.

Diagnosis

Hypoglycaemia with acetonaemic *foetor ex ore* is typically found and is accompanied by considerable ketonuria. Glucose loading leads to an increase in lactate. Liver transaminases may be markedly increased, but in most cases return to normal ranges during puberty. Increased creatine kinase reflects muscle affection, and cholesterol may be markedly increased. Confirmatory diagnostics are carried out by determination of enzyme activity in red blood cells or leucocytes. Moreover, mutation analysis is possible.

Treatment

A carbohydrate-balanced diet is recommended, but there is no need to restrict the intake of galactose and/or fructose. If needed, patients with GSD III may also receive nightly tube feeding in order to ensure appropriate growth. A protein-enriched diet may improve myopathic symptoms.

Monitoring

Depending to the affected organs, liver and kidney function should be monitored frequently. Once a year abdominal ultrasound including Doppler of the portal vein should be performed in order to identify cirrhotic remodelling of the liver at an early stage.

Prognosis

The hepatic component of GSD III usually improves during puberty, whereas the development of myopathic symptoms cannot be hindered. Some patients may develop cardiomyopathy, and bone density may be markedly reduced. Hence, physical activity is recommended. Female patients with GSD III have an increased risk for the development of polycystic ovaries.

5.11.3.3. Glycogenosis V (GSD V, McArdle's disease)

Definition

GSD V is an autosomal-recessively inherited deficiency of muscle phosphorylase (phosphorylase A).

Incidence

>1:200,000.

Pathogenesis

The underlying defect of the disease is a mutation in gene locus 11q13. In 50% of alleles in patients of European origin the mutation R49X is found. Another frequent mutation is F708del.

Muscle phosphorylase catalyses the formation of muscle ATP in glycogenolysis. The percentage of residual enzyme activity does not correlate with the severity of the disease.

Clinical spectrum

Typically, onset of the disease is within the second or third decade of life. However, even infants may already exhibit symptoms of GSD V. Reduced endurance may be accompanied by muscle weakness and cramps. Physical exercise leads to a decrease of lactate concentrations in serum. In part, the so-called "second wind" phenomenon is described, where symptoms resolve after short peak exertion. Continuous physical activity results in approximately 50% of patients in rhabdomyolysis and myoglobinuria.

Diagnosis

Apart from clinical symptoms myoglobinuria may be indicative for GSD V. Creatine kinase is increased, and often concentrations of uric acid are also elevated. When performing an ischaemia test (simulation of physical exercise) an increase of NH_3 is found, whereas lactate decreases. The enzymatic deficiency can be proven by muscle biopsy. P^{31}-MRI does not show an increase of intracellular muscle pH.

Treatment

Avoidance of physical exertion is the basis of treatment. Some patients show improvement from a protein and/or carbohydrate enriched diet.

Prognosis

Life expectancy is not reduced in general.

5.11.3.4. Glycogenosis IX (GSD IX)

Definition

GSD IX is caused by deficiency of phosphorylase-B-kinase. Two forms have to be distinguished, a skeletal muscle form (X-chromosomal) and a myo-hepatic variant (autosomal recessive).

Incidence

Approximately 1:150,000.

Pathogenesis

The limiting enzyme in glycogenolysis is phosphorylase. It is activated via a cascade of enzymes, one of which is phosphorylase-B-kinase. The enzyme consists of 4 subunits, whose corresponding genes are located on different chromosomes, and which are expressed in different tissues. A defect of the catalytic centre of the enzyme leads to liver cirrhosis. X-linked GSD IX is caused by a defect of the α-subunit of phosphorylase-B-kinase.

Clinical spectrum

As is the case in all other glycogenoses, accumulation of glycogen leads to hepatomegaly. Moreover, many affected patients develop growth delay.

Diagnosis

Apart from hepatomegaly and growth delay, a combination of hyperlipidaemia and increased concentrations of transaminases is found. In addition, blood glucose concentrations may be low. Diagnosis is confirmed by determination of enzyme deficiency in liver tissue and/or red blood cells.

Treatment

In particular during childhood, an adequate intake of carbohydrates is necessary to avoid symptoms.

Monitoring and prognosis

Presentation and monitoring in a specialised centre for metabolic diseases are recommended once a year, though GSD IX is the mildest form of glycogenoses, and usually shows a good course. The biochemical alterations and hepatomegaly resolve with ongoing age, so adult patients normally are asymptomatic. However, there are also severe courses described with cirrhotic remodelling of the liver.

5.12. Congenital hyperinsulinism

Definition

Congenital hyperinsulinism (CHI) is a group of different inborn errors of insulin secretion resulting in hyperinsulinaemic hypoglycaemia. CHI is associated with various disorders of the regulation of insulin secretion.

Incidence

Incidence is estimated to be 1:40,000 in Central Europe and increases in regions with high consanguinity up to 1:2,500.

Pathogenesis

Various disorders with disturbed regulation of insulin secretion can result in inappropriately high secretion of insulin in relation to corresponding glucose levels (☞ Figure 5.13). Most frequently, defects of the ATP-sensitive potassium channel (K_{ATP}) of pancreatic β-cells are found. Defects are localised in one of the subunits of the potassium channels (SUR1/Kir 6.2). Overactivity of glucokinase or glutamate dehydrogenase will also result in hyperinsulinism (GCK-HI or GDH-HI). CHI is most often caused by germline mutations affecting all cells including cells of the pancreas. In about 30% of patients a so-called "focal" CHI is caused by somatic mutations. In general, persistent CHI has to be distinguished from transient neonatal hyperinsulinism.

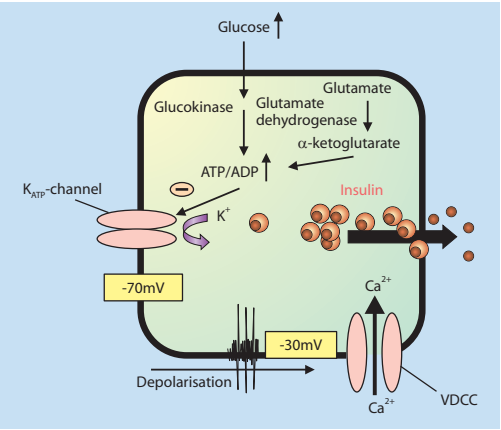

Figure 5.13: Disorders of insulin secretion resulting in congenital hyperinsulinism. Simplified figure of regulation of insulin secretion of pancreatic β-cells. Loss of function of the ATP-sensitive potassium channel (K_{ATP}) with two subunits SUR1 and Kir6.2 results in hyperinsulinism (K_{ATP}-HI) just as overactivity of glucokinase (GCK-HI) or glutamate dehydrogenase (GDH-HI).

Clinical spectrum

Neonatal manifestation is frequently seen. Most patients become symptomatic with hypoglycaemia during the first 48 hours of life. In some patients with neonatal onset macrosomia may be present at birth. Patients with the infantile form usually become symptomatic within the first month of life. Convulsions are the most common symptom of severe hypoglycaemia in these patients.

Diagnosis

In neonates diagnosis of CHI is based on increased glucose infusion rate to maintain euglycaemia (>10 mg/kg/min). Insulin concentration in plasma is increased in hypoglycaemia (>3 mU/l), whereas lactate is normal and ketone bodies and free fatty acids are decreased. Additional identification of the CHI subforms can be done by mutational analysis. However, in up to 50% of patients no specific mutation has been found so far. GDH-HI is suspected if concomitant asymptomatic hyperammonaemia is present (100-200 µmol/l).

To distinguish between focal and diffuse disease a 17-Fluoro-PET-scan is suitable.

Treatment

In neonatal onset, the prevention of severe hypoglycaemia is the first measure. Acute drug therapy is performed with somatostatin, the long-acting somatostatin analogue octreotide or glucagon s.c. or i.v. (☞ Table 5.16). Diazoxide or octreotide are used for maintenance therapy. Many patients, particularly neonates, and especially those with K_{ATP}-HI, do not or only partly respond to treatment with diazoxide. When a focal form is detected, the patients can be cured by targeted resection of the affected pancreas region. Today, near-total pancreatectomy is only necessary in very rare cases.

Drug	Dosage
Initial stabilising of glucose levels	
Glucagon	Continuous infusion (5-10 µg/kg/h, up to 1 mg/day) or single injections of 30-100 µg/kg per dose (i.m., i.v. or s.c.)
Somatostatin	0.5-3.5 µg/kg/h i.v. or s.c.
Long-term treatment	
Diazoxide	5-15 mg/kg/d in 3 doses p.o.
Nifedipine	0.5-2 mg/kg/d in 3 doses p.o. (only successful in single cases)
Octreotide	5-20 µg/kg/d in 3-4 doses s.c or continuously s.c. or 60-120 mg per month deep s.c.

Table 5.16: Drug treatment of congenital hyperinsulinism.

Prognosis

Early introduction of adequate treatment will protect the brain from recurrent episodes of hypoglycaemia. However, retrospective analyses revealed a high proportion of patients with psychomotor impairment and/or epilepsy. This is likely to be caused by late diagnosis or non-adequate treatment.

5.13. Lysosomal storage diseases (LSD)

The lysosomal storage diseases comprise about 50 congenital metabolic disorders. Deficiencies of lysosomal enzymes lead to the accumulation of high molecular weight substances (lipids, proteins,

glycoproteins, glycosaminoglycans) in lysosomes. This results in progressive organ damage. Frequently, parenchymatous organs, bones, connective tissue, eyes and the central nervous system are involved.

The total incidence of lysosomal storage disorders is about 1:8,000.

The lysosomal storage disorders are classified according to the affected enzyme and the accumulating substrate:

- Sphingolipidoses: Gaucher disease, Niemann-Pick disease Type A/B, Fabry disease and others
- Mucopolysaccharidoses: MPS I-IX
- Oligosaccharidoses: mannosidosis, sialidosis, and others
- Lipid storage diseases: M. Niemann-Pick type C and others
- Mucolipidoses
- Lysosomal transport disorders
- Neuronal ceroid lipofuscinoses
- Glycogenose type II (Pompe disease)

There are no causal therapies available for most disorders. Gaucher disease, Fabry disease, Pompe disease, Niemann-Pick disease type C and some of the mucopolysaccharidoses are treated causally with enzyme replacement therapy. Artificially produced enzyme is given intravenously, resulting in a degradation of the storage substances. Enzyme replacement therapy is also being trialed for other disorders, but is currently not approved for treatment (e.g., MPS type III, Niemann-Pick disease type A/B).

As an oral alternative, substrate reduction therapy is available for some disorders (Fabry disease, Niemann-Pick disease type C), which inhibits the synthesis of the respective storage substance.

Bone marrow transplants have been successfully performed, e.g., in patients with MPS type I .

Future treatment approaches, such as gene therapy or chaperone therapy, are being tested.

The following is a more detailed discussion of Gaucher's disease, Fabry's disease and mucopolysaccharidoses (MPS).

5.13.1. Gaucher's disease

Definition

Gaucher's disease is an autosomal-recessively inherited deficiency of glucocerebrosidase.

Incidence

The worldwide incidence of the non-neuronopathic form is estimated to be 1:40,000-1:60,000. The incidences of the acute neuronopathic form and the chronic neuronopathic form are each fewer than 1:100,000.

Pathogenesis

The deficiency of the enzyme glucocerebrosidase results in an accumulation of glucocerebroside in reticuloendothelial cells. These so-called Gaucher cells are found in spleen, liver and bone marrow, more rarely in the lungs. Storage leads to secondary macrophage activation with cytokine release. The consequence of both pathogenetic mechanisms is a functional disorder of the affected organ systems.

Clinical spectrum

A clinical division is made according to 3 courses of disease.

Hepatosplenomegaly, haematologic changes (anaemia, thrombocytopenia) and bone involvement (bone infarctions, painful crises, pathological fractures) are typical for the non-neuronopathic form. The diagnosis can be made according to the severity of the symptoms at each age.

In the case of the acute neuronopathic form difficulties with feeding problems, failure to thrive and frequent infections of the airways as well as neurological complications (muscular paralysis, brain stem involvement) occur in addition to the visceral symptoms. The disease usually leads to death within the first two years of life.

The chronic neuronopathic type, which also becomes symptomatic in childhood, is characterised by milder neurological symptoms. The visceral symptoms are similar to the non-neuronopathic form.

There is an increased risk of malignant haematologic disorders in patients with Gaucher's disease.

Diagnosis

The diagnosis is made by measuring glucocerebrosidase activity in leukocytes or fibroblasts as well as by genotyping.

An assessment of the severity can be made by the determination of the chitotriosidase, which is produced in the Gaucher cells and can be increased up to 1000-fold.

Treatment

Patients with non-neuronopathic and chronic neuronopathic forms are treated with enzyme replacement therapy (fortnightly intravenous administration of modified glucocerebrosidase).

An alternative therapy for adult patients who are not suited for enzyme replacement therapy is substrate reduction therapy, which is based on reduced production of glucocerebrosides.

Monitoring

The chitotriosidase concentration in plasma reflects the amount of stored glucocerebroside in the body and therefore serves to evaluate the therapeutic success.

Prognosis

Enzyme replacement therapy leads to reduction of visceral symptoms. Whether patients with the chronic neuronopathic form experience an improvement of their neurological symptoms has not yet been conclusively clarified. There is no therapy for patients with the acute neuronopathic form. The prognosis is unfavourable with a life expectancy of only a few years.

5.13.2. Fabry's disease

Definition

This disease is caused by an X-chromosome-linked inherited deficiency of α-galactosidase A.

Incidence

The incidence of Fabry's disease was estimated to be 1:50,000; in current studies, a significantly higher incidence of 1:3,100 is assumed due to the frequent detection of late-onset, mild forms.

Pathogenesis

The ubiquitous lysosomal accumulation of globotriaosylceramide leads to a multi-system disease with very heterogeneous clinical symptoms.

Clinical spectrum

Because of the X-chromosomal inheritance, men are usually affected earlier and show a more severe course than women.

The typical first symptom that occurs in childhood are burning pain of the hands and feet. In addition there are reddish–violet skin changes (angiokeratoma), hypohidrosis, corneal deposits, chronic abdominal pain, pain crises and fatigue.

Later, the CNS (stroke), the heart (left ventricular hypertrophy, cardiac arrhythmias) and the kidneys (renal failure) are affected in the course of the disease.

Diagnosis

In men, the diagnosis is performed enzymatically by determining the activity of α-galactosidase A in leukocytes. Heterozygous women can only be diagnosed by a molecular genetic examination, since the α-galactosidase A concentration in women can be within the normal range.

Treatment

Male and female patients with Fabry's disease are treated with α-galactosidase A by means of enzyme replacement therapy. The infusion is carried out fortnightly.

Monitoring

A biomarker reflecting successful treatment is not known so far.

Prognosis

Due to the complications of heart, kidney and central nervous system, patients with Fabry's disease have a markedly limited life expectancy.

Early diagnosis and initiation of enzyme replacement therapy can prevent irreversible organ damage.

5.13.3. Mucopolysaccharidoses

Definition

Deficiencies of different lysosomal enzymes lead to an accumulation of glycosaminoglycans. MPS type II is inherited X-chromosomally, the remaining mucopolysaccharidoses are of autosomal recessive heredity.

Incidence

The total incidence of all MPS forms in Germany is estimated at 1:29,000. The most common mucopolysaccharidosis is type III with an estimated incidence of 1:63,000 in Germany.

Pathogenesis

The accumulation of glycosaminoglycans leads to cell damage with progressive malfunction of multiple tissues and organs.

Clinical spectrum

Patients with MPS often appear completely unobtrusive at birth. In the course of time a coarsening of the facial features and a progressive involvement of the liver and spleen, skeletal system, heart, lung, central nervous system and eyes occur.

The typical symptoms of the individual MPS forms are summarised in Tab. 5.17.

Diagnosis

In the case of clinical suspicion, the glycosaminoglycans are examined in the collected urine. If a finding is conspicuous, the final diagnosis is made enzymatically from skin fibroblasts, leukocytes or serum.

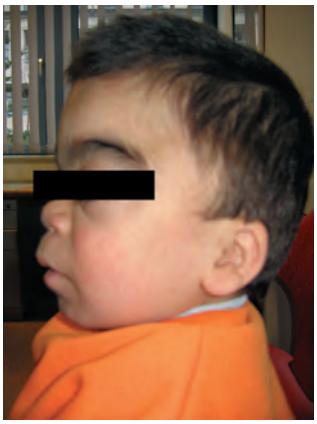

Figure 5.14: Typical face in mucopolysaccharidosis type I.

Treatment

For MPS type I, II, IVA and VI, intravenous enzyme replacement therapy is available.

In young children with MPS type I, stem cell transplantation can be considered before the occurrence of severe neurological symptoms.

Otherwise, a multidisciplinary symptomatic therapy is performed.

Monitoring

At present, there is no biomarker available for the evaluation of response to treatment.

Prognosis

In studies, a positive effect of enzyme replacement therapy on the progression of the disease was shown. However, intravenous enzyme replacement therapy has no effect on the prognosis of CNS symptoms. Intrathecal enzyme therapy for patients with MPS I, II, IIIA and IIIB is tested in clinical trials, as is intravenous enzyme replacement therapy for patients with MPS IIIB and MPS VII.

Mukopolysaccharidosis		Enzyme disorder	Clinical picture
Nr.	Eigenname		
MPS I		α-iduronidase	
I-H	Hurler		Coarse facial features, organomegaly, corneal opacity, skeletal deformities, short stature, cardiac and pulmonary involvement, mental retardation, limited life expectancy
I-H/S	Hurler/Scheie		Intermediary form
I-S	Scheie		Coarse facial features, corneal opacity, joint contractures, almost normal body size, normal intelligence
MPS II	Hunter	Iduronate-sulfatase	See Hurler, typical skin changes, no corneal opacity
MPS III			Few dysmorphisms, behavioural disorders, neurodegeneration
IIIA	Sanfilippo A	Sulfamidase	
IIIB	Sanfilippo B	α-glucosaminidase	
IIIC	Sanfilippo C	N-acetyltransferase	
IIID	Sanfilippo D	N-acetylglucosamine-6-sulfatase	
MPS IV			Especially skeletal deformities, normal intelligence
IVA	Morquio A	N-acetylgalactosamine-6-sulfatase	
IVB	Morquio B	β-galactosidase	
MPS VI	Maroteaux-Lamy	Arylsulfatase B	See Hurler, normal intelligence
MPS VII	Sly	Beta-glucuronidase	See Hurler, variable expression with very mild forms
MPS IX	Natowicz	Hyaluronidase	Short staure, periarticular swelling, normal intelligence

Table 5.17: Overview of enzyme deficiencies and symptoms of mucopolysaccharidoses.

5.14. Peroxisomal disorders

Peroxisomes are found in almost all cells (exception: mature erythrocytes). The most important peroxisomal functions are the α-oxidation of phytanic acid, the β-oxidation of long-chain fatty acids, the degradation of bile acids and the synthesis of plasmalogenes (etherphospholipid biosynthesis) or cholesterol. Various peroxins encoded by *PEX* genes are necessary for peroxisome formation and membrane transfer.

The peroxisomal diseases are a group of genetically determined diseases characterised by a development disorder of peroxisomes or by isolated defects of peroxisomal metabolic pathways.

Zellweger syndrome affects approximately 1: 100,000 newborns. The most common disorder, X-chromosomal adrenoleukodystrophy, has an incidence of approximately 1:25,000.

Peroxisomal diseases are divided into 2 groups (☞ Table 5.18).

5.14.1. Group I: Disorders of peroxisome biogenesis

Definition

The common cause of these diseases is a disturbed import of peroxisomal proteins from the cytoplasm into the peroxisomal matrix. Genetically induced defects in proteins, which interact in the formation of functioning peroxisomes, lead to severe disturbances in the biogenesis of peroxisomes.

Group	Disorder
Group I: Disorders of peroxisome biogenesis (development disorders of peroxisomes)	• "Zellweger spectrum" diseases: - Zellweger syndrome - Neonatal adrenoleukodystrophy - Infantile Refsum disease • Rhizomelic chondrodysplasia punctata type 1
Group II: Defects of peroxisomal pathways or functions	• Peroxisomal β-oxidation defects - X-chromosomal adrenoleucodystrophy - Acyl-CoA oxidase deficiency - D-bifunktional protein deficiency - Sterol carrier protein X deficiency - 2-methylacyl-CoA racemase deficiency • Peroxisomal α-oxidation defects - Classical Refsum disease • Etherphospholipid biosynthesis - Rhizomal chrondrodysplasia punctata type 2 and 3 • Glyoxylate metabolism - Hyperoxaluria type 1 • Bile acid synthesis disorders - Bile acid-CoA: amino acid-N-acyltransferase deficiency • Hydrogen peroxide homeostasis - Acatalasaemia

Table 5.18: Classification of peroxisomal disorders.

Diagnosis

- Very long-chain fatty acids (VLCFA) in plasma increased
- Disturbed biosynthesis of plasmalogens (erythrocytes)
- Concentration of phythanic acid in plasma increased (e.g. in Refsum disease)
- Increased bile acid metabolites in plasma/urine
- Enzyme studies
- Molecular genetic studies

Zellweger syndrome (cerebrohepatorenal syndrome)

Clinical symptoms

This is the most severe form of a disorder of peroxisome biogenesis defect. Characteristic clinical symptoms include:

- Craniofacial dysmorphic features (e.g. high forehead, hypertelorism, broad nasal bridge, epicanthus)
- Ocular abnormalities (retinitis pigmentosa, cataract, glaucoma, corneal cloudiness)
- Neurological dysfunctions (severe muscular hypotonia, feeding problems, epilepsy, encephalopathy and psychomotor impairment)
- Premature calcification of the patella
- Hepatointestinal dysfunction (neonatal hepatitis, hepatomegaly, cholestasis, cirrhosis)
- Renal cysts

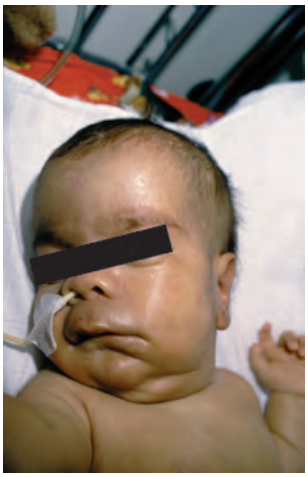

Figure 5.15: Newborn with Zellweger syndrome and facial dysmorphy.

Therapy

At present, there is no causal therapy.

Prognosis

Most of the patients die within the first year of life.

Neonatal adrenoleukodystrophy

Clinical symptoms

Most patients only show slight dysmorphic abnormalities and slow progression. Newborns often present with seizures. Further symptoms include: psychomotor impairment, liver function disturbances, retinitis pigmentosa, deafness and symptoms of adrenal insufficiency (vomiting, fatigue, pigmentation).

Therapy

At present, there is no causal therapy.

Prognosis

Most of the patients die within the first decade of life.

Infantile Morbus Refsum

Clinical symptoms

This disorder is the mildest variant of the disorders of peroxisome biogenesis. Affected children become symptomatic at an age of 1-3 years. Usually there are no dysmorphic features present. Neurological symptoms are milder than seen in the other disorders of this group. Characteristic symptoms include retinitis pigmentosa, hepatomegaly, adrenal atrophy and hearing loss.

Treatment

At present, no causal therapy exists.

Prognosis

Most of the patients die within the first decade of life.

5.14.2. Group II: Isolated defects of peroxisomal pathways

Genetic defects of single peroxisomal enzymes lead to specific disorders which are characterised by a functional loss of the affected enzyme.

X-linked adrenoleukodystrophy (ALD)

Definition

This disorder is caused by a defect of the peroxisomal ABC-transporter ABCD1. This defect leads to an accumulation of very long-chain fatty acids, inflammatory demyelinisation of the CNS, peripheral neuropathy and adrenal and/or testicular insufficiency.

Clinical symptoms

About 50% of affected patients present with the infantile-cerebral form. It is characterised by the most severe clinical course with rapidly progressing neurological symptoms. In boys, the disease usually starts at the age of 4-10 years with behavioural disturbances, intellectual regression, adrenal insufficiency and leukodystrophy. Within 2 to 4 years decerebration develops which eventually leads to death. Within the third decade of life, young men and adult heterozygous women develop symptoms of adrenomyeloneuropathy with spastic paraparesis of the legs, sphincter problems, mixed demyelinating and axonal peripheral neuropathy and adrenal insufficiency. In about 10% of all patients isolated adrenal insufficiency is found as the only clinical symptom.

Diagnosis

Increased concentration of very long-chain fatty acids (VLCFA) in plasma, cerebral demyelinisation in MRT, molecular genetic studies.

Treatment

An early bone marrow transplant at the initial stage can lead to cure. The administration of "Lorenzo's oil" (glycerol trioleate and glycerol trieucate in a ratio of 4:1) leads to a normalisation of long-chain fatty acids in the plasma, but can not decisively improve the long-term prognosis.

Prognosis

Prognosis depends on the clinical form. Early onset in infancy is usually lethal. Manifestation in adulthood has a better prognosis. 10% of all cases are asymptomatic.

Classical Morbus Refsum

Definition

This is caused by a defect in the degradation of phythanic acid (phytanoyl-CoA-hydroxylase deficiency), leading to accumulation of phytanic acid in plasma and tissues.

Clinical symptoms

Most patients show clinical symptoms at school age including retinitis pigmentosa, polyneuropathy, cerebellar ataxia or deafness. An early symptom is the occurrence of night blindness. Intelligence of affected children is usually normal.

Diagnosis

Characteristically phytanic acid in plasma is increased, whereas pristanic acid is decreased. In addition, protein content in CSF is increased. Further findings include decreased nerve velocity conduction, pathological acoustic and visual evoked potentials, as well as an abnormal electroretinogram. Confirmation diagnostics include measurement of enzyme activity in fibroblasts.

Treatment

The combination of a low phytanic diet together with plasmapheresis leads to a reduction of increased concentrations of phythanic acid.

Prognosis

Early introduction of treatment can diminish the aggravation of the symptoms of peripheral neuropathy.

5.15. Congenital disorders of glycosylation (CDG)

Definition

This is a group of metabolic diseases caused by defects in the synthesis of glycoproteins which is rapidly gaining importance.

Incidence

The most common type of CDG is phosphomannomutase deficiency (PMM2, formerly CDG type Ia) which accounts for about 70% of all cases. The exact incidence of the individual CDG types is currently very difficult to estimate.

Pathogenesis

All CDG types known so far are characterised by defective protein glycosylation. In the process of glycosylation, the native protein (e.g., membrane proteins, transport proteins, coagulation factors, enzymes, hormones, and the like) are provided with carbohydrate side chains. This is called post-translational modification and gives the protein its final function. The process of O-glycosylation is differentiated from N-glycosylation. In the future, a growing number of "new" CDG types is expected.

Groups	Disorders (selection)
Group A: Defects of protein-N-glycosylation	• PMM2-CDG (CDG type Ia): Phosphomannomutase deficiency • MPI-CDG (CDG type Ib): Phosphomannoseisomerase deficiency • MGAT2-CDG (CDG Typ IIa): N-acetylglucosaminyltransferase-II deficiency • GCS1-CDG (CDG type IIb): Glucosidase 1 deficiency • and many others
Group B: Defects of protein-O-glycosylation	• EXT1/EXT2-CDG: Galaktosyltransferase-I deficiency • and many others
Group C: Defects of glycosphingolipid and glycosylphosphatidylinositol-anchoring proteins	• ST3GAL5-CDG: Lactosylceramide α-2,3 sialyltransferase deficiency • PIGM-CDG: Glykosylphosphatidylinositol deficiency
Group D: Multiple glycosylation defects or disorders of other glycosylation metabolism pathways	• DPM1-CDG (CDG type Ie): Dolichyl-P-mannose synthase 1 deficiency • MPDU1-CDG (CDG type If): Disturbed use of dolichyl-P-mannose • B4GALT1-CDG (CDG type IId): β-1,4-galactosyltransferase deficiency • and many others

Table 5.19: Classification of congenital disorders of glycosylation.

Clinical symptoms

Congenital disorders of glycosylation cause multiple clinical symptoms. Many affected patients present with multiorgan involvement and neurological symptoms.

- Mental retardation
- Ataxia
- Cerebellar hypoplasia/atrophy
- Seizures
- Muscular hypotonia
- Strabism
- Abnormal coagulation studies
- Hepatopathy
- Unclear multisystemic disease
- Failure to thrive
- Cardiomyopathy
- Protein-losing enteropathy
- Nephrotic syndrome
- Unusual fat-pads
- Inverted nipples
- Immunological problems

Table 5.20: Clinical symptoms in congenital disorders of glycosylation.

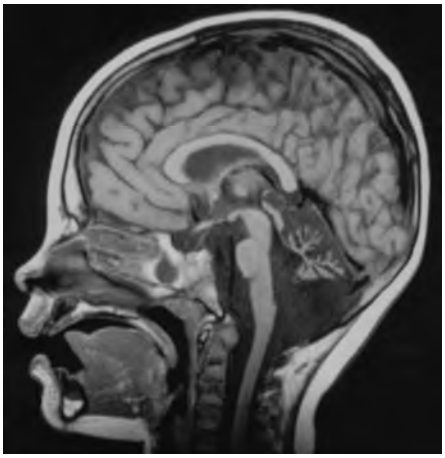

Figure 5.16: MRI showing cerebellar hypoplasia in a patient with PMM2-CDG.

Diagnosis

Diagnosis and differentiation into several types involves the demonstration of pathological glycosylation patterns in isoelectric focussing of transferrin (IEF). Final diagnosis is made by enzymatic or molecular genetic studies.

Treatment

With the exception of MPI-CDG (formerly CDG type Ib), SLC35C1-CDG (formerly CDG type IIc) and PIG-M-CDG, there is currently no effective treatment option available for any of the CDG types.

Prognosis

Prognosis is markedly dependent on the CDG type. Patients with mainly neurological involvement do not show tendencies to clinical improvement.

Because of the heterogeneity of the different types and because for some CDG types only single cases have been reported, more details will be given only for the most common defect (PMM2-CDG) and the two defects for which treatment exists so far (MPI-CDG and SLC35C1-CDG).

5.15.1. PMM2-CDG (formerly CDG type Ia)

This is by far the most common CDG type. CDG-Ia is characterised not only by muscular hypotonia, but also by a typical symptom triad in the infant: strabismus, inverted nipples and supragluteal fat pads.

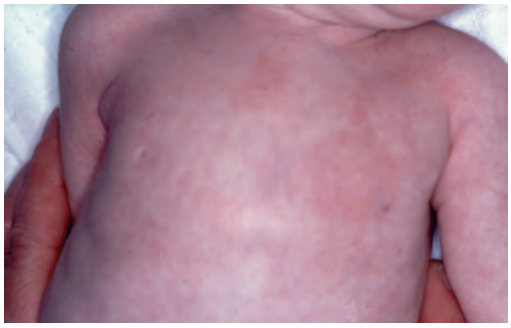

Figure 5.17: Patient with PMM2-CDG with inverted nipples.

In general, strabismus persists as a constant symptom whereas inverted nipples and the unusual fat-pads disappear with increasing age. Affected children are statomotorically and mentally retarded. Usually they are not able to walk. Further characteristic symptoms include hepatopathy, pericardial effusion, hypogonadism, retinitis pigmentosa, "stroke-like" episodes and seizures. MRI of the brain usually shows cerebellar hypoplasia. At present, there is no causal treatment.

5.15.2. MPI-CDG (formerly CDG type Ib)

This subtype is characterised by gastrointestinal symptoms. There are no neurological symptoms and no psychomotor retardation. Clinical features include:

- Protein-losing enteropathy
- Hypoglycaemia
- Fibrosis of the liver
- Abnormal coagulation studies (bleeding, thrombosis)

There exists an effective therapy in form of oral mannose.

5.15.3. SLC35C1-CDG (formerly CDG type IIc)

Patients with SLC35C1-CDG are clinically mainly characterised by dysmorphy, psychomotor impairment and an increased number of infections with significant leucoytosis. Affected children may benefit from oral substitution with fucose. However, not all symptoms can be completely treated with this therapy.

5.16. Disorders of purine and pyrimidine metabolism

Purines and pyrimidines play an important role for many metabolic pathways of cells, especially for preservation and transfer of genetic information, regulation of enzymes and supply of energy (nucleosides, nucleotides and derivatives such as cAMP (cyclic adenosine monophosphate) or ATP (adenosine triphosphate)). This explains the great clinical variability of genetic disorders concerning these pathways. Congenital disorders of purine and pyrimidine metabolism are shown in Table 5.21 with regard to affected organ systems and typical age of onset. Some diseases are briefly explained below.

Most of these disorders can be diagnosed by a urine test. It should be noted that, in principle, the uric acid concentration in plasma and urine must be in relation to one another, since, e.g., prepubertal children with increased uric acid production can maintain plasma concentrations in the normal

Affected organs					Age of manifestation				
	Kidney	Immunological/ hematological symptoms	CNS	Miscellaneous	New-born	Infants	Toddler	School age	Adult
Purine metabolism									
PRPSS	+	–	+	Gout			(+), with CNS symptoms		+ (<40y)
ASL	–	–	++	Short stature, muscle wasting	+	+			
AMPD1	–	–	–	Myopathy, asymptomatic			+	+	+
ADA	–	+++	+	Diarrhoea, failure to thrive	+	+			
PNP	–	++	+	–		+	+		
XDH	++	–	–	Arthropathy, myopathy, duodenal ulcer	+	+	+	+	+
HGPRT (=HPRT)	++	(+)	++	Gout, dystonia, autoaggressive behaviour		+			
FJHN	+++	–	–	Early renal failure				+	
APRT	++	–	–		+	+	+	+	+
Pyrimidine metabolism									
UMPS	(+)	++	+	Failure to thrive, psychomotor development delay	+	+			
UMH	–	++	–	Haemolysis and consequences			+		
DPD	–	–	+	5'-Fluoro-uracil toxicity		(+)	+		
DHP	–	–	+	5'-Fluoro-uracil toxicity		+	+		
UP	–	–	++	5'-Fluoro-uracil toxicity	(+)	+			

Table 5.21: Clinical synopsis of defects in purine and pyrimidine metabolism. **ADA**: Adenine desaminase (deficiency); **AMPD1**: adenosine monophosphate desaminase (deficiency) - synonymous: Myoadenylate desaminase (deficiency) **MDA** - another synonymous name is muscle adenosine monophosphate desaminase **MAD** (deficiency); **APRT**: Adenine phosphoribosyl transferase (deficiency); **ASL**: adenylosuccinate lyase (deficiency) - synonymous: adenylosuccinase (ASA) (deficiency); **DHP**: dihydropyrimidine amidohydrolase (deficiency) - synonymous: dihydropyrimidinase (deficiency); **DPD**: dihydropyrimidine dehydrogenase (deficiency) - also abbreviated DHPDH; **FJHN**: familial juvenile hyperuricemic nephropathy; **HGPRT**: hypoxanthine-guanine phosphoribosyl transferase (deficiency) - synonymous: **HPRT** or Lesch-Nyhan disease; **Mb-Cof**: molybdenum cofactor (deficiency); **PNP**: purine nucleoside phosphorylase (deficiency); **PRPSS**: phosphoribosyl-pyrophosphate synthase superactivity; **SO**: sulphite oxidase (deficiency); **UMH**: uridine monophosphate hydrolase (deficiency) - synonymous: pyrimidine 5'nucleotidase (deficiency); **UMPS**: uridine monophosphate synthase (deficiency); **UP**: ureidopropionase (deficiency); **XDH**: xanthine dehydrogenase (deficiency) - synonymous: xanthine oxidase (deficiency), **XO**.

range by compensatory increase of uric acid excretion. In the case of adenylosuccinase deficiency, immediate frozen morning urine is most reliable because the dominant marker metabolite (SAICAR) is unstable.

5.16.1. Increased production of uric acid

▶ Lesch-Nyhan syndrome (HPRT deficiency)

Because the salvage of guanine and hypoxanthine is deficient, inosine monophosphate (IMP) and guanosine monophosphate (GMP) cannot be synthesised and the purine bases are degraded to uric acid.

▶ Phosphoribosyl-pyrophosphate synthase superactivity (PRPSS)

Genetic superactivity of this enzyme generates increased purine synthesis and as a consequence uric acid may be increased in plasma and urine.

5.16.2. Reduced production of uric acid

▶ Xanthine oxidase deficiency and molybdenum cofactor deficiency (XDH, Mb-Cof)

The conversion of hypoxanthine to uric acid is blocked. The molybdenum cofactor is a cofactor of the xanthine oxidase, and a deficiency therefore leads to its functional failure.

▶ Purine nucleoside phosphorylase deficiency (PNP)

The degradation of guanosine and inosine is blocked.

5.16.3. Increased excretion of uric acid

Increased excretion of uric acid is found with tubulopathies of various origins. Furthermore, in several disorders there are secondary influences on uric acid excretion such as in cardiac failure, glycogenoses, Down syndrome and others.

▶ Adenylosuccinase deficiency

This disease is probably underdiagnosed in Central Europe. The symptoms are exclusively neurological and characterised by:

- **Developmental delay**
- **Epilepsy which is difficult to treat**, and begins in the newborn age in 50% of the cases
- **Handwashing motions** and stereotypical movements, even in infants
- **Autistic traits** in approximately 30% of patients

In imaging diagnostics there is a spectrum of mildly pronounced global atrophy, from cerebellar hypoplasia up to severe delay of gyration and myelinisation. High concentrations of succinyl aminoimidazole carboxamide (SAICA) riboside and succinyl adenosine in the urine are of diagnostic significance.

▶ Purine nucleoside phosphorylase deficiency (PNP)

The most important symptoms of these patients relate to a defect of their cellular immune responses. However, there are often neurological symptoms (spasticity, ataxia, tremor, intellectual disability) and progressive microcephalus as well which in some cases precede the obvious onset of immunodeficiency.

5.16.4. Therapeutic options in disorders of purine and pyrimidine metabolism

- **Allopurinol and purine-restricted diet:** in hyperuricaemia, in APRT, possibly in XDH as well
- **Enzyme replacement therapy or bone marrow transplant:** for ADA and PNP deficiencies
- **Uridine:** curative in UMPS deficiency (very rare), possibly helpful in ASL deficiency
- **β-Alanine, β-aminoisobutyrate:** may be tried in severe cases of pyrimidine degradation disorders DPD, DHP and UP.

5.17. Disorders of creatine metabolism

Definition

Two autosomal recessively inherited defects cause a malfunction in creatine synthesis: Guanidinoacetate methyltransferase (GAMT) deficiency and arginine:glycine amidinotransferase (AGAT) deficiency. Creatine transporter deficiency is inherited in an X-linked manner and is characterised by a disturbed import of creatine into brain and muscle. All disorders of creatine metabolism are characterised by cerebral convulsions, language development disorders and intellectual deficits.

Incidence

Guanidinoacetate methyltransferase (GAMT) deficiency is the most commonly diagnosed disorder of creatine synthesis. Its incidence is estimated to be between 1:500,000 and 1:2,500,000. Arginine: glycine amidinotransferase (AGAT) deficiency is extremely rare, so far less than 20 patients have been diagnosed.

Pathogenesis

Creatine is synthesised in a two-step process by the action of AGAT and GAMT (☞ Figure 5.18). The creatine transporter (CRTR) is necessary for the uptake of creatine into brain and muscle. A deficiency of one of those two enzymes or of the creatine transporter leads to a deficiency of creatine, especially in the brain. Because the creatine/creatinephosphate-system plays a special role in energy storage in the brain and muscle, disturbances of creatine synthesis or transport cause severe, mainly clinical symptoms.

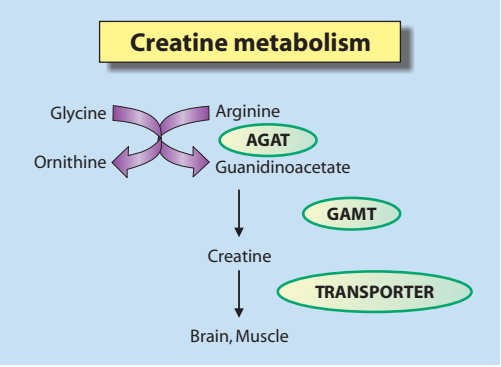

Figure 5.18: Creatine synthesis. AGAT=Arginine: glycine amidinotransferase; GAMT=Guanidinoacetate methyltransferase.

5.17.1. Guanidinoacetate methyltransferase (GAMT) deficiency

Clinical spectrum

Patients present with developmental delay, autistic behaviour, treatment-resistant epilepsy, and dystonic/dyskinetic movement disorder.

Diagnosis

Concentrations of guanidinoacetate are elevated in all body fluids (plasma, urine, cerebrospinal fluid). In addition, the relation of creatine to creatinine in urine is decreased. Brain MR spectroscopy detects cerebral creatine deficiency. Brain morphology is usually not affected. If molecular genetic analysis is not conclusive, diagnosis can be confirmed by enzymatic studies in lymphoblasts, fibroblasts, or liver tissue.

Treatment

Therapeutically, high doses of creatine are given in order to correct cerebral creatine deficiency. Ornithine and/or dietary restriction of arginine aim at the suppression of the synthesis of guanidinoacetate which has been shown to be epileptogenic.

Monitoring

Treatmend monitoring includes measurement of ornithine and arginine in plasma, guanidinoacetate in plasma or urine. Intracerebral concentration of creatine can be measured by MR spectroscopy.

Prognosis

Treatment, especially if started early, can partially improve the neurological symptoms.

5.17.2. Arginine:glycine-amidinotransferase (AGAT) deficiency

Clinical spectrum

This disease is mainly characterised by psychomotor disability and severe speech delay.

Diagnosis

Guanidinoacetate in plasma and urine is decreased, whereas the ratio of creatine to creatinine in urine may be decreased or within the normal range. MR spectroscopy shows cerebral creatine deficiency. The diagnosis is confirmed by measurement of enzyme activity in lymphoblasts or fibroblasts and by mutational analysis.

Treatment

Treatment includes oral doses of creatine.

Monitoring

Measurement of intracerebral concentration of creatine (by MR spectroscopy).

Prognosis

Creatine supplementation can improve neurological functions, e.g. fine motor skills.

5.17.3. Creatine transporter deficiency

Clinical spectrum

This disease is characterised by psychomotor disability with or without mild epilepsy. Often there is a speech delay, movement disorders, autistic behaviour disorders as well as attention deficit hyperactivity disorders. Cerebral atrophy is often found in cerebral imaging. Heterozygous females can be asymptomatic or show a severe clinical phenotype like male hemizygote patients.

Diagnosis

Intracerebrally decreased creatine can be detected by brain MR spectroscopy. Concentrations of creatine in plasma and urine may be increased, whereas guanidinoacetate in plasma and urine is normal. The diagnosis is confirmed by creatine uptake assays in fibroblasts and mutational analysis.

Treatment

Therapeutically, oral administration of creatine and its precursors arginine and glycine should be tried.

Prognosis

Treatment does not seem to influence the disease course positively.

5.18. Hyperlipidaemias

Primary disorders of lipid metabolism belong to the most frequent inborn errors of metabolism. In addition, the incidence of secondary hyperlipidaemias is also increasing in children, especially in the context of overweight and obesity.

The Fredrickson classification (☞ Table 5.22) is used for the phenotypic classification of hyperlipidaemias, however, it does not allow a clear assignment to the underlying genetic defects.

Type	Accumulating lipoproteins	Triglycerides	Total cholesterol
I	Chylomicrons	↑	n-↑
IIa	LDL	n	↑
IIb	LDL, VLDL	↑	↑
III	VLDL remnants, chylomicrons	↑	↑
IV	VLDL	↑	n-↑
V	Chylomicrons, VLDL	↑	↑

Tab. 5.22: Phenotypic classification of hyperlipidaemias according to Fredrickson.

5.18.1. Hypercholesterolaemia

Definition

An increase in total and LDL cholesterol can be caused by genetic defects (familial hypercholesterolaemia) or occur secondary due to overweight and obesity or the excessive consumption of saturated fatty acids and cholesterol.

Incidence

Familial hypercholesterolaemia is one of the most frequent disorders of lipid metabolism. Heterozygous mutations of the LDL receptor occur with an incidence of 1:500. Homozygous mutations in the LDL receptor gene associated with excessive hypercholesterolaemia occur with an incidence of 1:1,000,000.

Pathogenesis

In addition to autosomal-codominantly inherited mutations in the LDL receptor gene, defects of apoliprotein B-100, which is required for the binding to the LDL receptor and the uptake of LDL into the liver cells, proprotein covertase subtilisin/kexin 9 (PCSK9) and the LDL receptor adaptor protein (LDLRAP1) lead to elevated levels of total and LDL cholesterol in plasma. Polygenic forms of hypercholesterolaemia may also present with a type IIa hyperlipidaemia phenotype.

Clinical spectrum

Elevated cholesterol levels are a major risk factor for the premature development of atherosclerosis and the occurrence of cardiovascular events. Ultra-

sound can detected an increase in intima–media thickness already in childhood or adolescence. Homozygous LDL receptor mutations lead to excessively elevated cholesterol levels, tendon and skin xanthomas, and ocular cholesterol deposits (arcus cornealis). Patients often already experience myocardial infarction or strokes during childhood or adolescence.

Diagnosis

Diagnosis is based on positive family history and elevated cholesterol levels (in particular LDL cholesterol). Triglycerides are usually within the normal range. Molecular analysis is useful for counselling patients and their families, but is not a necessary prerequisite for the initiation of treatment. It is known that selective screening (e.g. screning based on family history) overlooks many patients with hypercholesterolaemia.

Treatment

Treatment aims to lower LDL cholesterol levels and to reduce the occurence of atherosclerosis cardiovascular risk. In childhood and adolescence "lifestyle modifications", i.e., diet changes and promotion of physical activity are the basis of therapy. Other risk factors, e.g. smoking, should be avoided. Arterial hypertension or diabetes mellitus must be treated consistently. Normalisation of weight is absolutely essential.

Dietary restriction of intake of fat (<30% of daily energy intake, saturated fat <10% of daily energy intake) and cholesterol (<300 mg daily) is considered effective and safe and is recommended from the age of 2 years. If this does not lead to a sufficent reduction of cholesterol levels, a more rigorous restriction (<7% of daily energy intake from saturated fats, <200 mg of cholesterol daily) may be necessary. In addition, an increased supply of fibre and fish oil can be effective. Plant sterols, e.g. in the form of sitostanol-enriched margarine, lowers cholesterol levels by inhibition of cholesterol uptake in the intestine, but there are no data proving its effectiveness in terms of cardiovascular risk reduction. Phytosterinaemia (sitosterolaemia), a rare disorder in which plant sterols are absorbed excessviely in the intestine, is a contraindication for taking plant sterols.

Dietary measures can reduce LDL cholesterol by up to 15-20%. If a sufficient reduction of LDL cholesterol cannot be achieved by lifestyle modifications, drug treatment may be indicated depending on the presence of other CVD risk factors. In children below 10 years of age, drug treatment is generally only initiated in cases of severe hyperlipidaemia or in the presence of additional serious risk factors.

HMG-CoA reductase inhibitors (statins) regarded as first-line tretament because of their efficacy and tolerability in children and adolescents. However, long-term data on safety and effectiveness in terms of primary prevention in children and adolescents

Term	Electrophoretic mobility	Lipid amount	Main lipids	Apoproteins	Tissue source	Function
Chylomicrons	Remains at origin	98%	Triglycerides	B48, A-I, A-II, C-II, C-III, E	Intestine	Transport of exogenous triglycerides from intestine to liver
VLDL	Pre-β-band	90%	Triglycerides	B100, C-II, E	Liver, intestine	Transport of endogenous triglycerides from liver to extrahepatic tissue
LDL	β-band	75%	Cholesterol	B100	Degradation product of VLDL	Cholesterol transport to extrahepatic tissue
HDL	α-band	50%	Cholesterol, Phospholipids	A-I, A-II, C, E	Liver, intestine	Cholesterol transport from extrahepatic tissue to the liver

Table 5.23: Characteristics of important lipoproteins.

are still missing. By inhibiting the HMG-CoA reductase, statins lead to reduced cholesterol synthesis and increased LDL uptake into the liver and can lead to a reduction of LDL cholesterol by 20-40%. Several statins are approved for children. Serious side effects such as rhabdomyolysis or liver damage rarely occur in children. Lipid profile, creatine kinase, transaminases should be carried out regularly under statin treatment (four and eight weeks after initiation of therapy, later biannually).

Ezetimib selectively inhibits intestinal cholesterol uptake and leads to a reduction of cholesterol levels by 15-20%. It is generally well tolerated and are approved from 10 years of age.

Anion exchange resins lower the cholesterol level by 10-15%. Due to their low therapeutic effect and poor compliance because of frequently occurring dose-dependent side effects (including flatulence, fullness, constipation, nausea) and an unpleasant taste, they are hardly used today for the treatment of hypercholesterolaemia. Homozygous familial hypercholesterolaemia is a very rare condition. LDL levels may exceed 1000 mg/dl, and patients are at high risk for maocardial infarctions already in the first decade of life. These patients require aggressive LDL reduction, usually by LDL apheresis at biweekly or weekly intervals.

5.18.2. Hypertriglyceridaemia

Mild to moderate elevations of plasma triglycerides are common and usually associated with overweight and obesity. An excessive intake of simple carbohydrates causes an increase in triglyceride levels. Insulin resistance is also associated with elevated triglycerides. In addition, secondary elevations of triglyceride levels are observed in the context of various underlying diseases (e.g., chronic renal insufficiency, nephrotic syndrome, HIV infection, rheumatic diseases) or use of pharmaceuticals (steroids, beta-blockers, thiazide diuretics, etc.).

Severe hypertriglyceridaemias with triglyceride levels above 1000 mg/dl (11.5 mmol/l) are rare and usually due to the disorders described below.

The role of increased triglyceride levels in the development of cardiovascular diseases has long been controversially discussed. By now hypertriglyceridaemia has been recognised as a cardiovascular risk factor.

5.18.2.1. Hyperchylomicronaemia

Definition

Hyperchylomicronaemia is a rare autosomal recessively inherited disease characterised by the appearance of chylomicrons in fasting plasma. It is caused by disturbed hydrolysis of chylomicrons due to deficiency of lipoprotein lipase (LPL) or of its cofactor Apo C-II.

Clinical spectrum

Triglyceride levels are massively elevated and often exceed 2,000 mg/dl (23 mmol/l) in neonates. The serum of affected patients appears milky. Severe hypertriglyceridaemia can cause various confounding laboratory abnormalities.

Triglyceride levels above 1,000 mg/dl are associated with acute pancreatitis. Hyperchylomicronaemia syndrome, characterised by abdominal pain, pancreatitis, altered consciousness, lipaemia retinalis, eriptive xanthomas and disturbed peripheral blood circulation, is due to increased plasma viscosity in the context of excessive triglyceride elevations.

Treatment

Treatment aims at lowering plasma triglyceride levels below 1,000 mg/dl (11.5 mmol/l) in order to prevent complications such as pancreatitis or hyperchylomicronaemia syndrome. A strict restriction of dietary fat intake is essential. Medium chain fatty acids (MCT) are absorbed directly via the portal vein without the formation of chylomicrons and can be added to the diet in form of MCT oil or margarine. Omega 3 fatty acids as found in fish oil are recommended as well. Alcohol, oestrogens and other drugs that increase triglyceride levels are contraindicated. Fibrates are very rarely used.

Acute complications of hypertriglyceridaemia may require lipoprotein apheresis. Fresh frozen plasma contains Apo C-II and can be given to patients with Apo C-II deficiency.

Alipogene tiparvovec is the first approved gene therapy treatment for adult patients with LPL defi-

ciency and suffering from recurrent and severe pancreatitis.

5.18.2.2. Familial hypertriglyceridaemia

Definition

In familial hypertriglyceridaemia, heterozygous LPL mutations lead to a type IV phenotype with moderately elevated triglyceride levels of 200-500 mg/dl (2.3-5.7 mmol/l).

Clinical spectrum

Serious acute complications, such as in hyperchylomicronaemia usually do not occur. However, increased triglyceride levels are associated with an increased risk of cardiovascular disease.

Treatment

Therapeutic attempts to reduce elevated triglyceride levels include dietary measures and increased physical activity.

5.18.3. Mixed hyperlipidaemias

Mixed or combined hyperlipidaemias present with an increase of cholesterol and triglycerides (type III phenotype).

5.18.3.1. Familial combined hyperlipidaemia

Definition

In familial combined hyperlipidaemia, a disturbed metabolism of apoliporotein B leads to an increase in triglycerides and LDL cholesterol and a decrease of HDL cholesterol. The biochemical phenotype is variable, and penetrance in childhood and adolescence is incomplete.

The risk of premature cardiovascular events is increased.

Incidence

With an incidence of 1:200, familial combined hyperlipidaemia is one of the most common inborn causes of hyperlipidaemia.

Treatment

Lifestyle modifications and lipid-lowering drugs can positively influence the lipid profile and cardiovascular risk.

5.18.3.2. Familial dysbetalipoproteinaemia (remnant hyperlipidaemia, broad beta disease)

Definition

Familial dysbetalipoproteinaemia caused by changes in apolipoprotein E presents with an elevation of VLDL remnants and increased concentrations of cholesterol and triglycerides (type III phenotype).

Clinical spectrum

The disease rarely manifests before adulthood. It is characterised by early cardiovascular complications and tubo-eruptive xanthomas. Yellowish hand lines are pathognomonic (xanthoma striatum palmare).

Treatment

As in familial combined hyperlipidaemia, the lipid profile and the cardiovascular risk can be favourably influenced by lifestyle modifications and, if indicated, medication.

6. Tables – special metabolic investigations, dietetic treatment, emergency medication

Parameter	Inborn error of metabolism (examples)
Creatinine (decreased)	Disorders of creatine synthesis
Uric acid (increased)	MCAD deficiency
	Glycogenosis type 1
	Disorders of purine metabolism
	Mitochondriopathies
Uric acid (decreased)	Molybdenum cofactor deficiency
	Disorders of purine metabolism
Tri-glycerides (decreased)	Abetalipoproteinaemia
	Hypobetalipoproteinaemia
Tri-glycerides (increased)	Glycogenosis type 1
	Lipoproteinlipase deficiency
	Dysbetalipoproteinaemia
	Hepatic lipase deficiency
	Lecithin-cholesterol acyltrans-ferase (LCAT) deficiency
Cholesterol (decreased)	Abetalipoproteinaemia
	Hypobetalipoproteinaemia
	Mevalonic aciduria
	Barth Syndrome
	Smith-Lemli-Opitz syndrome
	Disorders of peroxisomal metabolism
	Bile acids synthesis defects
	CDG (e.g. type Ic)
Cholesterol (increased)	Lipoproteinlipase deficiency
	Dysbetalipoproteinaemia
	Hepatic lipase deficiency
	LCAT deficiency
Creatine kinase (CK) (increased)	Fatty acid oxidation defects (e.g. VLCAD, LCHAD, TFP)
	Glycogenosis (e.g. type II, III, V)
	CDG (e.g. type Ic)
	Mevalonic aciduria
	Mitochondriopathies
	3-Methylglutaconaciduria type 1
α-Feto-protein (increased)	Tyrosinaemia type I
Ferritin (increased)	Lysinuric protein intolerance
Anaemia (macro-zytic)	Disorders of cobalamine and folate metabolism
Neutropenia	Glycogenosis type 1 non-a
	Methylmalonic aciduria
	Propionic aciduria
	3-Methlyglutaconic aciduria type 2
	Lysinuric protein intolerance
Thrombo-cytopenia	Mevalonic aciduria
	Methylmalonic aciduria
	Propionic aciduria
	Lysinuric protein intolerance
Alkaline phosphatase (AP) (increased)	Bile acids synthesis defects
Lactate dehydro-genase (LDH) (increased)	Lysinuric potein intolerance
	Glycogenosis type V
Vacuolised lymphocytes (periphereal blood smear)	Lysosomal storage disorders
Reticulo-cytes (increased)	γ-Glutamylcysteine-synthetase deficiency
	γ-Glutamyltranspeptidase deficiency
	Glycolysis defects

Table 6.1: Selection of laboratory routine investigations in blood (serum, plasma), which indicate an underlying inborn error of metabolism.

Amino acid	Inborn error(s) of metabolism (examples)
Alanine (increased)	Urea cycle defects and all disorders with hyperammonaemia
	Mitochondriopathies/disorders of lactate/pyruvate metabolism
β-Alanine (increased)	β-Alaninaemia (DD vigabatrin treatment)
Allo-Isoleucine (increaed)	Maple syrup urine disease (MSUD)
Arginine (increased)	Arginase deficiency
Arginine (decreased)	Urea cycle defects (except arginase deficiency)
	HHH syndrome
	Ornithine aminotransferase deficiency (gyrate atrophy)
Argininosuccinate (increased)	Argininosuccinate lyase deficiency
Citrulline (increased)	Citrullinaemia
	Argininosuccinate lyase deficiency
	Pyruvate carboxylase deficiency type B
Citrulline (decreased)	δ-Pyrroline-5-carboxylate-synthase deficiency
	Lysinuric protein intolerance
	NAGS, CPS or OTC deficiency
	Respiratory chain disorders
Cystathionine (increased)	Disorders of cobalamine metabolism
	Cystathionine β-synthase deficiency
	Methlylene tetrahydrofolate reductase (MTHFR) deficiency
Cystine (decreased)	Molybdenum cofactor deficiency
	Sulphite oxidase deficiency
Glutamine (increased)	Disorders with hyperammonaemia (e.g. CPS or OTC deficiency)
Glycine (increased)	Non-ketotic hyperglycinaemia
	Propionic aciduria
	Methlymalonic aciduria
	Disorders of cobalamine metabolism
Homocyst(e)ine (increased)	Cystathionine β-synthase deficiency
	Disorders of folate and cobalamine metabolism
	Methionine adenosyltransferase deficiency
Isoleucine (increased)	Maple syrup urine disease (MSUD)
Leucine (increased)	Maple syrup urine disease (MSUD)
Lysine (increased)	Pyruvate carboxylase deficiency type B
Lysine (decreased)	HHH syndrome
	Ornithine aminotransferase deficiency (gyrate atrophy)
	Disorders of creatine synthesis
Methionine (increased)	Adenosine deaminase deficiency
	Cystathionine β-synthase deficiency
Methionine (decreased)	Disorders of cobalamine metabolism
Methionine sulfoxide (increased)	Cystathionine β-synthase deficiency
Ornithine (increased)	Disorders of creatine synthesis
	HHH syndrome
	Ornithine amino transferase deficiency (gyrate atrophy)
Ornithine (decreased)	δ-Pyrroline-5-carboxylate-synthase deficiency
Phenylalanine (increased)	Phenylketonuria (PKU)/ Hyperphenylalaninaemia
	Disorders of pterine metabolism
	Tyrosinaemia type I
Pipecolic acid (increased)	Hyperlysinaemia, disorders of peroxisomal metabolism, vitamin B_6-responsive epilepsy
Proline (increased)	Hyperprolinaemia I and II
	Pyruvate carboxylase deficiency type B

Proline (decreased)	δ-Pyrroline-5-carboxylate-synthase deficiency
Saccharo-pine (increased)	Saccharopinuria
Sarcosine (increased)	Sarcosinaemia
	Mitochondriopathies
	Glutaric aciduria type II
Serine (decreased)	Defects of serine metabolism
	Cystathionine β-synthase deficiency
S-sulfo-cysteine (increased)	Molybdenum cofactor deficiency
	Sulphite oxidase deficiency
Tyrosine (increased)	Tyrosinaemia type I, II and III
	4-Hydroxyphenylpyruvate oxidase deficiency
Tyrosine (decreased)	Phenylketonuria (PKU)
	Disorders of pterine metabolism
Valine (increased)	Maple syrup urine disease (MSUD)

Table 6.2: Selection of abnormal concentrations of amino acids in blood and probable underlying inborn errors of metabolism.

Amino acid	Inborn error(s) of metabolism (Example)
All amino acids	"Classical" galactosaemia (GALT deficiency)
	Tyrosinaemia type I
	Hereditary fructose intolerance
	Lowe syndrome
Neutral amino acids	Hartnup disease
Arginine	Cystinuria
	Dibasic aminoaciduria
	Lysinuric protein intolerance
Cystine	Cystinuria
	Hyperlysinaemia
	Hyperornithinaemia
Glutathione	γ-Glutamyltranspeptidase deficiency
Hawkinsin	Hawkinsinuria
Homo-citrulline	HHH syndrome
Homo-cyst(e)ine	Disorders of folate and cobalamine metabolism
	Cystathionine β-synthase deficiency
Imino-peptide	Prolidase deficiency
Lysine	Cystinuria
	Dibasic aminoaciduria
	Lysinuric protein intolerance
Ornithine	Cystinuria
	Dibasic aminoaciduria
	Lysinuric protein intolerance

Table 6.3: Selection of increased concentrations of amino acids in urine and probable underlying inborn errors of metabolism.

Substance	Inborn error(s) of metabolism (examples)
Decendione acid, decadiendione acid	VLCAD deficiency
Ethlymalonic acid	Mitochondriopathies
	Glutaraciduria type II
	SCAD deficiency
Fumaric acid	Fumaraciduria
Homogentisinic acid	Alcaptonuria
4-Hydroxy-butyric acid	Succinatsemialdehyde dehydrogenase (SSADH) deficiency
3-Hydroxy-dicarboxylic acids	LCHAD deficiency, TFP deficiency
3-Hydroxyglutaric acids, glutaric acid, glutaconic acid	Glutaraciduria type 1
3-Hydroxy-isovaleric acid	Disorders of biotin metabolims, all defects of leucine metabolism
Isovalerylglycine	Isovaleric aciduria
Malonic acid	Malonyl-CoA decarboxylase deficiency
Methylcitrate	Disorders of propionate metabolism
3-Methylglutaconic acid	3-Methylglutaconic acidurias
2-Methyl-3-hydroxybutyric acid, tiglylglycine, 2-methylacetoacetic acid	3-Oxothiolase deficiency
Methlymalonic acid	Methlymalonic aciduria
	Disturbances in vitamin B_{12} metabolism
N-Acetylaspartic acid	Canavan's disease
5-Oxoproline	Glutathione synthetase deficiency
Suberic acid, sebacic acid, hexanoylglycine, hexanoine acid, octanoic acid, phenylpropionyl-glycine	MCAD deficiency
Succinylacetone	Tyrosinaemia type I

Table 6.4: Selection of organic acids which, in cases of increased concentration, may indicate an underlying inborn error of metabolism.

Acylcarnitine	Inborn error(s) of metabolims (Examples)
Carnitine (total) (decreased)	Carnitine transporter deficiency
	Glutaric aciduria type I, MCAD, VLCAD or LCHAD deficiency
Propionyl (C3)	Propionic aciduria
	Methylmalonic acid-uria
Butyryl/ isobutyryl (C4)	SCAD deficiency
	Multiple acyl-CoA dehydrogenase (MAD) deficiency
Tiglyl/3-methylcrotonyl (C5 :1)	3-Oxothiolase defiency, 3-Methyl-crotonyl-CoA-carboxylase (3-MMC) deficiency
Isovaleryl/2-Methyl-butyryl (C5)	Isovaleric aciduria
3-Hydroxyisovaleryl (C5-OH)	3-MMC deficiency
Methylmalonyl (C4-DC)	Methylmalonic acid-uria
Glutaryl (C5-DC)	Glutaraciduria type I
Hexanoyl (C6), octanoyl (c8), decenoyl (C10:1)	MCAD deficiency
Methylglutaryl (C6-DC)	HMG-CoA lyase deficiency
Decanoyl (C10:1), dodecanoyl (C12)	MAD deficiency
Tetradodecenoyl (C14.2), tetradecenoyl (C14:1), tetradecanoyl (C14), palmitoyl (C16), linoleoyl (C18:1)	VLCAD deficiency
3-Hydroxypalmitoyl (C16-OH), 3-hydroxylinoleoyl (C18:1-OH)	LCHAD deficiency, trifunctional protein (TFP) deficiency

Table 6.5: Selection of abnormal increased concentration of acylcarnitines in blood (by tandem mass spectrometry) and differential diagnosis of probable underlying inborn errors of metabolism.

Disorder	Relevant investigations in cerebrospinal fluid (CSF)
Glucose transporter protein (GLUT1) deficiency	Glucose (CSF/blood-ratio)
Non-ketotic hyperglycinaemia	Glycine (CSF/blood-ratio)
Serine synthesis defects	Amino acids (serine; CSF/blood-ratio)
Defects in metabolism of biogenic amines	Metabolites of biogenic amines
GABA transaminase deficiency	GABA
Methylene tetrahydrofolate reductase (MTHFR) deficiency	5-MTHF
Mitochondrial encephalopathies	Lactate (alanine)
Disturbances in metabolism of leukotrienes	Cysteinyl-leukotrienes

Table 6.6: Selection of inborn errors of metabolism in whom investigations of CSF can contribute to diagnosis.

Disorder	Dietetic treatment principle
Phenylketonuria (PKU)	Restriction of phenylalanine
Maple syrup urine disease (MSUD)	Restriction of leucine, isoleucine and valine
Homocystinuria (cystathionine β-synthase-deficiency)	Restriction of methionine, administration of vitamine B_6 and betaine
Tyrosinaemia type I	Phenylalanine- and tyrosine reduced diet, NTBC
Lysinuric protein intolerance	Protein restriction
Urea cycle defects	Protein restriction
Propionic aciduria	Restriction of isoleucine, valine, methionine and threonine
Methylmalonic aciduria	Restriction of isoleucine, valine, methionine and threonine
Isovaleric aciduria	In severe cases, restriction of leucine; in mild cases, protein restriction
Glutaric aciduria type I	Restriction of lysine and reduction of tryptophan
"Classical" Galactosaemia (GALT-deficiency)	Restriction of galactose and strict avoidance of lactose
Hereditary Fructoseintolerance	Restriction of fructose and saccharose
Glycogenosis type I	Frequent feeding with glucose and glucose-polymers, restriction of galactose, lactose and fructose
Disorders of creatine synthesis (GAMT and AGAT defciency)	Restriction of arginine

Table 6.7: Selection of inborn errors of metabolism which can be treated dietetically.

Medication	Dosis
Ammunol® (Sodium benzoate + Sodium phenylacetate)	Initially 2.5 ml/kg/2 h; 2.5 ml/kg/24 h as continous infusion
Biotin	5-20 mg/24 h p.o. (1 dose)
Carglumic acid	100-250 mg/kg/24 h p.o. (2-4 doses)
Diazoxide	5-15 mg/kg/24 h p.o. (3 doses)
Glucagon	30-100 µg/kg as bolus i.v., 5-10 µg/kg/h as continous infusion (max. 1-2 mg/24 h)
Hydroxycobalamine (vitamin B_{12})	1 mg/24 h i.m. or i.v. (1 dose)
L-arginine-HCl	Initially 2 mmol/kg/1-2 h; as continous infusion 2 mmol/kg/24 h
L-carnitine	50-200 mg/kg/24 h as continous infusion
L-isoleucine	up to 100 mg/kg/24 h p.o. (3-5 doses)
L-valine	up to 100 mg/kg/24 h p.o. (3-5 doses)
Sodium benzoate	Initially 250 mg/kg/2 h; as continous infusion 250 mg/kg/24 h
Sodium-phenylbutyrate	250 mg/kg/24 h p.o. (3 doses)
Nitisinone (NTBC)	1 mg/kg/24 h p.o. (2 doses)
Pyridoxine-HCl (vitamin B_6)	100 mg i.v. (1 dose), repeat if necessary
Riboflavin (vitamin B_2)	100-300 mg/24 h i.v. (3 doses)
Somatostatin	0.5-3.5 µg/kg/h i.v.
Thiamine-HCl (vitamin B_1)	150-300 mg/24 h i.v. (3 doses)

Table 6.8: Selection of medications which may be used in cases of a metabolic emergency.

7. Literature and internet links

7.1. General literature

Blau N, Duran M, Gibson KM, Dionisis-Vici C, Eds. Physician´s guide to the diagnosis, treatment, and follow-up inherited of metabolic diseases. Springer, Heidelberg, 2014.

Clarke JTR. A clinical guide to inherited metabolic diseases. 3rd edition. Cambridge University Press, Cambridge, 2010.

Saudubray JM, Van den Berghe G, Walter JH, Eds., Inborn metabolic diseases, 5th edition. Springer, Heidelberg, 2012.

Hoffmann GF, Zschocke J, Nyhan WL. Inherited metabolic diseases. Springer, Heidelberg, 2010.

Nyhan WL, Barshop BA, Ozand PT. Atlas of metabolic diseases, 2nd edition. Oxford University Press, London, 2005.

Valle D, Beaudet AL, Vogelstein B, Kinzler KW, Antonarakis SE, Ballabio A, Gibson KM. Mitrchell G. The online metabolic and molecular bases of inherited diseases (OMMBID). www.ommbid.mhmedical.com

Zschocke J, Hoffmann GF. Vademecum Metabolicum – Diagnose und Therapie erblicher Stoffwechselkrankheiten, 4. Auflage, Schattauer, Stuttgart, 2012.

7.2. Internet links

- www.ncbi.nlm.nih.gov/omim
  (Disease-related online-version of "Mendelian Inheritance in Man", a summary of genetic/ metabolic diseases)
- www.orpha.net
  (French/European database for several metabolic diseases and diagnostic advices)
- www.rarediseases.org
  (Clinical Database of the National Organization for Rare Disorders (NORD) with more than 1000 listed diseases)
- www.eddnal.com
  (List of European laboratories offering genetic analyses)
- www.ninds.nih.gov/health_and_medical/disorders
  (Information and links to different inborn errors of metabolism with special focus on neurological disturbances)
- www.hgmd.cf.ac.uk
  (Human Gene Mutation Database, HGMD)
- www.dig-pku.de
  (Information for patients with phenylketonuria (PKU) and parents as well as for parents and patients with similar inborn errors, e.g. organic acidurias, urea cycle defects, non-ketotic hyperglycinaemia and tyrosinaemia)
- www.galid.de
  (Information on galactosaemia for patients and their parents)
- www.glykogenose.de
  (Information for patients and parents related to glycgenoses)
- www.cdg-syndrom.de
  (Information for patients and parents related to CDG)
- www.ggd-ev.de
  (Information for patients and parents related to Gaucher's disease)
- www.mps-ev.de
  (Information for patients and parents related to mucopolysaccharidoses)
- www.fabry-selbsthilfegruppe.de
  (Information for patients and parents related to Fabry's disease)
- www.ssiem.org
  (Homepage of the Society for the Study of Inborn Errors of Metabolism)
- www.simd.org
  (Homepage of the Society for Inherited Metabolic Diseases)
- www.aps-med.de
  (Homepage of the Arbeitsgemeinschaft fuer Paediatrische Stoffwechselstoerungen)

8. Abbreviations

AFP	α-fetoprotein
AGAT	arginine:glycine-amidinotransferase
ASL	argininosuccinate lyase
ASS	argininosuccinate synthetase
BH_4	tetrahydrobiopterin
CACT	carnitine/acylcarnitine-translocase
CBS	cystathione-β-synthetase
CDG	congenital disorders of glycosylation
CHI	congenital hyperinsulinism
CK	creatine kinase
CPS	carbamoylphosphate synthetase
CPT	carnitine-palmitoyl-CoA-transferase
EDTA	ethylenediaminetetraacetate
GA-I	glutaric aciduria type I
GALT	galactose-1-phosphate-uridyl-transferase
GAMT	guanidinoacetate methyltransferase
GDH	glutamate dehydrogenase
GSD	glycogen storage disease
HFI	hereditary fructose intolerance
HHH	hyperammonaemia, hyperornithinaemia, homocitrullinuria
HMG	3-hydroxy-3-methylglutarate
HPA	hyperphenylalaninaemia
IEF	isoelectric focussing
IVA	isovaleric aciduria
LCHAD	long-chain hydroxyacyl-CoA dehydrogenase
LPI	lysinuric protein intolerance
MAD	multiple acyl CoA dehydrogenase
MCAD	medium-chain acyl-CoA dehydrogenase
MMA	methylmalonic aciduria
MPS	mucopolysaccharid(osis)
MRI	magnetic resonance imaging
MS	mass spectrometry
MSUD	maple syrup urine disease
MTHFR	methylenetetrahydrofolate reductase
NAGS	N-acetylglutamate synthetase
NH_3	ammonia
OH	hydroxy
OTC	ornithine transcarbamylase
PA	propionic aciduria
PC	pyruvate carboxylase
PDH	pyruvate dehydrogenase
Phe	phenylalanine
PKU	phenylketonuria
SCAD	short-chain acyl-CoA dehydrogenase
SLO	Smith-Lemli-Opitz
TFP	trifunctional protein
Tyr	tyrosine
VLCAD	very long-chain acyl-CoA dehydrogenase
VLCFA	very long-chain fatty acids

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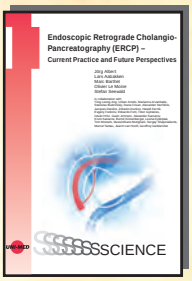

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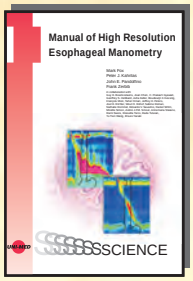

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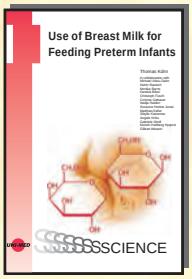

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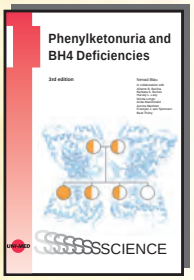

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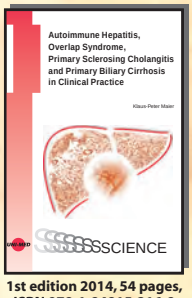

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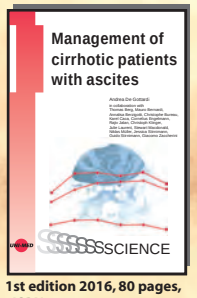

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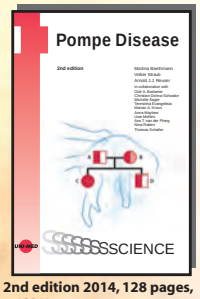

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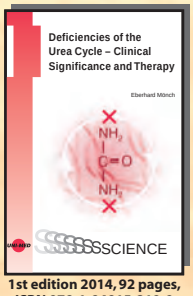

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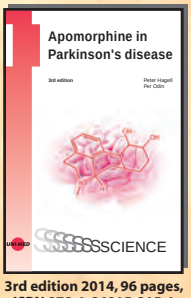

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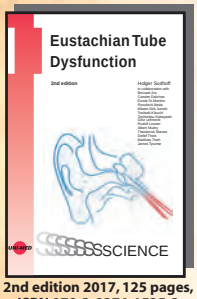

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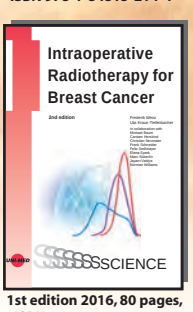

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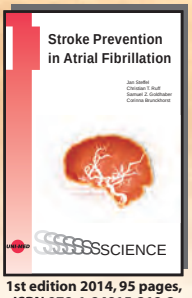

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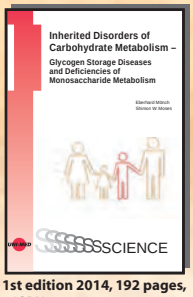

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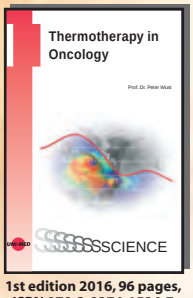

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