Inborn errors of carbohydrate metabolism

Ertan Mayatepek, MD, Professor of Pediatrics, Director *, Björn Hoffmann, MD, Fellow, Thomas Meissner, MD, Attending
Department of General Pediatrics, University Children’s Hospital, Moorenstrasse 5, 40225 Düsseldorf, Germany

Keywords:
Glycogen storage disease
Hepatomegaly
Hypoglycaemia
Liver adenoma
Classical galactosaemia
Hereditary fructose intolerance
Fructose-1,6-bisphosphate deficiency

Glycogen storage diseases (GSD) and inborn errors of galactose and fructose metabolism are the most common representatives of inborn errors of carbohydrate metabolism. In this review the focus is set on the current knowledge about clinical symptoms, diagnosis and treatment. Hepatomegaly and hypoglycaemia are the main findings in liver-affecting GSD like type I, III and IX. Diagnosis is usually made by non invasive investigations, e.g. mutation analysis. In GSD I, a carbohydrate balanced diet with frequent meals and nocturnal continuous tube feeding or addition of uncooked corn starch are the mainstays of treatment to prevent hypoglycaemia. Liver transplantation has been performed in different types of GSD. It should only be considered in high risk patients e.g. with substantial cirrhosis. Many countries have included classical galactosaemia in their newborn screening programs. A lactose-free infant formula can be life-saving in affected neonates whereas a strict fructose-restricted diet is indicated in hereditary fructose intolerance.

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Inborn errors of carbohydrate metabolism represent a special challenge in general practice. In this review a systemic summary of the most important inherited disorders of carbohydrate disorders (glycogen storage diseases (GSD), inborn errors of galactose and fructose metabolism) is presented. The

* Corresponding author. Tel.: +49 (0)211 8117640; fax: +49 (0)211 8118757.
E-mail addresses: mayatepek@uni-duesseldorf.de (E. Mayatepek), hoffmann@med.uni-duesseldorf.de (B. Hoffmann), thomas.meissner@med.uni-duesseldorf.de (T. Meissner).
focus is set on practical and evidence-based knowledge of key clinical issues, diagnosis, treatment and patient management.

**Glycogen storage diseases**

Glycogen storage diseases (GSD) are a group of inherited disorders of glycogen metabolism with abnormal concentration and/or structure of glycogen in different tissues. Today, 12 different types of GSD are classified based on the deficient enzymes and affected tissues. Liver and muscles are the organs most commonly and seriously involved. The overall incidence of GSD is estimated 1:20,000–40,000 cases per live birth. The most common types with hepatic involvement are GSD I, III and IX. [1] Here, we focus on GSD affecting mainly the liver.

**Pathogenesis and genetics**

GSD I is an autosomal recessively inherited error of carbohydrate metabolism. Demonstration of glucose-6-phosphatase deficiency in GSD I in 1952 was one of the first descriptions of an enzyme defect identified in a hereditary disorder. [2] The defect affects glycogenolysis as well as gluconeogenesis. Two major forms of the disease have been identified. GSD Ia is caused by mutations in the gene encoding for glucose-6-phosphatase (G6Pase or G6PC) whereas GSD Ib is caused by mutations in the glucose-6-phosphate translocase (G6PT) gene (SLC37A4) which transports glucose-6-phosphatase from cytoplasm to microsomes. G6PC is expressed in liver, kidney and intestine whereas G6PT is expressed ubiquitously. The enzyme deficiency results in excessive accumulation of glycogen and lipids in affected organs. Endogenous glucose production by the G6PT pathway seems to be essential for normal neutrophil function. [3]

In GSD III deficiency of the glycogen debrancher enzyme results in massively accumulated glycogen resembling glycogen with a shorter outer chain which is harmful for hepatocytes. The liver and muscle affecting form GSD IIIa accounts for 80% of all cases whereas GSD IIIb involves solely the liver. Glycogen debrancher enzyme has two independent catalytic enzymes and selective loss of only one of the two debranching activities results in GSD IIIc (glucosidase deficiency) and GSD IIId (transferase deficiency) which are very rare. In GSD IV the defect of the debranching enzyme causes unbranched long outer chains in affected tissues. GSD VI and IX involve the hepatic phosphorylase system. GSD VI is a due to defect of the hepatic phosphorylase itself whereas GSD IX is caused by deficient activity of phosphorylase kinase complex, a hexadecameric enzyme comprising four copies each of four unique subunits encoded by four different genes. The phosphorylase kinase (PHK) activates hepatic phosphorylase. There exist different subtypes of GSD IX since these defects can be tissue specific. The most common form is the X-linked recessive GSD IX (XLG; GSD IXa) which is caused by mutations in the PHKA2 gene encoding for the liver isoform of the α-subunit of the enzyme complex. This subtype is biochemically further differentiated into two types: the first one with loss of PHK enzyme activity in peripheral blood cells and liver tissue (XLG-I) and the second one with normal PHK activity in blood cells (XLG-II). The rare autosomal recessive form of GSD IX might be caused by mutations in the PHKB gene (GSD IXb) or PHKG2 gene (GSD IXc) encoding for the isoform of the γ-subunit.

**Clinical symptoms**

Disorders of glycogen metabolism may affect the liver or muscles or even both. Hepatomegaly and hypoglycaemia are the main findings in liver-affecting GSD. Laboratory investigations may show lactic acidosis, elevated transaminases, hyperlipidaemia, hypothyroidism, prolonged bleeding time, iron refractory anaemia and hyperuricaemia with considerable heterogeneity within the different types.

**GSD I** is the most serious type of all hepatic GSD because the glucose release from liver is completely blocked and glycogenolysis as well as gluconeogenesis are severely impaired. Therefore, main clinical symptoms in infancy are severe fasting hypoglycaemia and hepatomegaly.

Beside these, in **GSD Ib** haematological problems are regularly found with increasing age and, in addition, inflammatory bowel disease might occur. Progressive neutropenia and impaired neutrophil function will develop during the first year of life. Platelet count is usually elevated. With increasing age
a decrease of haemoglobin, leucocytes and platelets is found. Clinical manifestations of reduced neutrophil activity are recurrent bacterial infections, abscesses and oral as well as intestinal mucosa ulcerations. In the second or third decade inflammatory bowel disease may occur.

Multiple hepatic adenomas develop in adulthood which are usually benign (Fig. 1).

However, malignant transformation might occur resulting in hepatocellular carcinoma (HCC) and/or liver failure.

Most patients with GSD III show liver as well as muscle involvement (GSD IIIa). In about 15% of cases the disease is limited to the liver (GSD IIIb). Hepatomegaly, hyperlipidaemia and growth retardation will improve with age and may even disappear after puberty. Tendency to hypoglycaemia is much less than in GSD I.

Liver fibrosis is seen early in the disease process. However, hepatic involvement is considered to be self-limited usually without any symptoms of hypoglycaemia or active liver disease after the second decade of life. Onset of overt cirrhosis is atypical in the vast majority and liver cirrhosis or HCC has been reported only in few cases. [4]

GSD IV is clinically extremely heterogeneous. Typically, patients appear to be normal at birth presenting within the first year of life with hepatosplenomegaly and failure to thrive. The natural course is often fatal with progressive liver cirrhosis resulting in death before the age of 6 years. However, rarely milder courses of liver disease have been observed. Hypotonia and muscle weakness demonstrate involvement of the neuromuscular system. In addition, severe cardiomyopathy might develop. An adult onset form with only muscle involvement is also known.

Fig. 1. 20 years old patient with glycogen storage disease type I. MRI of the liver, T2-weighted images: Multiple hepatic adenomas, the largest in segment 6 displays an older intrallesional bleeding.
Clinical symptoms of **GSD VI** are milder than in GSDI or GSDIII. Hepatomegaly might be the only sign of impaired glycogen metabolism. Muscle hypotonia and tendency to fasting hypoglycaemia as well as abnormalities of laboratory values are mild and improve by age.

**X-linked GSD IX** (GSD IXa) is characterised by mild growth retardation, hepatomegaly, moderate hyperlipidaemia, mild fasting glycogenemia with hyperketosis and moderate elevation of liver enzymes. It is usually a mild disease with amelioration of symptoms during puberty. The rare autosomal recessive form of GSD IX might be mild (GSD IXb) or severe (GSD IXc) depending on the subtype. GSD IXc has a more severe phenotype with frequent hypoglycemic episodes and fibrosis leading to adenoma and cirrhosis.

Development of adenoma and malignant transformation of HCA to HCC is a well known complication in GSD I and rarely seen in GSD III.

Adenoma usually occurs after puberty. In about 70–80% of the GSD I patients at the age of 25 years at least one lesion is found. Progression in size or number occurs in about 50%. The incidence of HCC was estimated to be up to 16% for GSD I. [5]

**Diagnosis**

The presenting symptom of GSD with liver involvement is usually a marked hepatomegaly. Family history, clinical phenotype with or without muscle involvement, tendency to hypoglycaemia, and the typical laboratory abnormalities help to differentiate between GSD I or other types of GSD. Biotinidase activity has been proposed to be a useful screening parameter with a sensitivity of 100% for patients with GSD I and GSD VI, 62% for GSD III, and 77% for GSD IX. However, confirmational diagnostic investigations for the specific type are always necessary. Diagnostic procedures to confirm a suspected GSD are given in Table 1.

Today, definite diagnosis is usually established by non invasive investigations as measurement of enzyme activity in blood cells or mutational analysis, if possible. If these investigations are not conclusive, a liver biopsy is done to measure enzyme activity in liver tissue, a part of the material should be analysed for glycogen content (Fig. 2).

Specific work-up for the different GSD’s: GSD Ia and Ib are usually diagnosed by clinical and laboratory parameters and confirmed by mutational analysis. A diagnostic flow-chart has been proposed. [6] Depending on the prevalence of neutropenia mutational analysis will be started in the G6Pase or G6P translocase gene. If this is not conclusive, a liver biopsy will become necessary for measurement of glycogen content and enzyme activities in liver tissue.

Usually enzyme activity measurements for GSD III and IX are done within the same diagnostic step from blood erythrocytes since these GSD forms have a similar clinical phenotype. Further analysis in liver tissue might become necessary if the activity is normal in erythrocytes.

Diagnosis of GSD IX is often difficult, complicated by the highly complex nature of PHK and because the loss of enzyme activity is not always found in erythrocytes. Enzyme activity measurements cannot differentiate between the subtypes furthermore.

Diagnostic work-up is usually tried first in erythrocytes and if reduced activity is not found here, mutational analysis is the next diagnostic step. If this is also not conclusive, liver biopsy with

<table>
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<th>Type</th>
<th>Name</th>
<th>Enzyme defect</th>
<th>Recommended confirmation of diagnosis</th>
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<tr>
<td>I</td>
<td>Van Gierke</td>
<td>Ia: glucose-6-phosphatase-Ib</td>
<td>Mutational analysis, enzyme activity in liver tissue</td>
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<td>(non-a): glucose-6-phosphate translocase</td>
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<td>III</td>
<td>Cori-Forbes</td>
<td>Debranching enzyme subtypes: a–d</td>
<td>Enzyme activity in red blood cells, mutational analysis, enzyme activity in liver tissue</td>
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<td>IV</td>
<td>Andersen</td>
<td>Branching enzyme</td>
<td>Enzyme activity in leucocytes</td>
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<td>VI</td>
<td>Hers</td>
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<td>IX</td>
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<td>Phosphorylase kinase complex subtypes: a–d</td>
<td>Enzyme activity in red blood cells, mutational analysis for XLG, liver tissue when normal in erythrocytes</td>
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measurement of glycogen content and enzyme activity of PHK is recommended. However, mutational analysis may provide the accurate diagnosis for the majority of cases.

**Treatment**

In GSD I a carbohydrate balanced diet with frequent feeding/meals during the day and nocturnal continuous tube feeding and/or addition of uncooked corn starch are the mainstays of treatment to prevent severe hypoglycaemia. Age dependent medium glucose requirement is usually between 3 and 9 mg/kg/min. [7] Recently, new improved cornstarch products have advanced the dietary management of GSD. [8] Fasting periods have to be individually determined and regularly adapted. The aim of nutritional treatment are glucose levels >3.5–4.0 mmol/l in the preprandial state. Urinary lactate/creatinine ratio should be less than 0.06 mmol/mmol. The aim for triglyceride concentration is <6.0 mmol/l. Medium-chain triglycerides may have additional benefits on metabolic control, but larger studies are needed to confirm this form of treatment. Hyperuricaemia is treated with allopurinol to keep uric acid levels within normal ranges.

Granulocyte–Colony Stimulating Factor (G-CSF) is used in patients with neutropenia and frequent infections in GSD Ib. Next to a decrease of the number and severity of infection G-CSF might improve inflammatory bowel disease. Starting dose is 2.5 μg/kg/day every other day and this might be adjusted if leucocytes count does not reach the aim of >1.0 × 10^9/l in 5 μg/kg steps. The most serious complications of G-CSF treatment are a mostly reversible splenomegaly and osteopenia. Oral antibiotic prophylaxis has been recommended for patients with GSD Ib and recurrent infections or leucocytes

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**Fig. 2.** Diagnostic work-up for suspected glycogen storage diseases.
counts less than 0.5 × 10⁹/L. [9] For inflammatory bowel disease next to G-CSF, 5-aminosalicylic acid (5-ASA) has been recommended. Corticosteroid treatment has been avoided in GSD I since the induction of glycogenolysis may induce or even worsen lactic acidosis and hyperlipidaemia. Hyperlipidaemia can be treated with lipid lowering drugs such as HMG-CoA reductase inhibitors or fibrates. Microalbuminuria as an early indicator of renal dysfunction is treated with low doses of angiotensin-converting enzyme (ACE) inhibitors. [10]

In GSD III nutritional treatment is much less intensive than in GSD I and a late meal at night rich in complex carbohydrates is usually adequate. There is currently no effective treatment for myopathic symptoms.

Liver transplantation (LT) has been performed in different types of GSD (I, III, IV). It reverses the underlying hepatic enzyme deficiency and cures liver disease. LT should only be considered when there is high risk for HCC or evidence of substantial cirrhosis or progressive liver dysfunction. [11] For patients with progressive liver form of GSD IV LT is the only effective therapeutic approach. In GSD I renal dysfunction persists after LT and may even worsen resulting in renal failure, a main complication after transplantation next to acute or chronic rejection of the transplant. Etiology of renal dysfunction is not entirely clear and may be due to intrinsic renal dysfunction but also aggravated by calcineurin inhibitor therapy as immunosuppressive agent after LT. In GSD Ib significant morbidity is associated with neutropenia, neutrophil dysfunction and post-transplant immunomodulation. Indication for LT in GSD always has to be carefully evaluated on an individual basis.

Prognosis

Dietary therapy improved survival of patients with GSD I. Prognosis and occurrence of complications depend on the long-term metabolic control with regard to life-threatening hypoglycaemia or lactic acidosis. In GSD I patients may be neurologically completely normal under adequate dietary treatment. However, as a consequence of recurrent severe hypoglycaemia they may also be mentally handicapped. Normal growth and pubertal development can be expected today. Further GSD I-specific complications include osteoporosis and pathological fractures. Hyperuricaemia may lead to symptomatic gout. Pancreatitis is a complication of hypertriglyceridaemia. In some cases, hypothyroidism is found. Renal complications are Fanconi syndrome, nephrocalcinosis, hypercalciuria, and proteinuria. In 70% of GSD Ia patients after the age of 15 years renal dysfunction, especially proteinuria, was observed and at the age of 25 years the incidence of proteinuria was 100%. [7] Renal failure might develop based on a focal glomerulosclerosis. Severe pulmonary arterial hypertension of unknown etiology has only been also reported in single patients.

In GSD III hepatomegaly, hypoglycaemia, hyperlipidaemia, and growth retardation improve with age and disappear after puberty. However, liver cirrhosis and/or hepatocellular carcinoma may occur. Muscle weakness can become prominent in adults.

GSD IV is usually a devasting disease with liver cirrhosis leading to death before the age of 5 years without transplantation. Milder non-progressive forms have been also described. In GSD VI a typically benign course has been reported, with remission of symptoms as the children grow up. GSD IXa (XLG) is usually a benign disease with clinical symptoms gradually improving with age. Patients with GSD IXb have also a mild phenotype contrasting sharply with patients with GSD IXc. This severe form of autosomal recessive GSD type IX is characterised by fibrosis usually developing to cirrhosis and adenoma.

Classical galactosaemia

Breast or cow-milk based industrial formulae are most recommended infant foods. Their major carbohydrate is lactose consisting of galactose and glucose. Combination of both carbohydrates in one nutrient allows two different ways of energy utilisation: glucose is available for immediate energy supply whereas galactose first has to be converted into glucose ensuring prolonged carbohydrate availability. Three enzymes are necessary for this pathway, and three corresponding enzyme deficiencies have been described (Fig. 3). [12]

Deficiencies of galactose-1,4-epimerase and galaktokinase are less often, show less severe clinical courses, if any, and impact only moderately on the patients’ life and outcome. In contrast, deficiency of
galactose-1-phosphate-uridyltransferase (GALT) may be life-threatening, and even under treatment patients of all ages are severely affected by GALT-deficiency (classical galactosaemia). In the following, we focus on this clinically most relevant inborn error of galactose metabolism.

The overall incidence of autosomal recessive inherited classical galactosaemia is thought to be about 1:47,000. To date, more than 230 different mutations of the GALT-gene have been described leading to a residual GALT-activity of less than 5%.

The most common mutation in Caucasians is Q188R (c563 A>G). Of note, the mutation N314D (c.940 A>G; Duarte-I-variant) leads to a residual GALT-activity of about 25% but these individuals do not need to follow any diet.

Clinical symptoms

Galactosaemia is a disease with multi-disciplinary problems and complications may arise in all ages. Typically, clinical symptoms occur within the first days of life. Untreated newborns with GALT-deficiency are intoxicated by galactose and its metabolites galactose-1-phosphate and galactitol (Fig. 2). Liver function is severely perturbed, and jaundice and coagulation disturbances may appear early in life. Formation of cataracts is thought to be due to the formation of galactitol and its probably dose-depending effect on lens water and protein contents.

In females with galactosaemia, ovarian dysfunction has been found in more than 75% of the patients. [12] Hypergonadotropic hypogonadism may unmask e.g. as amenorrhoea, and prenatal damage to the ovaries is suspected. [13] Males with GALT-deficiency have not been reported to develop fertility problems.

Peak bone mass in early adulthood is of major importance to prevent osteoporosis in later life. Moreover, milk is the most important calcium source. Due to their dietary restrictions patients with GALT-deficiency are thought to have a higher risk of developing osteoporosis in later life. In females with hypergonadotropic hypogonadism, this risk is even more increased.
Neurological symptoms in galactosaemia may include ataxia, tremor, apraxia of speech and cognitive impairment. The whole pattern is inconsistent, and some patients may be unobtrusive at all. [14] Speech abnormalities may first be seen in early childhood but typically persist into adulthood. All attempts to correlate IQ-scores e.g. with age at diagnosis, age at onset of treatment, highest bilirubin concentration in the neonatal period or long-term galactose-1-phosphate concentration in red blood cells failed. [14]

Diagnosis

Many countries have included newborn screening for galactosaemia in their screening programs for inborn errors of metabolism. Suspicion of GALT-deficiency by newborn screening needs confirmation by a second independent method, e.g. determination of GALT-activity in red blood cells or proof of a pathogenic mutation of the GALT-gene.

In countries without newborn screening for galactosaemia (e.g. UK and Netherlands) any child with jaundice, failure to thrive, feeding difficulties and/or vomiting has to be regarded as a patient with classical galactosaemia until it is ruled out.

Treatment

Adherence to dietary recommendations is the mainstay of treatment. A lactose-free infant formula may be life-saving in neonates. In principle, patients have to follow a lactose-free, galactose-restricted diet throughout life.

Galactose is set free from regular body turnover, and concentration of galactose and its metabolites in red blood cells remain continuously increased in GALT-deficiency. A certain tolerance regarding galactose is discussed.

Prognosis

To achieve optimal outcome in apraxia of speech, early diagnosis and continuous speech therapy is essential. However, this approach might be disappointing, and some patients are completely non-responsive to speech therapy.

At least from age 10 years onwards yearly determination of gonadotropines (LH and FSH) as well as oestradiol in serum should be performed. In addition, puberty development should be monitored by use of the Tanner classification. An X-ray of the left hand may be helpful to decide about the institution of hormone replacement therapy, but psychological concerns may play an important role in the decision about the onset of hormone replacement therapy. Nevertheless, treatment before the age of 12 years and without proper biochemical work-up is inadequate.

To prevent premature osteoporosis, sufficient intake of calcium and vitamin D is important and regular monitoring of bone density should be performed (e.g. once a year from school age onwards). Timely onset of hormone replacement may also contribute to bone mineral density, particularly in females.

The majority of patients with galactosaemia achieve an educational attainment significantly lower than their healthy peers. [15]

Disorders of fructose metabolism

Fructose is a monosaccharide that is present in high concentrations in fruits and honey and is a constituent of sucrose and sorbitol. Three inborn errors are known in the pathway of fructose metabolism which may be asymptomatic or cause severe clinical symptoms.

Essential fructosuria

Essential fructosuria is a rare non-disease caused by a deficiency of fructokinase. It leads to benign elevation of fructose levels in blood and urine (benign fructosuria). Inheritance is autosomal recessive with an incidence of about 1:130,000. The condition is asymptomatic and diagnosed accidentally when
a non-glucose reducing substrate is detected by routine screening for reducing sugars in urine. Dietary treatment is not indicated and the prognosis is excellent. [16]

**Hereditary fructose intolerance**

Hereditary fructose intolerance (HFI) is caused by deficiency of the enzyme aldolase B which splits fructose-1-phosphate into dihydroxyacetone phosphate and glyceraldehyde and converts the triphosphates into glucose and lactate. Accumulation of fructose-1-phosphate inhibits both hepatic glycogenolysis and gluconeogenesis, hence inducing hypoglycaemia, and results in depletion of adenosine triphosphate. The latter results in a number of disturbances, e.g. inhibition of protein synthesis and ultrastructural lesions, causing hepatic and renal dysfunction. [17] Inheritance is autosomal recessive with an incidence estimated at 1:20,000.

**Clinical symptoms**

Infants and children are healthy until they ingest fructose, sucrose and/or sorbitol. In general practice, no metabolic derangement occurs during breast-feeding. First symptoms of HFI may occur with introduction of supplementary food, preferably fruits and vegetables. Clinical symptoms include vomiting, nausea, restlessness, pallor, sweating, lethargy, coagulation disturbances and in some cases, apathy, coma, jerks and convulsions. Laboratory data may show signs for acute liver failure (elevated serum transaminases, hyperbilirubinemia, derranged blood clotting factors) and general dysfunction of the renal proximal tubules (e.g. proteinuria, generalised hyperaminoaciduria, metabolic acidosis). If at that stage fructose is not excluded from the diet, the course will be chronic with failure to thrive, liver disease characterised by hepatomegaly, jaundice, steatosis, coagulation disturbances, oedema, ascites and signs of proximal renal tubular dysfunction. Hypoglycaemia after fructose ingestion may be an acute clinical problem, however, since it is short-lived it might be masked by concomitant glucose intake. Especially older children may develop a natural aversion to fructose-containing food even before diagnosis. At school age, HFI is occasionally recognized when hepatomegaly or growth retardation is found.

**Diagnosis**

Of special importance in the diagnosis of HFI is a very careful nutritional history, with special emphasis on the time of weaning when fruits and vegetables were introduced. The best non invasive approach for confirmation of diagnosis is carried out by DNA analysis from EDTA-anticoagulated blood. If no mutation can be found despite strong nutritional history or clinical symptoms, enzymatic determination of the residual activity of aldolase B in a liver biopsy should be performed. Blood cells, skin fibroblasts and muscle contain a different isozyme, aldolase A leading to normal aldolase activity. Therefore, these cell types are not suitable for diagnostic purposes. Intravenous or oral fructose tolerance testing is not recommended any more.

**Treatment**

Treatment consists of elimination of fructose from nutrition. Under this diet clinical symptoms and laboratory alterations resolve. Certain medications (e.g. syrups, immunoglobulin solutions) may contain fructose or sorbitol and therefore have to be taken with caution. This also relates to infant formulae without adequate declaration of the carbohydrate composition. In addition, multivitamin preparations, especially in form of ascorbic acid and folates, should be prescribed because of the lack of fruits and vegetables in the diet.

**Prognosis**

With treatment the overall prognosis is excellent. Most abnormalities disappear rapidly. Typically, patients have no caries throughout their life. With increasing age, the tolerance against fructose increases slightly. Hepatomegaly or alterations of liver structure may persist for years.
However, their clinical relevance is unclear. It may be necessary to repeat dietary advice in adolescence to ensure adherence to the diet. Patients should always be aware that infusions containing fructose or sorbitol are life-threatening. Therefore, diagnosis of HFI should be reported on any hospital admission.

**Fructose-1,6-bisphosphate (FBP) deficiency**

FBP is a key enzyme in gluconeogenesis. Deficiency of this enzyme results in an impaired formation of glucose from all gluconeogenic precursors, including dietary fructose, leading to fasting hypoglycaemia, ketosis and acidosis. Inheritance is autosomal recessive. Its incidence is unknown, it might be around 1:350,000.

**Clinical symptoms**

FBP deficiency can be fatal and life-threatening, especially in neonates because their glycogen reserves are limited (as when fasting). Therefore, about 50% of all cases present during the first days of life with severe hyperventilation due to massive lactic acidosis (lactate up to 15–25 mM with an increased lactate/pyruvate ratio up to 30) and hypoglycaemia. [18] With increasing age of manifestation, additional clinical symptoms may include episodes of irritability, somnolence, coma, dyspnoea, tachycardia, muscular hypotonia and moderate hepatomegaly. Febrile illness with subsequent refusal of feed and vomiting can trigger such episodes. Large amounts of fructose especially after a fasting period may also lead to typical attacks. As in HFI intravenous fructose is contraindicated and may lead to death. Tolerance to fasting as well as the frequency of attacks generally improves with age. In between attacks, patients are usually well, despite mild, intermittent or chronic acidosis.

**Diagnosis**

Diagnosis can be made by DNA analysis from EDTA-anticoagulated blood. If the results are not conclusive, determination of enzymatic activity in a liver biopsy should be performed. Enzyme activity can also be measured in leukocytes. However, it has to be noted that normal activity in leukocytes does not rule out FBPase deficiency in the liver. Loading tests e.g. with fructose or fasting tests may only point to a functional disturbance in the fructose 6-phosphate-fructose-1,6-bisphosphate substrate cycle but do not lead to a final diagnosis.

**Treatment**

Acute treatment consists of intravenous or oral glucose. Acute, life-threatening episodes should be treated with an intravenous bolus of 20% glucose followed by continuous infusion of glucose at high rates (10–12 mg/kg for neonates) and bicarbonate to control acidosis.

Long-term treatment includes avoiding of fasting, especially during febrile illness, with frequent feeding, the use of slowly absorbed carbohydrates (such as uncooked cornstarch) and a gastric dip, if necessary. Only in small children restriction of fructose, sucrose, sorbitol as well as fat (15–20% of energy requirements) is recommended.

**Prognosis**

After early diagnosis and under adequate management prognosis is usually good without impairment of growth or psychomotor development. Fasting tolerance improves with age. However, due to overfeeding and continuous special eating habits avoiding catabolism many patients become obese.
Practice points

- There is a broad clinical variation between different types of GSD but also within each single GSD
- Main clinical symptoms in liver-affecting GSD are hepatomegaly and hypoglycaemia
- To prevent severe hypoglycaemia a carbohydrate balanced diet with frequent meals and nocturnal continuous tube feeding or addition of uncooked corn starch is necessary
- Most patients with liver-affecting GDS have to be carefully monitored since cirrhosis and hepatocellular carcinoma might occur
- Classical galactosaemia is included in most newborn screening programs
- Complications in classical galactosaemia may arise in all ages and include neurological symptoms, ovarian dysfunction or osteoporosis
- Nutritional history is of special importance for the diagnosis of HFI

Research agenda

- Prospective studies are needed to evaluate the benefit from liver transplantation for different GSD's
- Adeno-associated virus-mediated gene therapy may be a curative therapy for single GSD's in future
- Quality of life after long-term treatment in inborn errors of galactose and fructose metabolism needs to be further studied

Role of the funding source

There are no sources of funding for this manuscript.

Conflict of interest

None.

Acknowledgements

The authors are thankful to Dr. Jörg Schaper, Düsseldorf, for providing Fig. 1.

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