The Glycogen Storage Diseases and Related Disorders

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J.-M. Saudubray et. al (Eds.), *Inborn Metabolic Diseases,* DOI 10.1007/978-3-642-15720-2_6,

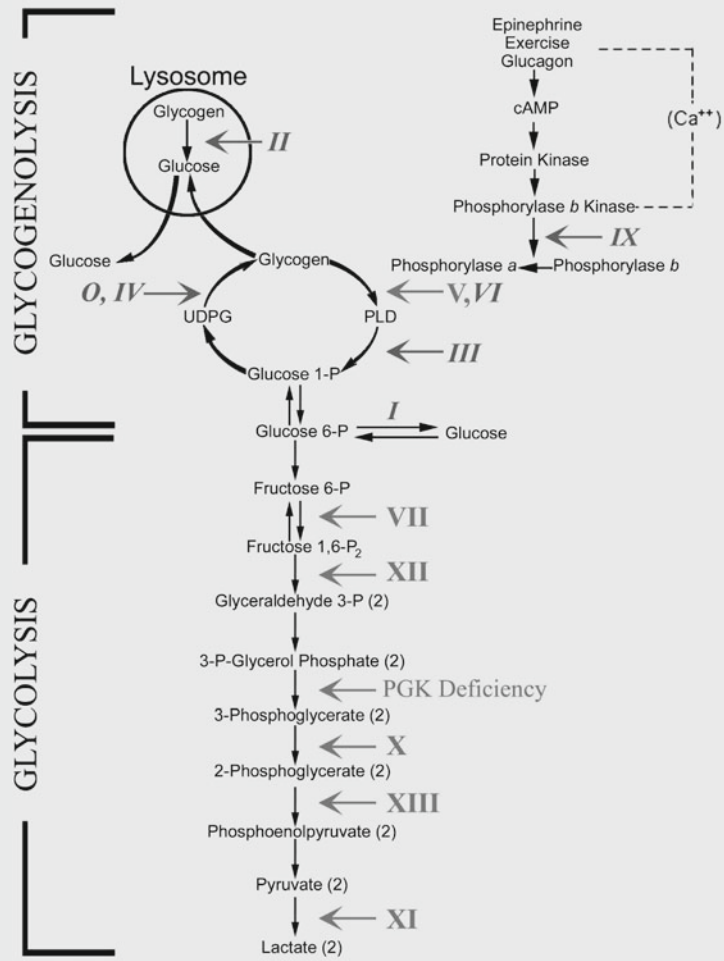
Glycogen Metabolism

Glycogen is a macromolecule composed of up to 60,000 glucose molecules joined into straight chains by α-1-4 linkages and with branching points formed by α-1,6-linkages at intervals of 4-10 glucose residues. Glycogen, the primary energy source between meals, is found in many tissues but is especially abundant in liver and muscle. In the liver, glycogen serves as a glucose reserve for the maintenance of normoglycaemia in times of fasting [1]. In muscle, glycogen provides energy for muscle contraction. Numerous enzymes intervene in the synthesis and degradation of glycogen (◘ Fig. 6.1), and deficiencies of virtually all of these cause glycogen storage disease (GSD) owing to aberrant storage or utilisation of glycogen. The different GSDs are each denoted by a roman numeral that reflects the historical sequence of their discovery, by the deficient enzyme, or by the name of the author of the first description [2].

The clinical features of the GSDs depend on the site of abnormal glycogen metabolism: the liver, muscle, heart, or brain.

Hepatic GSDs present with hepatomegaly and/or hypoglycaemia. GSDs presenting principally with **hypoglycaemia** are GSD I (glucose-6-phophatase deficiency), GSD III (debranching enzyme deficiency, GSD 0 (hepatic glycogen synthase deficiency), and GSD XI (Glut-2 deficiency). GSDs presenting mostly with **isolated hepatomegaly** are GSD VI (phosphorylase deficiency), GSD IX (phosphorylase kinase deficiency) and GSD IV (hepatic branching enzyme deficiency) [3].

Muscle/cardiac GSDs fall into three clinical groups. GSDs presenting with **exercise intolerance** often followed by **rhabdomyolysis** are type V (muscle phosphorylase deficiency) and type VII (phosphofructokinase deficiency). GSD X, GSD XII, and GSD XIII also belong in this group, but these are extremely rare.



◘ **Fig. 6.1.** Scheme of glycogen metabolism and glycolysis. *PGK*, Phosphoglycerate kinase; *P*, phosphate; *PLD*, phosphorylase limit dextrin; *UDPG*, uridine diphosphate glucose. *Roman numerals* indicate enzymes whose deficiencies cause liver (*italics*) and/or muscle glycogenoses: **0** glycogen synthase; **I**, glucose-6-phosphatase; **II**, acid maltase (α-glucosidase); **III**, debranching enzyme; **IV**, branching enzyme; **V**, myophosphorylase; **VI**, liver phosphorylase; **VII**, phosphofructokinase; **IX**, phosphorylase-b-kinase; **X**, phosphoglycerate mutase; **XI**, lactate dehydrogenase; **XII**, fructose-1,6-bisphosphatase aldolase A; **XIII**, β-enolase

GSDs presenting with **myopathy/cardiomyopathy** are type IIa (lysosomal acid maltase deficiency) and type IIb (lysosomal–associated membrane protein 2 deficiency). The extremely rare myopathic forms of GSD 0 and glycogenin 1 deficiency also fit in this category. Unlike the other forms of GSD, GSD III and GSD IXb are the only types that affect both the liver and muscle. A rare GSD presenting with **adult cardiomyopathy** and **Wolff-Parkinson-White syndrome** is represented by the AMP-activated protein kinase (AMPK) deficiency [4].

Brain GSDs present with adult neurodegeneration/epilepsy syndromes associated with accumulation of polyglucosan bodies and encompass several disorders. In brain, all enzymes for synthesis (branching and glycogen synthase) and catabolism (debranching and phosphorylase) are present in both astrocytes and neurons. However, there is no glycogen synthesis in neurons. In astrocytes, glycogen is synthesised and degraded for emergency energy needs during brief episodes of hypoglycaemia and hypoxia. Glycogenolysis in astrocytes produces lactate, which is exported by a monocarboxylic transporter to neurons where it is oxidised in the mitochondria. Consequently lactate can be used as a potent alternative fuel to glucose in the neurons of GSD patients, especially in case of hypoglycaemia**.** Recent work on myoclonus epilepsy with Lafora bodies (Lafora disease) suggests that this is a glycogenosis, probably due to abnormal glycogen synthesis [5].

6.1 Liver Glycogenoses

The liver GSDs comprise GSD I, the hepatic presentations of GSD III, GSD IV, GSD VI, the liver forms of GSD IX, and GSD 0. GSD I, -III, -VI, and -IX present with hypoglycaemia, marked hepatomegaly, and retarded growth [6]. GSD I is the most severe of these four conditions, because both glycogenolysis and gluconeogenesis are impaired. Patients with GSD III have a syndrome that includes hepatopathy, myopathy and often cardiomyopathy. Unlike the other hepatic forms of GSD, GSD IV usually manifests in infancy or childhood as hepatic failure with cirrhosis leading to end-stage liver disease. GSD VI and the hepatic forms of GSD IX are classically the mildest forms, but there is recent evidence that optimised therapy decreases the rate of liver pathology and improves growth. GSD 0 presents in infancy or early childhood with fasting ketotic hypoglycaemia contrasting with postprandial hyperglycaemia and hyperlactataemia. It is the only hepatic form of GSD without hepatomegaly [3]. The muscle forms of GSD III and -IX are also discussed in this section. Fanconi-Bickel syndrome, which is due to deficiency in GLUT2, is a further cause of glycogen storage, hepatomegaly and fasting hypoglycaemia. This disorder is also associated with postprandial hyperglycaemia and renal tubular dysfunction and is discussed in ► Chapter 11.

6.1.1 Glycogen Storage Disease Type I (Glucose-6-Phosphatase or Translocase Deficiency)

GSD I, first described by von Gierke, comprises GSD Ia caused by deficiency of the catalytic subunit of glucose-6-phosphatase (G6Pase) and GSD Ib caused by a deficiency of the endoplasmic reticulum (ER) glucose-6-phosphate (G6P) translocase [7]. There is controversy about the existence of ER phosphate translocase deficiency (GSD Ic) and ER glucose transporter deficiency (GSD Id) as distinct entities. In this chapter, the term GSD Ib includes all GSD I non-a forms.

▪ Clinical Presentation

Individuals with GSD I usually present at 3-6 months of age with seizures, lethargy, failure to thrive, tachypnoea and developmental delay due to profound hypoglycaemia and lactic acidosis associated with increased intervals between meals and intercurrent illness. Affected infants are usually fussy and unable to sleep through the night without feeding. Hyperlipidaemia and hyperuricaemia are present due to shunting of metabolites through alternate pathways. A protuberant abdomen, truncal obesity, rounded doll-like face, hypotrophic muscles and growth delay are conspicuous clinical findings when patients are diagnosed beyond infancy [8].

Type GSD I occurs in approximately 1 in 100,000 individuals. About one in eight GSD I patients has type Ib [9]. Patients with GSD Ib have symptoms similar to those of patients with GSD Ia, but with the addition of neutropenia and inflammatory bowel disease (IBD) [10]. Neutropenia is a consequence of disturbed myeloid maturation and is also associated with functional defects of circulating neutrophils and monocytes, including impaired motility and migration and impaired metabolic burst [11]. The neutropenia can be either cyclic or constant, and approximately two thirds of patients will have the initial episode of neutropenia before 12 months of age. While the severity of the neutrophil dysfunction is variable, recurrent bacte-

rial infections (predominantly from *S. aureus, S. pneumoniae* and *E. coli)* and oral ulcers are common [12]. An IBD resembling Crohn's disease develops in the majority of patients by the teenage years, which classically is worst in the small intestine [13]. IBD is usually the major cause of morbidity in patients with GSD Ib. Neutropenia and impaired neutrophilic function are thought to be involved in the pathogenesis of IBD, but it continues to occur frequently in GSD Ib patients even during granulocyte colony-stimulating factor (GCSF) therapy.

■ Metabolic Derangement

Among the enzymes involved in hepatic glycogen metabolism G6Pase is unique, since its catalytic site is situated inside the lumen of the ER. This means that its substrate, G6P, must cross the ER membrane and requires a transporter. There is still debate over different proposed models of G6Pase, over the existence of additional transporters for its products, phosphate and glucose [14] and over the existence of GSD Ic (putative ER phosphate/pyrophosphate transporter deficiency) and GSD Id (putative ER glucose transporter deficiency). In particular, patients diagnosed by enzyme studies as having GSD Ic have been found to have the same mutations in the G6P translocase gene as in GSD Ib (► Genetics) [15]. The description of a GSD Id patient has been withdrawn [16].

Hypoglycaemia occurs during fasting as soon as exogenous sources of glucose are exhausted, since the final steps in both glycogenolysis and gluconeogenesis are blocked. There is evidence that hypoglycaemia may improve with age owing to the presence of an isoform of G6Pase after puberty, but severe hypoglycaemia can still occur if therapy is delayed [17]. Hyperlactataemia is a consequence of excess G6P that cannot be hydrolysed to glucose and is further metabolised in the glycolytic pathway. This process is intensified under hormonal stimulation as soon as the exogenous provision of glucose fails. Substrates such as galactose, fructose and glycerol need liver G6Pase to be metabolised to glucose. Consequently ingestion of sucrose and lactose results in hyperlactataemia with no to minimal change in the blood glucose concentration [18].

The serum of untreated patients has a milky appearance due to hyperlipidaemia, primarily from increased triglycerides. The hyperlipidaemia responds to intensive dietary treatment [19]. The increased concentrations of triglycerides and cholesterol are reflected in increased numbers of VLDL and LDL particles, whereas the HDL particles are decreased [20]. VLDL particles are also increased in size due to the accumulation of triglycerides. Hyperlipidaemia is a result of both increased synthesis from excess of acetyl-coenzyme A (CoA) via malonyl-CoA, and decreased serum lipid clearance [21]. Decreased plasma clearance is a result of impaired uptake and impaired lipolysis of circulating lipoproteins. Reduced ketone production during fasting is a consequence of the increased malonyl-CoA levels, which inhibit mitochondrial β-oxidation [22].

Hyperuricaemia is a result of both increased production and decreased renal clearance. Increased production is caused by increased degradation of adenine nucleotides to uric acid, associated with decreased intrahepatic phosphate concentration and ATP depletion [23]. Decreased renal clearance is caused by competitive inhibition of uric acid excretion by lactate [24].

■ Genetics

GSD Ia and -Ib are both autosomal recessive disorders. In 1993, the gene encoding G6Pase (*G6PC*) was identified on chromosome 17q21. Today more than 80 different mutations have been reported [25], with a particularly common mutation in the Ashkenazi Jewish population, where 1 in 72 people are carriers [26]. Subsequently, the gene encoding the G6P transporter (*G6PT*) was identified on chromosome 11q23. More than 65 different mutations have been reported [7]. Patients formerly diagnosed by enzyme studies with GSD Ic and the putative Id shared the same mutations in *G6PT* [27]. Recently, however, a GSD Ic patient without mutations in *G6PT* was described, suggesting the existence of a distinct GSD Ic locus [28].

■ Diagnosis

Most patients with GSD I can be diagnosed by means of a combination of biochemical and genetic testing [9]. Patients with GSD I have a classic pattern, with hypoglycaemia and hyperlactatemia noted after a brief fast of 3-4 h and associated hyperlipidaemia and hyperuricaemia. The diagnosis of GSD Ia can be established through sequencing of the *G6PC* gene, while mutation analyses of *G6PT* should be performed first if patients suffer from neutropenia and/or recurrent infections [25]. If no mutation can be identified but the suspicion of GSD I remains, enzyme assays in fresh liver tissue should be considered. GSD Ia is characterised by deficient G6Pase activity in intact and disrupted liver microsomes, whereas deficient G6Pase activity in intact microsomes and (sub)normal G6Pase activity in disrupted microsomes indicates a defect in the G6P transporter [2].

■ Treatment

■■ Dietary Treatment

The goal of treatment is to provide a continuous source of glucose and maintain normoglycaemia (glucose >4 mmol/l [70 mg/dl]) and prevent secondary metabolic

Table 6.1. Biomedical targets in GSDI

1.	Preprandial blood glucose >3.5-4.0 mmol/l (adjusted to target 2)
2.	Urine lactate/creatinine ratio <0.06 mmol/mmol (or urine lactate <0.4-0.6 mmol/l)
3.	Serum uric acid concentration in high normal range for age and laboratory
4.	Venous blood base excess >5 mmol/l and venous blood bicarbonate >20 mmol/l
5.	Serum triglyceride concentration <6.0 (<10.0 mmol/l in adult patients)
6.	Normal faecal alpha-1-antitrypsin for GSD Ib patients
7.	Body mass index <+2.0 SDS (in growing children between 0 and +2.0 SDS)

derangements (Table 6.1). In infancy, normoglycaemia should be maintained by frequent lactose-free formula feeds, which can be enriched with maltodextrin every 1.5-3 h. Continuous overnight feeds through a nasogastric or gastrostomy tube may also be used [29]. Because of the many advantages (emotional, composition, practical) breast milk is, in spite of its high quantity of lactose, not contraindicated. If poor growth, increased hepatomegaly, hypoglycaemia or hyperlactataemia is noted, it may be necessary to change over partly or fully to lactose-free bottle-feeding. After the age of 4 months the feeds can be bound with up to 6% rice flour. Later on, wheat products can be used as well. Supplementary feeding can be started as usual at the age of 6 months, taking into account the limitations of lactose and fructose [30].

In 1982, uncooked cornstarch (UCCS) was introduced as a treatment option, and it allows the duration between feeds to be increased [31]. Uncooked cornstarch can be introduced at 6 months of age, but may not be tolerated until 1 year of age due to deficient pancreatic amylase. Boluses of uncooked cornstarch along with complex carbohydrate-rich frequent meals and snacks are the mainstay of therapy from 12 months to adulthood in North America [32]. Uncooked cornstarch is given mixed in water or artificially sweetened drinks. Doses are given 3- to 5-hourly as tolerated. Recent introduction of extended release cornstarch may prevent the need for frequent cornstarch dosing at night, improving quality of life [33, 34]. Blood glucose levels remain more stable overnight, with extended release cornstarch leading to better metabolic control; use during the day must be individualised, however, as it may not provide glucose rapidly enough for adequate cover of activity. When used appropriately, cornstarch supplementation is not associated with obesity. Overnight continuous feeds can also be used for maintenance of blood glucose concentrations. Both methods can be successfully used, but overnight continuous feeds must be used with caution, since any interruption of the therapy can result in rapid development of severe hypoglycaemia, seizures or even death. In addition, early morning hypoglycaemia may occur following discontinuation of the overnight feed, and breakfast should be ingested within 30 min after the nocturnal feeding has stopped.

Whether continuous feeds or cornstarch therapy is used, the glucose requirement in children can be calculated using the formula:

$$y=0.0014x^3-0.214x^2+10.411x - 9.084$$

where y is milligram glucose per minute and x is body weight in kilograms (ideal body weight should be used in overweight patients).

It is of critical importance that enough therapy is administered to avoid lactic acid formation, but excessive intake of cornstarch or carbohydrate can lead to excessive weight gain, increased hepatomegaly or glucose fluctuations from excessive insulin production. During childhood, frequent assessment of dosing should occur, and home monitoring of glucose and lactate is typically supplemented by in-patient assessment of metabolic control.

Patients with GSD I are treated with a strict dietary regimen. Fructose, sucrose and lactose intake should be restricted since these sugars are taken up by the liver and lead to glycogen accumulation or production of uric acid, triglycerides and lactate [35]. Fat should be restricted to less than 30% of total caloric intake, with cholesterol intake of less than 300 mg. Attention should be paid to the inclusion of polyunsaturated (essential) fatty acids in the diet. Protein intake should meet general recommendations, but excessive protein intake can exacerbate hyperuricaemia. Vitamin and mineral deficiencies might develop due to a restrictive diet. In particular, zinc, iron, calcium and vitamins B, C and D are commonly deficient, and supplementation with a multivitamin is therefore recommended. Additional iron supplementation may be required owing to insufficient intake of iron and abnormal hepatic hepcidin regulation [36]. Most patients will require extra vitamin D and calcium because of to the lack of dairy products in the GSD diet [37], and there is recent evidence that medium-chain fatty acid supplementation may improve growth and markers of metabolic control [38].

All patients with GSD I should have an emergency protocol in place for intercurrent illnesses. During illness, continuous feeds with a high-carbohydrate formula (e.g. Tolerex) can be used in an attempt to avoid hospitalisation. If hypoglycaemia or severe lactic acidosis occurs,

intravenous administration of 10% dextrose solution should be started at 1.25-1.5 times maintenance values to maintain glucose above 4 mmol/l (70 mg/dl). Once the acidosis has resolved, intravenous fluids should be tapered off slowly to avoid hypoglycaemia being induced by the increased insulin state.

■■ Pharmacological Treatment

Diet and nutritional supplements remain the mainstay of treatment for GSD. Pharmacological interventions are sometimes required to prevent or treat complications of GSD. With optimal control, hyperlactataemia abates. When elevated lactate persists despite attempts to improve control, *sodium bicarbonate* can be used to buffer lactate in order to keep plasma bicarbonate >20 mmol/l. Bicarbonate also induces alkalisation of the urine, thereby diminishing the risk of urolithiasis and nephrocalcinosis. While bicarbonate therapy may help prevent kidney stones, it is no longer the preferred treatment for prevention of this complication. Progressive hypocitraturia develops with age [39], so that alkalisation with *citrate* (typically *potassium citrate*) is even more beneficial in preventing or ameliorating renal calcification.

Uric acid is a potent radical scavenger, and it may be a protective factor against the development of atherosclerosis [40]. Consequently, it is recommended that serum uric acid be maintained within the high normal range. When levels get elevated, however, patients may be prone to development of gout and urate nephropathy, and treatment with a *xanthine-oxidase inhibitor* (*allopurinol*) should be considered.

With improved therapy, GSD nephropathy is becoming less common, even though hyperfiltration occurs almost universally in this population [41]. If control is not optimal, however, focal segmental glomerulosclerosis may develop, which manifests as hypertension, microalbuminuria, proteinuria and then decreased creatinine clearance. If persistent microalbuminuria is present, a (long-acting) *angiotensin-converting enzyme* (ACE) inhibitor *or angiotensin II receptor antagonist* should be started to reduce or prevent further deterioration of renal function [42, 43]. Protein intake should not exceed RDA recommendations.

Hypertriglyceridaemia is also related to metabolic control, and it usually can be controlled with optimised dietary management [44]. When significant hyperlipidaemia is present (triglycerides over 1000 mg/dl [11.4 mmol/l]) *triglyceride-lowering therapies* (nicotinic acid, fibrates, fish oil) are recommended to reduce the risk of pancreatitis. Studies are conflicting regarding the risk of atherosclerosis in GSD I [45-47]. *Cholesterol-lowering drugs* are not indicated in younger patients. In adult patients, however, progressive renal insufficiency may worsen the hyperlipidaemia and atherogenecity, and in such cases *statins* may be indicated, although there is at present no evidence of their efficacy in this condition. It is critical to always optimise dietary treatment first.

Growth hormone therapy is strictly contraindicated in this condition. Poor growth in glycogen storage disease is a result of chronic acidosis, and near-normal growth occurs with optimal metabolic control [48]. In addition to being unnecessary because there is no growth hormone deficiency, growth hormone increases glycogenolysis and worsens metabolic control. As a result, growth hormone therapy does not improve final height, and may increase the rate of complications. Similarly, neither *oestrogen* nor *testosterone* is indicated to enhance pubertal development, as they do not improve final height scores and they may stimulate hepatic adenoma formation. A barrier method is therefore advised for contraception, but therapy with high doses of progestagen from the 5th to the 25th day of the cycle or with daily administration of low doses of progestagen can be used an alternative [49].

The benefits of prophylaxis with oral antibiotics have not been studied in neutropenic GSD Ib patients. However, prophylaxis with *cotrimoxazol* may be of benefit in symptomatic patients or in those with a neutrophil count $<500\times10^6$/l [50]. *Granulocyte colony-stimulating factor* (GCSF) has been used extensively in the GSD Ib population from 1989. Limitation of the use of GCSF to one or more of the following indications is advised: (1) a persistent neutrophil count below 200×10^6/1; (2) a single life-threatening infection requiring antibiotics intravenously; (3) serious IBD documented by abnormal colonoscopy and through biopsies; and (4) severe diarrhoea requiring hospitalisation or disrupting normal life [51]. Toxicity related to GCSF therapy has been common in the GSD population, and use of the lowest possible dose to prevent infections is recommended. A starting dose of 2.5 μg/kg daily or every other day is recommended, and the dose should be adjusted based upon the clinical response and not the absolute neutrophil count. Complications appear to be dose related. The most serious frequent complication is splenomegaly including hypersplenism. Reports of acute myelogenous leukaemia [52] and renal carcinoma [53] arising during long-term use of GCSF make stringent follow-up necessary. The risk of malignancy appears very low, however, and routine bone marrow aspiration or biopsies are no longer recommended.

■ Follow-up, Complications, Prognosis, Pregnancy

Intensive dietary treatment with improved metabolic control has led to reduced morbidity and mortality and

to improved quality of life [8, 32, 54]. Long-term cerebral function is normal if hypoglycaemic damage is prevented. Most patients are able to lead fairly normal lives, but patients may develop complications of different organ systems [55].

Proximal and **distal renal tubular** and **glomerular functions** are at risk [42, 43, 56]. Proximal renal tubular dysfunction is observed in patients with poor metabolic control and improves after the start of intensive dietary treatment [57]. However, distal renal tubular dysfunction can occur even in patients with optimal metabolic control and may lead to hypercalciuria and hypocitraturia [39, 58]. Progressive glomerular renal disease starts with a silent period of hyperfiltration that begins in the 1st years of life [56]. Microalbuminuria and hypertension may develop at the end of the 1st or in the 2nd decade of life, and this is an early manifestation of the progression of renal disease [59]. In the setting of suboptimal control, proteinuria can worsen, and deterioration of renal function leading to end-stage renal disease in the 3rd-5th decade of life can occur. The similarities in the natural history of renal disease in GSD I and of nephropathy in insulin-dependent diabetes mellitus is striking. The pathogenesis, however, is still unclear. As in diabetic nephropathy, ACE inhibitors should be started if microalbuminuria persists over a period of 3 months with a moderate dietary restriction of protein and sodium [43]. Haemodialysis, continuous ambulatory peritoneal dialysis and renal transplantation are therapeutic options for end-stage renal disease in GSD I.

Hepatic adenomas remain the most common complication in GSD I, and they occur in 70% of patients irrespective of dietary management. Adenomas have been described in patients as young as 3 years of age, but most present during puberty [60, 61]. The cause of hepatic adenoma development is multifactorial with both genetic and environmental influences, but recent evidence suggests that the risk of adenoma development is lower in the setting of good metabolic control [62, 63]. A reduction in the size and/or number has been observed in some patients following attainment of optimal metabolic control. Haemorrhage and malignant transformation are possible complications, but most adenomas stop growing following puberty. To screen for adenomas and to follow their size and number, ultrasonography should be performed at least annually. An increase in the size of nodules or loss of definition of their margins necessitate further investigations, such as CT scans or MRI. In addition, serum α-fetoprotein can be used to screen for malignant transformation, but it has not been found to be a sensitive marker for malignant transformation [64]. The management of liver adenomas is either conservative or surgical. In severe cases of adenomas, enucleation or partial liver resection are therapeutic options [65, 66]. Where there is a recurrence of adenomas or suspected malignant transformation, liver transplantation is a therapeutic option provided there are no metastases [67]. Liver transplantation also corrects glucose homeostasis, but it does not correct the neutropenia, neutrophil dysfunction and enterocolitis common in GSD Ib. Notably, immunosuppression may worsen renal function, and there is a high prevalence of renal failure in GSD I patients who have undergone liver transplantation [68].

Osteoporosis is common in both GSD Ia and GSD Ib, developing without abnormalities in calcium, phosphate, parathyroid hormone or vitamin D metabolism [69]. The aetiology is probably multifactoral, including systemic acidosis, elevated cortisol concentrations, delayed pubertal development, inadequate dietary calcium and lack of physical activity [70]. Adequate supplementation with calcium and vitamin D intake is critical, and bone density measurement is recommended every 2 years after puberty [37].

Anaemia is common in both GSD Ia and GSD Ib [8, 32]. Whilst mild anaemia is often a result of iron deficiency, a more severe and unremitting anaemia may be seen in the setting of large hepatic adenomas as a result of inappropriate production of hepcidin, a peptide hormone that controls the release of iron from intestinal cells and macrophages [36]. Hepcidin-associated anaemia is also common in GSD Ib, but the pathogenesis is different. Instead of aberrant production in tumours, hepcidin is induced by IL-6 production from GSD Ib-associated enterocolitis, and severe anaemia in GSD Ib should warrant a gastrointestinal evaluation if inflammatory bowel disease has not been diagnosed [71].

Polycystic ovaries (PCOs) have been observed in adolescent and adult female patients [72]. Their pathophysiology is unresolved, and their effects on reproductive function are unclear. PCOs may cause acute abdominal pain as a result of sudden increase in size and/or vascular disturbances. This should be differentiated from pancreatitis and haemorrhage into a liver adenoma.

Despite severe hyperlipidaemia, **cardiovascular morbidity** and **mortality** are infrequent and, when present, may be related to secondary metabolic changes caused by the progressive renal disease. The preservation of normal endothelial function [45, 46] may result from diminished platelet aggregation [73], increased levels of apolipoprotein E [74], decreased susceptibility of LDL to oxidation – possibly related to the altered lipoprotein fatty acid profile in GSD Ia – and increased antioxidative defences in plasma protecting against lipid peroxidation [45]. A rare vascular complication that may cause more morbidity

and mortality in the ageing patient is **pulmonary hypertension** followed by progressive heart failure [75]. It may develop in the 2nd decade or later, and it appears to be a complication of poor metabolic control.

Successful **pregnancies** have been reported in both GSD Ia and GSD Ib [76, 77]. Close supervision and intensive dietary treatment are necessary, particularly in the 3rd trimester when glucose requirements rise rapidly. Home monitoring of lactate may be beneficial [78], and prematurity has been rare when glucose and lactate concentrations have been kept normal. Adenoma growth during pregnancy has not proved to be problematic, but renal disease can worsen if GSD nephropathy is present [76].

6.1.2 Glycogen Storage Disease Type III (Debranching Enzyme Deficiency)

The release of glucose from glycogen requires the activity of both phosphorylase and glycogen debranching enzyme (GDE). GSD III, also known as Cori or Forbes disease, is an autosomal recessive disorder that is due to deficiency of GDE, which causes storage of glycogen with an abnormally compact structure, known as limit dextrin [1]. Differences in tissue expression of the deficient GDE explain the existence of various subtypes of GSD III [9]. Eighty-five per cent of patients with GSD III have a generalised defect in which enzyme activity is deficient in liver, muscle, heart, leukocytes and cultured fibroblasts, and have a syndrome that includes both hepatic and myopathic symptoms, and often cardiomyopathy (GSD IIIa). About 15% of patients only have symptoms of liver disease and are classified as having GSD IIIb. Subgroups based on the selective deficiency of either the glucosidase activity (GSD IIIc) or of the transferase activity (GSD IIId) are very rare [2, 79].

■ Clinical Presentation

■■ Hepatic Presentation

GSD III presents in the 1st year of life with ketotic hypoglycaemia and hepatomegaly. Hepatic transaminases are markedly elevated and are often in excess of 1000 U/l in the untreated state. Hypertriglyceridaemia is present, but uric acid and lactate concentrations are relatively normal. During childhood, hepatomegaly, short stature, hypoglycaemia, and hyperlipidaemia predominate, and this presentation may be indistinguishable from GSD I [3]. Splenomegaly can be present, but the kidneys are not enlarged and renal function is normal. With increasing age, these symptoms improve in most GSD III patients.

■■ Myopathic Presentation

Clinically evident myopathy may be absent or minimal in childhood, but creatine kinase elevations may be noted as soon as toddlers become ambulatory. Hypotonia and delayed attainment of motor milestones can occur, but clinical manifestations are not usually present until the 2nd decade, when muscle cramps and decreased exercise tolerance manifest. Weakness progresses, worsening with age, and proximal muscles are usually more involved than the distal musculature [80].

Adult-onset myopathies may be distal or generalised. Patients with distal myopathy develop atrophy of leg and intrinsic hand muscles, often leading to the diagnosis of motor neuron disease or peripheral neuropathy [81]. The course is slowly progressive, and the myopathy is rarely crippling. The generalised myopathy tends to be more severe, often affecting respiratory muscles. In the EMG, myopathic features are mixed with irritative features (fibrillations, positive sharp waves, myotonic discharges), a pattern that may reinforce the diagnosis of motor neuron disease in patients with distal muscle atrophy. Nerve conduction velocities are often decreased [82]. Although GDE works hand-in-hand with myophosphorylase and one would therefore expect GDE deficiency to cause symptoms similar to those of McArdle disease, cramps and myoglobinuria are exceedingly rare.

■ Metabolic Derangement

Between meals, insulin levels fall and glucagon secretion increases. These hormones stimulate cleavage of glucose molecules from the terminal strands of glycogen as glucose-1-phosphate via the enzyme glycogen phosphorylase. This process continues until four glucose moieties remain before the α-1,6 bond. The human debranching enzyme has two distinct catalytic activities: 1,4-α-D-glucan 4-α-D-glycosyl transferase and amylo-1,6-glucosidase (AGL). The transferase component transfers the terminal three glucose molecules to the parent chain and the glucosidase component cleaves the α-1,6 bond to release free glucose [1, 2].

The inability to mobilise hepatic glycogen results in hypoglycaemia especially in young patients despite intact gluconeogenesis. Beta-oxidation, however, is normal, and patients develop associated ketosis and hyperlipidaemia [83]. In contrast to GSD I, the fasting blood lactate concentration is normal, but a moderate postprandial lactate elevation (3-5 mmol/l) usually occurs following carbohydrate-rich meals. Elevated levels of serum creatine kinase (CK) and aldolase suggest muscle involvement, but normal values do not exclude the future development of myopathy.

Genetics

The gene for GDE (*AGL)* is located on chromosome 1p21. At least 48 different mutations in *AGL* have been associated with GSD III [84, 85]. GSD IIIb is associated with mutations in exon 3, while mutations beyond exon 3 are associated with GSD IIIa [9]. When all known GSD III mutations are taken into consideration, there is no clear correlation between the type of mutation and the severity of the disease. This makes prognostic counselling based on mutations difficult [86].

Diagnosis

Mutation analysis has become the principal method for diagnosing GSD III if this diagnosis is suspected. Mutations in exon 3 of *AGL* have been associated with GSD type IIIb. Measurement of enzyme activity in skin fibroblasts or lymphocytes can be used to screen for GSD III, but these studies may not be definitive and cannot be used for subtyping. While liver and muscle biopsies are no longer required, they are occasionally still performed as part of evaluation of hepatomegaly or myopathy. Demonstration of abnormal glycogen (limit dextrin) and abnormal enzyme activity in a liver containing glycogen-filled hepatocytes is used to make the diagnosis. Fibrosis is more common than in GSD I. Muscle biopsy typically shows a vacuolar myopathy. The vacuoles contain PAS-positive material and corresponds to large pools of glycogen, most of which is free in the cytoplasm [2].

Treatment

Continuous provision of glucose is required to maintain blood glucose above 4.0 mmol/l (70 mg/dl) [87]. In infancy, frequent formula feeds every 3-4 h maintain normoglycaemia, and some patients require continuous nocturnal drip feeds to prevent hypoglycaemia. No special formulas are required, as lactose and fructose can be utilised but should be limited to individual tailored amounts to avoid over-storage of glycogen. Breast feeding is permitted. Beyond infancy, treatment consists of a high-protein diet (3 g/kg/day during childhood and 2 g/kg/day for adults) in GSD IIIa, along with uncooked cornstarch supplementation, nocturnal feeds or nocturnal drip feeding. Protein can be utilised as gluconeogenesis is intact and provision of adequate dietary protein reverses and may even prevent myopathy and cardiomyopathy [88]. A dose of 1 g/kg of uncooked cornstarch is used initially 3-4 times a day, and the dose of cornstarch is titrated to use the minimum required to maintain normoglycaemia and prevent ketosis. Monitoring blood glucose and ketones helps with optimising dietary control and titrating therapy [87]. In older children and adults, early morning glucose may be normal due to counter-regulatory mechanisms, but monitoring blood glucose concentrations between 2 a.m. and 4 a.m. may detect hypoglycaemia. Fructose and galactose is permitted in GSD III, but excessive amounts of simple sugars and cornstarch should be avoided since they may lead to worsening of the hepatomegaly and cardiomyopathy.

Complications, Prognosis, Pregnancy

Hepatic adenomas occur in approximately 10% of adults with GSD III, and cases of hepatocellular carcinoma have been reported [60, 89]. Hepatic fibrosis can occur, and some adult patients develop cirrhosis, portal hypertension and, rarely, liver failure. Liver transplantation has been performed in patients with end-stage cirrhosis and/or hepatocellular carcinoma [90], but it is not curative since in GSD IIIa the heart and muscle remain untreated [68].

In GSD IIIa, myopathy typically becomes more prominent in the 3rd to 4th decades of life, manifesting as slowly progressive muscle weakness. Exercise causes elevations in serum creatine kinase and aldolase concentrations. Patients with muscle involvement can develop cardiac complications. Concentric left ventricular hypertrophy, detectable by echocardiography, develops after puberty; however, ventricular function is usually normal [91]. Severe cardiac dysfunction and arrhythmias can occur, and rare cases of severe cardiomyopathy in infants and children have been reported [92]. Pregnancies have been successful in GSD III, but monitoring of glucose and ketones is recommended due to changing nutritional needs in pregnancy [93].

Patients with GSD III are prone to adverse effects from several medication classes. In particular, use of succinylcholine and other nonpolarising medications during surgery can trigger substantial muscle damage and rhabdomyolysis. Beta-blockers and statins are not recommended, and they must be used with extreme caution if required [87].

6.1.3 Glycogen Storage Disease Type IV (Branching Enzyme Deficiency)

GSD IV, or Andersen disease, is an autosomal recessive disorder due to a deficiency of glycogen branching enzyme (GBE). Deficiency of GBE results in the formation of an amylopectin-like compact glycogen molecule with fewer branching points and longer outer chains [2]. The pathophysiological consequences of this abnormal glycogen for the liver still need to be elucidated. Patients with the classic form of GSD IV develop progressive liver disease early in life. The nonprogressive hepatic variant of GSD IV is less frequent, and these patients usually survive

into adulthood. Besides these liver-related presentations there are rare neuromuscular forms of GSD IV [94].

Clinical Presentation

Hepatic Forms

Patients are normal at birth and present generally in early childhood with hepatomegaly, failure to thrive and liver cirrhosis. The cirrhosis is progressive and causes portal hypertension, ascites, and oesophageal varices. Some patients may also develop hepatocellular carcinoma [95]. Life expectancy is limited due to severe progressive liver failure and – without liver transplantation – death generally occurs when patients are 4-5 years of age [90, 96].

Patients with the nonprogressive form present with hepatomegaly and sometimes elevated transaminases. Although fibrosis can be detected in liver biopsies, this is apparently nonprogressive. No cardiac or skeletal muscle involvement is seen. These patients have normal parameters for growth.

Neuromuscular Forms

Neuromuscular forms can be divided into four clinical presentations according to the age of onset. A neonatal form, which is extremely rare, presents as fetal akinesia deformation sequence (FADS), consisting of arthrogryposis multiplex congenita, hydrops fetalis and perinatal death. A congenital form presents with hypotonia, cardiomyopathy and death in early infancy. A third form manifests in childhood with either myopathy or cardiomyopathy. Lastly, the adult form may present as a myopathy or as a multisystemic disease also called adult polyglucosan body disease (APBD) [97] (► Section 6.3.2).

Muscle biopsy in the neuromuscular forms shows the typical foci of polyglucosan accumulation, which are intensely PAS-positive and diastase-resistant. Similar deposits are seen in the cardiomyocytes of children with cardiomyopathy and in motor neurons of infants with a Werdnig-Hoffmann-like presentation [98].

Metabolic Derangement

Hypoglycaemia is rarely seen, only occurring when liver cirrhosis is advanced and liver failure sets in. The clinical and biochemical findings under these circumstances are identical to those typical of other causes of cirrhosis, with elevated liver transaminases and abnormal values for blood clotting factors, including prothrombin and thromboplastin generation time.

Genetics

The *GBE* gene has been mapped to chromosome 3p14. Three important point mutations, R515C, F257L and R524X, were found in patients with the classic progressive liver cirrhosis form [99]. In patients with the nonprogressive liver cirrhosis form, the Y329S mutation has been reported. This mutation results in a significant preservation of GBE activity, thereby explaining the milder course of the disease. Interestingly, the mutation found in patients with APBD [97] also appears to be relatively mild, which may explain the late onset of this disorder.

Diagnosis

The diagnosis is usually not suspected until histological examination of a liver or muscle biopsy which shows large deposits that stain with periodic acid-Schiff but are partially resistant to diastase digestion. Electron microscopy shows accumulation of fibrillar aggregations that are typical for amylopectin. The enzymatic diagnosis is based on the demonstration of GBE deficiency in liver, muscle, fibroblasts or leukocytes. Prenatal diagnosis is possible using DNA mutation analysis in informative families, but it is difficult to determine by measuring the enzyme activity in cultured amniocytes or chorionic villi because of high residual enzyme activity.

Treatment

There is no specific dietary or pharmacological treatment for GSD IV. Liver transplantation is the only effective therapeutic approach at present for those with the classic progressive liver disease [90, 96] For patients with hypoglycaemia, cornstarch can be prescribed as a late evening feed with the goal of achieving normoglycaemia. Until transplantation is realised dietary treatment similar to that for GSD III will improve the general condition of the patient.

Complications, Prognosis, Pregnancy

The ultimate prognosis depends on the results of liver transplantation, which was favourable in 13 GSD IV patients [96]. The prognosis also depends on the occurrence of amylopectin storage in extrahepatic tissues. This risk seems to be especially high for cardiac tissue. Of 13 patients with GSD IV who underwent liver transplantation, 2 died from heart failure due to amylopectin storage in the myocardium [96]. A positive result of liver transplantation may be the development of systemic microchimerism, with donor cells present in various tissues. This would lead to a transfer of enzyme activity from normal to deficient cells outside the liver. No pregnancies have been reported in classic GSD IV.

Patients with the nonprogressive liver variant have been reported to survive into their mid-forties. With increasing age, liver size tends to decrease and elevated transaminases return to (near-)normal values.

6.1.4 Glycogen Storage Disease Type VI (Glycogen Phosphorylase Deficiency)

GSD VI or Hers disease is an autosomal recessive disorder due to a deficiency of the hepatic glycogen phosphorylase. Phosphorylase breaks the straight chains of glycogen down to glucose-1-phosphate in a concerted action with debranching enzyme. Glucose-1-phosphate in turn is converted into glucose-6-phosphate and then into free glucose [1].

▪ Clinical Presentation

GSD VI is a rare disorder with a generally benign course. Patients are clinically indistinguishable from those with liver GSD type IX caused by phosphorylase kinase (PHK) deficiency and present with hepatomegaly and growth retardation in early childhood. The hallmark for this disease is ketotic hypoglycaemia in infancy, which is present after an overnight fast, but many patients are diagnosed on the basis of hepatomegaly found incidentally during physical examination. Cardiac and skeletal muscles are not involved. Hepatomegaly decreases with age and usually disappears around puberty [100].

▪ Metabolic Derangement

The tendency to hypoglycaemia is not as severe as seen in GSD I or GSD III, and often the hypoglycaemia is unrecognised in this disorder unless testing is performed in the middle of the night or during illness. Hyperketosis is the predominant abnormality, whilst hyperlipidaemia and hepatic transaminase elevation are usually mild. Lactic acid and uric acid are within normal limits [6].

▪ Genetics

Three isoforms of phosphorylase are known, encoded by three different genes. The gene encoding the liver isoform, *PYGL*, is on chromosome 14q21-q22, and over 40 mutations have been described [101, 102]. A common mutation has been described in the Mennonite population [103].

▪ Diagnosis

Mutation analysis is the preferred method for diagnosing GSD VI. Deficient phosphorylase activity can be documented in liver tissue, but a liver biopsy is not recommended if the diagnosis is suspected.

▪ Treatment

Treatment of liver phosphorylase deficiency is symptomatic and consists in preventing hypoglycaemia and ketosis. This is achieved by prescribing frequent meals along with uncooked cornstarch supplementation: one to three times a day and as a late-evening meal [104]. When hypoglycaemia is not a clinical concern, uncooked cornstarch therapy improves growth, energy, stamina and well-being. Lactose and fructose are permitted, but excessive amounts of simple sugars should be avoided as they may increase hepatomegaly.

▪ Complications, Prognosis, and Pregnancy

The prognosis for those with GSD VI is excellent, but improves with aggressive treatment. Without therapy, delayed puberty and osteoporosis can occur related to chronic ketosis. Hepatic adenomas are rare in GSD VI. Alcohol consumption, however, is problematic in this disorder, as it can precipitate a metabolic crisis and severe hypoglycaemia by impairing gluconeogenesis. It may also predispose patients to scarring and cirrhosis. Hypoglycaemia can occur during pregnancy when metabolic needs increase.

6.1.5 Glycogen Storage Disease Type IX (Phosphorylase Kinase Deficiency)

GSD IX, or phosphorylase kinase (PHK) deficiency, is the most frequent glycogen storage disease. According to the mode of inheritance and clinical presentation six different subtypes are distinguished: (1) X-linked liver glycogenosis (XLG or GSD IXa), by far the most frequent subtype; (2) combined liver and muscle PHK deficiency (GSD IXb); (3) autosomal liver PHK deficiency (GSD IXc); (4) X-linked muscle glycogenosis (GSD IXd); (5) autosomal muscle PHK deficiency (GSD IXe); and (6) heart PHK deficiency (GSD IXf), which, however, is now recognised as being due to mutations in the γ2-subunit of AMP-activated protein kinase rather than to PHK deficiency (► Section 0) [9, 105-107].

▪ Clinical Presentation

▪▪ Hepatic Presentation

The main clinical symptoms are hepatomegaly, growth retardation, elevated liver transaminases, hypercholesterolaemia and hypertriglyceridaemia. While this disorder is classically mild, it is the most heterogeneous of the hepatic GSDs, and some children may phenotypically look like GSD I or GSD III patients, with marked hypoglycaemia and transaminase elevation [108].

▪▪ Myopathic Presentation

The myopathic variants present in a form that is clinically similar to a mild form of McArdle disease, with exercise intolerance, cramps and recurrent myoglobinuria in

young adults. Less frequent presentations include infantile weakness and respiratory insufficiency or late-onset weakness. Muscle morphology shows subsarcolemmal deposits of normal-looking glycogen [109].

▪ Metabolic Derangement

The degradation of glycogen is controlled both in liver and in muscle by a cascade of reactions resulting in the activation of phosphorylase. This cascade involves the enzymes adenylate cyclase and PHK. PHK is a decahexameric protein composed of four subunits, α, β, γ, and δ: the α- and β-subunits are regulatory, the γ-subunit is catalytic, and the δ-subunit is a calmodulin and confers calcium sensitivity to the enzyme. The hormonal activating signals for glycogenolysis are glucagon for the liver and adrenaline for muscle. Glucagon and adrenaline activate the membrane-bound adenylate cyclase, which transforms ATP into cyclic AMP (cAMP) and interacts with the regulatory subunit of the cAMP-dependent protein kinase, resulting in phosphorylation of PHK. Ultimately, this activated PHK transforms glycogen phosphorylase into its active conformation, a process that is defective in GSD type IX [1].

▪ Genetics

Two different isoforms of the α-subunit (α_L for liver and α_M for muscle) are encoded by two different genes on the X chromosome (*PHKA2* and *PHKA1* respectively), whilst the β-subunit (encoded by *PHKB*), two different isoforms of the γ-subunit (γ_T for testis/liver and γ_M for muscle, encoded by *PKHG2* and *PKHG1*, respectively), and three isoforms of calmodulin (*CALM1*, *CALM2*, *CALM3*) are encoded by autosomal genes. The *PHKA2* gene has been mapped to chromosome Xp22.2-p22.1, the *PHKB* gene to chromosome 16q12-q13, and the *PKHG2* gene to chromosome 16p12-p11 [110-112].

The most common hepatic variant, XLG or GSD IXa (resulting from *PHKA2* mutations), comprises two different entities: XLG1, the classic type, and XLG2, the less common variant. In XLG1, the PHK activity is deficient in liver and decreased in blood cells. In XLG2, PHK activity is normal in liver, erythrocytes and leukocytes. Therefore, normal PHK activity in erythrocytes or even liver tissue does not exclude XLG. This phenomenon may be explained by the fact that XLG2 is due to minor mutations with regulatory effects on PHK activity, which is not decreased in vitro [105, 113]. While a strict genotype-phenotype relationship has not been elucidated, mutations in the γ-subunit and some in the α-subunit have been associated with a more severe phenotype with severe hypoglycaemia, lactic acidosis, hepatic fibrosis, and cirrhosis [114, 115].

The predominance of affected men with the myopathic presentation suggested that the X-linked α_M-isoform may be involved predominantly, a concept bolstered by reports of mutations in the *PHKA1* gene in two patients [116]. However, a thorough molecular study of six myopathic patients, five men and one woman, revealed only one novel mutation in *PHKA1*, whereas no pathogenic mutations were found in any of the six genes (*PHKA1*, *PHKB*, *PHKG1*, *CALM1*, *CALM2*, *CALM3*) encoding muscle subunits of PHK in the other five patients. This surprising result suggested that most myopathic patients with low PHK activity harbour either elusive mutations in PHK genes or mutations in other unidentified genes [109].

▪ Diagnosis

Assays of PHK in various tissues may not allow for a definitive diagnosis. Where possible, this should be based on the identification of mutations within the different *PHK* genes [9].

▪ Treatment and Prognosis

Treatment of liver phosphorylase deficiency is symptomatic and consists in preventing hypoglycaemia and ketosis. This is achieved by eating frequent meals, along with uncooked cornstarch supplementation to achieve the aforementioned goals. While some children do not need cornstarch, others need dosing similar to that applied in GSD I, and treatment should be individualised [117]. As outlined for GSD VI, prevention of ketosis improves growth and normalises puberty. Alcohol similarly should be avoided. The prognosis is generally favourable for the hepatic types, and more uncertain for the myopathic variants.

6.1.6 Glycogen Storage Disease Type 0 (Glycogen Synthase Deficiency)

Type 0 glycogen storage disease (GSD 0) is caused by a deficiency of the hepatic isoform of glycogen synthase, which leads to a marked decrease in liver glycogen content [118]. While this disorder has decreased hepatic glycogen, it is characterised as a glycogen storage disease since glycogen is not available during periods of fasting, resulting in a phenotype similar to that of the classic glycogenoses.

▪ Clinical Presentation

Children with GSD 0 usually present with ketotic hypoglycaemia found during an illness or a period of fasting. Developmental delay can occur, but neurological sequelae

are uncommon [119]. Growth retardation from chronic ketosis is common, and patients may paradoxically present with hyperglycaemia as they are found postprandially with hyperglycaemia [120]; children tested in the morning after an overnight fast and breakfast have been misdiagnosed as having diabetes because of the presence of hyperglycaemia and ketosis. The lack of physical findings and less severe clinical course has almost certainly led to underdiagnosis of this condition [119, 121].

▪ Metabolic Derangement

The inability to store glucose leads to a unique pattern of postprandial hyperglycaemia associated with hyperlactataemia alternating with fasting ketotic hypoglycaemia. All patients have overnight ketosis, and the presence of ketones in a morning blood sample can be used to determine which patients with ketotic hypoglycaemia warrant consideration of this diagnosis.

▪ Genetics

The gene that encodes GS, *GYS2,* is located on chromosome 12p12.2, and 15 different mutations are known [119, 122]. No dominant mutation has been identified.

▪ Diagnosis

Mutation analysis is the preferred method for diagnosing this condition. Diagnosis of GSD 0 can also be based on the demonstration of decreased hepatic glycogen content and deficiency of the GS enzyme in a liver biopsy.

▪ Treatment

The goal of treatment is to prevent hypoglycaemia and minimise the associated hyperlactataemia and ketosis. Treatment involves a diet high in protein to provide a substrate for gluconeogenesis and low-glycaemic-index complex carbohydrates to minimise postprandrial hyperglycaemia and hyperlactacidaemia. Uncooked cornstarch (1-1.5 g/kg) administered at bedtime prevents morning hypoglycaemia and ketosis. Daytime hypoglycaemia tends to be mild, and snacks administered every 3-4 h often prevent it; a small dose of cornstarch may be beneficial for children and adults who are particularly active.

▪ Complications, Prognosis and Pregnancy

The prognosis for those with GSD 0 is excellent, and complications are rare. Treatment, however, improves growth, energy, and stamina. As with the other ketotic forms of GSD, alcohol consumption can result in hypoglycaemia, and it must be consumed with caution. Hypoglycaemia can occur during pregnancy when metabolic needs increase [123].

6.2 Muscle and Cardiac Glycogenoses

At rest, muscle predominantly utilises fatty acids. During submaximal exercise, it additionally uses energy from blood glucose, mostly derived from liver glycogen. In contrast, during very intense exercise, the main source of energy is anaerobic glycolysis following breakdown of muscle glycogen. When the latter is exhausted, fatigue ensues. Enzyme defects within the pathway affect muscle function.

6.2.1 GSDs With Exercise Intolerance Without Cardiac Involvement

▪ Glycogen Storage Disease Type V (Myophosphorylase Deficiency, McArdle Disease)

▪▪ Clinical Presentation

GSD V, the most common muscle glycogenosis, was first described in 1951 by McArdle. It is characterised by exercise intolerance with myalgia and stiffness of exercising muscles, which are relieved by rest. Onset of the disease occurs during childhood, but diagnosis is frequently missed at an early age because affected children are often considered to be just lazy. Two types of effort are more likely to cause symptoms: brief intense isometric exercise, such as lifting heavy weights, or less intense but sustained dynamic exercise, such as running or climbing a hill. Moderate exercise, such as walking on level ground, is usually well tolerated. All patients experience a constant phenomenon, named the »second wind«: if they rest briefly after the onset of exercise-induced myalgia, they are then able to continue to exercise with a lower level of pain and fatigue. This phenomenon is considered to be related to the ability to metabolise free glucose that is mobilised in the bloodstream. Myoglobinuria is the major complication, and occurs in about half of the patients. Creatine kinase (CK) can increase to more than 100,000-1,000,000 UI/l during episodes of rhabdomyolysis, leading to a risk of developing acute renal failure. With carnitine palmitoyl transferase II (CPTII) deficiency, GSD V is the second most common disorder leading to episodes of recurrent myoglobinuria in adults [124], although lipin1 deficiency is now also recognised as a relatively frequent cause (► Chapter 35). Neurological evaluation is usually normal between crises, but proximal muscle weakness and wasting occur in approximately 35% of the patients over 40 years of age [125]. Two patterns of muscle weakness may be observed: (1) proximal and symmetrical, or (2) scapulohumeral and asymmetrical. Resting serum CK is consistently elevated in McArdle patients. Clinical vari-

ants of GSD V with a fatal infantile myopathy have been described in a few cases [79]. Electromyography (EMG) can be normal or show nonspecific myopathic features at rest, but documents electrical silence in contracted muscles.

■■ Metabolic Derangement

There are three isoforms of glycogen phosphorylase: brain/heart, liver and muscle, all encoded by different genes. GSD V is caused by deficient myophosphorylase activity.

■■ Genetics

GSD V is an autosomal recessive disorder. The gene for the muscle isoform (*PYGM*) has been mapped to chromosome 11q13. The number of known pathogenic mutations has rapidly increased to over 100 [126]. By far the most common mutation in Caucasians is the p.R50X mutation, which accounts for 81% of the alleles in British patients [127] and 63% of alleles in US patients [128]. This mutation has never been described in Japan, however, where a single codon deletion 708/709 seems to prevail [129].

No genotype-phenotype correlations have been detected. In addition, an angiotensin-converting enzyme (ACE) insertion/deletion polymorphism might play a significant role as a phenotype modulator in individuals with GSD V [130].

■■ Diagnosis

The ischaemic forearm exercise test (IFET) was first used by McArdle to describe the absence of elevation of lactate during exercise, but its main drawbacks are muscle pain with possible rhabdomyolysis (▶ Chapter 4). Consequently the IFET should be abandoned and replaced by the standardised nonischaemic FET, which has a sensitivity of 100% in McArdle's disease [131]. Ammonia levels should be also assessed in parallel with lactate, as an abnormal increase in ammonia is always observed in GSD V. This measurement of ammonia also allows discrimination of patients with disorders of glycogenolysis from those with nonorganic muscle symptoms, because in the latter the lack of an increase in both lactate and ammonia indicates insufficient effort due to lack of cooperation. Alternative diagnostic tests include (1) a cycling test at a moderate and constant workload, during which patients with GSD V show a consistent decrease in heart rate between the 7th and the 15th minutes of exercise, indicating the second wind phenomenon [132] or (2) ^{31}P-magnetic resonance spectroscopy to demonstrate abnormal alkalinisation after exercise [133]. Muscle biopsy shows vacuoles and subsarcolemmal accumulation of glycogen that is normally digested by diastase. Negative staining using a specific myophosphorylase confirms the diagnosis, but muscle biopsy should always be performed several weeks after an episode of rhabdomyolysis, as the histochemical abnormalities may be overshadowed by the intensity of the necrotic process. Muscle biopsy can be avoided in caucasian patients by identification of the common mutation (p.R50X) in genomic DNA.

■■ Treatment

There is no pharmacological treatment, but exercise intolerance may be alleviated by aerobic conditioning programmes [134] or by ingestion of oral sucrose (37 g), which may have a prophylactic effect when taken 5 min before planned activity [135]. This effect is explained by the fact that sucrose is rapidly split into glucose and fructose; both bypass the metabolic block in GSD V and hence contribute to glycolysis [136]. A recent study indicates that work capacity and exercise tolerance are improved after a carbohydrate-rich diet, an effect that needs to be explored in larger controlled trials [137]. Patients should also avoid strenuous efforts and leisure activities that put them at risk, such as swimming far from the shore and mountaineering.

■ Disorders of Glycolysis

Seven enzyme deficiencies affecting the glycolytic pathway have been described. They all present with exercise intolerance and possibly also with episodes of rhabdomyolysis similar to those in GSD V. Additional clinical, biological and morphological features may allow these very rare disorders to be distinguished from GSD V (◘ Table 6.2).

■■ Clinical Presentation

Phosphofructokinase (PFK) Deficiency: PFK deficiency or GSD VII, first described by Tarui, is the more frequent glycolytic disorder. GSD VII is indistinguishable from GSD V, except that there is no second wind phenomenon and exercise intolerance worsens, rather than improves, after a high-carbohydrate meal, explained by the fact that glucose lowers the blood concentration of the alternative muscle fuels, free fatty acids and ketone bodies [138]. There are two clinical variants, one manifesting as a fixed weakness in adult life (although most patients recognise having suffered from exercise intolerance in their youth), the other affecting infants or young children, who have both generalised weakness and symptoms of multisystem involvement (seizures, cortical blindness, corneal opacifications or cardiomyopathy) [79].

Phosphoglycerate Kinase (PGK) Deficiency: PGK is an ubiquitous enzyme, and the clinical presentation of PGK

Table 6.2. Main features of glycogen storage diseases and related disorders

Type (synonym/s)	Defective enzyme or transporter	Main tissue involved	Main clinical features
Disorders presenting primarily with hepatomegaly and hypoglycaemia			
Ia (Von Gierke)	Glucose-6-phosphatase	Liver, kidney	Hepatomegaly, short stature, hypoglycaemia, lactataemia, hyperlipidaemia
Ib or non-1a	Glucose-6-phosphate translocase	Liver, kidney, leukocytes	Same as Ia, neutropenia, infections
III (Cori, Forbes)	Debranching enzyme and subtypes	Liver, muscle	Hepatomegaly, (cardio)myopathy, short stature, hypoglycaemia
IV (Andersen)	Branching enzyme	Liver	Hepato(spleno)megaly, liver cirrhosis, rare neuromuscular forms
VI (Hers)	Liver phosphorylase	Liver	Hepatomegaly, short stature, hypoglycaemia
IX	Phosphorylase kinase and subtypes	Liver and/or muscle	Hepatomegaly, short stature (myopathy), hypoglycaemia
0	Liver glycogen synthase	Liver	Hypoglycaemia
Fanconi-Bickel	GLUT2	Liver, kidney	Hepatomegaly, short stature, hypoglycaemia, renal tubular disease
Disorders presenting primarily with exercise intolerance due to skeletal myopathy			
V (McArdle)	Myophosphorylase	Muscle	Myalgia, exercise intolerance, weakness
VII (Tarui)	Phosphofructokinase	Muscle, erythrocytes	Myopathy, haemolytic anaemia, multisystem involvement (seizures, cardiopathy)
–	Phosphoglycerate kinase	Muscle, erythrocytes, central nervous system	Exercise intolerance, haemolytic anaemia convulsions
X	Phosphoglycerate mutase	Muscle	Exercise intolerance, cramps
XI	Lactate dehydrogenase	Muscle	Exercise intolerance, cramps, skin lesions
XII	Aldolase A	Muscle	Exercise intolerance, cramps
XIII	β-Enolase	Muscle	Exercise intolerance, cramps
XIV	Phosphoglucomutase	Muscle	Exercise intolerance, cramps
Disorders with cardiac involvement			
I (Pompe)	Acid α-glucosidase	Muscle Heart	Myopathy Cardiomyopathy
IIb (Danon)	LAMP-2	Muscle, heart	Cardiomyopathy, myopathy
GSD III	Debranching enzyme	Muscle, heart	Myopathy, cardiomyopathy
Muscle glycogen depletion syndromes	Muscle glycogen synthase, glycogenin	Muscle, heart	Myopathy, cardiomyopathy,
Cardiomyopathy and WPW syndrome	AMP-activated protein kinase (AMPK)	Heart	Cardiomyopathy, dysrhythmia
Disorders with neurodegeneration			
Lafora disease	Laforin/malin complex (neurons)	Brain	Myoclonic epilepsy, dementia, visual loss
Adult polyglucosan disease	Branching enzyme (astrocytes)	Brain, motor neuron, peripheral nerve	Gait disturbance, bladder dysfunction, dementia: infantile, juvenile, adult forms

WPW, Wolff-Parkinson-White syndrome

deficiency depends on the isolated or associated involvement of three tissues: erythrocytes (haemolytic anaemia), central nervous system (CNS), (seizures, mental retardation, strokes) and skeletal muscle (exercise intolerance, cramps, myoglobinuria). The most common clinical manifestations are nonspherocytic haemolytic anaemia, CNS involvement with anaemia and exercise intolerance with recurrent myoglobinuria. Anaemia and myopathy had been reported in only one patient [139].

Other glycolysis enzyme deficiencies are very rare. GSD X or phosphoglycerate mutase (PGAM) deficiency has been described in about a dozen patients, and GSD XI, -XII, -XIII and –XIV, each in fewer or as single cases. The clinical picture is stereotypical: exercise intolerance and cramps after vigorous exercise, often followed by myoglobinuria.

■■ Metabolic Derangement and Genetics

GSD VII (Muscle PFK Deficiency): PFK is a tetrameric enzyme under the control of three genetic loci that code for muscle (M), liver (L) and platelet (P) subunits. Mature human muscle expresses only an M homotetramer (M4), whereas erythrocytes contain five isoenzymes combining the M and the L subunits. In patients with typical PFK deficiency, mutations in *PFK-M* cause total lack of activity in muscle but only partial PFK deficiency in red blood cells, where the residual activity approximates 50% and is accounted for by the L4 isozyme [79].

PGK is encoded by an X-linked gene (*PGK1*) and is expressed in all tissues except spermatogenic cells.

GSD X: PGAM is a dimeric enzyme with a muscle-specific (M) and a brain-specific (B) subunit. Normal adult human muscle has a marked predominance of the MM isozyme, whereas in most other tissues PGAM-BB is the only isozyme demonstrable by electrophoresis [79]. Molecular defects in the *PGAMM* gene have been identified in patients with GSD X.

GSD XI (Muscle Lactate Dehydrogenase [LD] Deficiency): LD is a tetrameric enzyme composed of a muscle-specific subunit (M or A) and a cardiac subunit (H or B). Mutations have been identified in the gene *LDHM* coding for the muscle subunit.

GSD XII (Aldolase A Deficiency): Aldolase exists in three isoforms (A, B and C): skeletal muscle and erythrocytes contain predominantly the A isoform, which is encoded by the gene *ALDOA*.

GSD XIII: β-Enolase is a dimeric enzyme and exists in different isoforms resulting from various combinations of three subunits, α, β and γ. The β-subunit is encoded by the gene *ENO3*.

GSD XIV: Four isoforms of phosphoglucomutase (PGM) are implicated in phosphotransferase reactions during glycolysis and gluconeogenesis. Mutations have been detected in the *PGM1* gene coding for the PGM1 isoform, representing about 90% of the total PGM activity [140].

■■ Diagnosis

Some routine laboratory results are useful for diagnosis, including an increased bilirubin concentration and reticulocyte count, reflecting a compensated haemolysis that may occur in PFK and PGK deficiencies. Hyperuricaemia is commonly found in PFK deficiency and is attributed to excessive degradation of purine nucleotides in the exercising muscles. Discrepancies between a high level of CK and a low level of LDH are suggestive of LDH deficiency.

When a disorder of glycolysis is suspected, the first step in the evaluation of patient should be a forearm exercise test for measurement of lactate and ammonia levels. Absent or blunted lactate production with an abnormal rise of ammonia levels is a characteristic but inconsistent feature, which should always be followed by a muscle biopsy. ^{31}P-NMR spectroscopy allows detection of an abnormal increase in the phosphomonoester peak in PFK and PGK deficiencies, a useful criterion for distinguishing these enzyme deficiencies [133].

Muscle histology shows inconstant subsarcolemmal vacuoles and glycogen accumulation on PAS staining. This glycogen is normally digested by diastase, except in PFK deficiency, which can also lead to accumulation of abnormally branched glycogen (polyglucosan) with a hyaline aspect on standard haematein-eosin stain and resistance to diastase digestion. Specific anomalies such as tubular aggregates may be observed in PGAM deficiency. A specific histochemical reaction is also available for PFK and may help to confirm the diagnosis of GSD VII.

Conclusive evidence comes from the biochemical analysis of enzyme deficiencies either on muscle biopsy for all enzymes, or in erythrocytes for PFK, PGK and aldolase A [141-144].

■■ Treatment

There is no specific therapy, and in contrast to GSD V, in PFK deficiency sucrose and high-carbohydrate diet should be avoided. Aerobic exercise might be useful, but clinical studies remain difficult for such rare disorders.

6.2.2 GSDs with Cardiac Involvement

■ Glycogen Storage Disease Type II (Pompe Disease)

GSD II, also named Pompe disease, acid α-glucosidase deficiency or acid maltase deficiency, is the only lysosomal storage disease among the different glycogenoses and is caused by deficiency of the lysosomal enzyme acid

α-glucosidase. It is the second most common cause of muscle glycogenosis after GSD V.

■■ Clinical Presentation

Pompe disease presents as a spectrum, with infantile, juvenile and adult forms named according to the age at onset, rate of progression and extent of organ involvement [145].

The classic infantile form usually presents within the first months of life with hypotonia (floppy infant syndrome) and hypertrophic cardiomyopathy, which can be detected on chest X-ray and electrocardiogram. Additional clinical features can be enlargement of the tongue and liver, and major motor milestones are not achieved. Patients most often die from cardiopulmonary failure or aspiration pneumonia without reaching 1 year of age [146].

The juvenile forms are characterised by predominant skeletal muscle dysfunction, with motor and respiratory problems, but rarely cardiac involvement. Calf hypertrophy can be present, mimicking Duchenne muscular dystrophy in boys. Myopathy and respiratory insufficiency deteriorate gradually, and patients often become dependent on ventilator or wheelchair.

The adult form develops in the 3rd or 4th decade and affects the trunk and proximal limb muscles, mimicking inherited limb-girdle muscle dystrophies [147]. Involvement of the diaphragm is frequent, and acute respiratory failure may be the initial symptom in some patients. Therefore, the presence of a severe respiratory insufficiency in a patient with moderate limb-girdle muscle weakness is a major clue in the diagnosis of adult-onset Pompe disease. By contrast with the infantile form, the heart is generally not affected. The major cause of death in adults is respiratory insufficiency. Pulmonary function tests should be undertaken annually and respiratory support started when necessary, as in some patients this can prolong life for decades. Rarer causes of death are strokes related to intracranial aneurysm or arteriopathy due to accumulation of glycogen in vascular smooth-muscle cells [148, 149].

■■ Metabolic Derangement

The enzyme defect results in the accumulation of glycogen within the lysosomes, with different critical thresholds depending on the organ, explaining why the heart is unaffected in adults who have significant residual enzyme activity. Intermediary metabolism is unaffected. Autophagy probably also has a major role in the pathogenic process, with recent works showing an autophagic build-up due to dysfunction of endocytic and autophagic pathways in the muscle fibres [150]. A failure to digest glycogen could result in local starvation, inducing autophagy with a pathological cycle due to lysosomal dysfunction.

■■ Genetics

Over 200 mutations have been reported in the gene encoding acid α-glucosidase, about 75% of these being pathogenic mutations (www.pompecenter.nl). There is some degree of genotype-phenotype correlation with severe mutations (such as del exon18) associated with the infantile form and 'leaky' mutations associated with the adult variant. The most common mutation in adults and children with a slowly progressive course is c.-32-13T>G (approximately 80% of patients).

■■ Diagnosis

The diagnosis always relies on demonstrating acid α-glucosidase deficiency; infants with the classic infantile form have less than 1% residual activity, whereas children and adults have residual activity no more than 30% of normal values. Sensitivity and specificity of enzymatic assays performed in various tissues may be altered by interference with neutral α-glucosidase activities, and skin fibroblasts are the best tissue for diagnosis owing to lower biochemical interferences. New screening methods for acid α-glucosidase deficiency using assays in dried blood spots have recently been developed [151] and could be suitable for neonatal screening. Enzymatic prenatal diagnosis is also possible on chorionic villi, but DNA analysis is a far better procedure in this context if mutations have already been detected in the parents or a previously affected child.

Muscle biopsy shows a severe vacuolar myopathy with accumulation of both lysosomal and free glycogen in the infantile form, but this procedure is not recommended in babies because of the anaesthetic risks. Conversely, the diagnosis is frequently established in adults from the result of a muscle biopsy performed in the context of diagnostic work-up of a muscle dystrophy. A vacuolar myopathy with PAS-positive material is present in approximately two thirds of adults, but in one third of cases the muscle biopsy may be normal or show nonspecific changes, potentially leading to a mistaken diagnosis [152]. Electromyography may also help in establishing the diagnosis in the myopathic forms of the disease, showing pseudomyotonic discharges, more frequently in paraspinal muscles, in addition to the myopathic features.

■■ Treatment

Palliative therapy relies on prevention of cardiorespiratory failure, with the possibility of long-lasting survival in adults with ventilatory support. A major step towards treatment of Pompe disease has been achieved with the

large-scale production of recombinant acid α-glucosidase (rhGAA), initially in milk of transgenic rabbit and further in CHO cells (alglucosidase alpha). Alglucosidase alpha has been commercially approved since 2006, and two large studies in infants showed major beneficial effects on cardiomyopathy and muscle weakness, with increased survival [153]. Doses of 20 mg/kg by infusion every other week are recommended. However, less than half of the children on enzyme replacement therapy (ERT) gain normal motor function status and become ventilator free [154]. Several factors may limit the efficacy of ERT in children, such as a severe condition of the patient with extensive muscle damage at the start of treatment or the appearance of high levels of IgG antibodies to rhGAA. A double-blind placebo-controlled trial in adults showed improvement of the walking distance and stabilisation of vital capacity after 18 months of treatment [155]. Long-term follow-up data are currently being collected across the entire spectrum of Pompe disease in order to expand understanding of the effects of ERT and to formulate guidelines for treatment.

▪ Danon Disease (LAMP-2 Deficiency)

Danon disease is a rare X-linked disorder caused by a primary deficiency of lysosomal-associated membrane protein 2 (LAMP-2).

▪▪ Clinical Presentation

The disease presents after the 1st decade, and the characteristic clinical features in male patients include cardiomyopathy in all cases and mild skeletal myopathy and mental retardation in approximately 70%. Fundal examination may detect either retinopathy or maculopathy, and these visual abnormalities may be important clues to this diagnosis in patients with unexplained hypertrophic cardiomyopathy [156]. Hemizygous females can also be affected, with a later age at onset and either hypertrophic or dilated cardiomyopathy.

▪▪ Metabolic Derangement

This disease has been classified with glycogenoses because of the appearance on muscle biopsy, in most cases, of small cytoplasmic vacuoles containing autophagic material and glycogen in muscle fibres [157].

▪▪ Genetics

Danon disease is caused by mutations in the gene encoding LAMP2 on Xq24.

▪▪ Diagnosis

The diagnosis may be confirmed by the absence of LAMP-2 staining on immunohistochemistry and detection of mutations in the *LAMP2* gene [158].

▪▪ Treatment

No specific therapy is available, but cardiac transplantation should be considered [159].

▪ Glycogen Depletion Syndromes (Muscle Glycogen Storage disease Type 0 or Glycogen Synthase Deficiency and Glycogenin 1 Deficiency)

Two muscular glycogenoses that are due to deficiencies of enzymes involved in the initial steps of glycogen synthesis, glycogenin and glycogen synthase, have recently been identified [160, 161].

▪▪ Clinical Presentation

Both disorders present with myopathy and cardiomyopathy.

▪▪ Metabolic Derangement

In both diseases the major pathological hallmark is a profound depletion of glycogen in muscle on PAS staining, associated with a marked predominance of oxidative (type 1) muscle fibres and mitochondrial proliferation. However, there is an unexplained difference between them in the cardiac pathology, with an absence of glycogen in cardiomyocytes in GSD 0, whilst PAS-positive material lacking the normal ultrastructural appearance of glycogen is present in glycogenin-1 deficiency.

▪▪ Genetics

Glycogenin1 Deficiency. Glycogenin is a autoglycosylated glycosyltransferase that catalyses the formation of a short glucose polymer of approximately ten glucose residues. There are two glycogenin isoforms: glycogenin-1, encoded by *GYG1*, is the muscle isoform, but is also expressed in other tissues to a minor degree; glycogenin-2, encoded by *GYG2*, is the liver isoform and is also expressed in cardiac muscle and other tissues, but not in skeletal muscle. Recessively inherited mutations of *GYG1*, leading to inactivation of autoglycosylation of glycogenin-1, have been detected in a young patient with exercise intolerance, muscle weakness and cardiac arrhythmia associated with hypertrophic cardiomyopathy [160].

Muscle Glycogen Synthase Deficiency (Muscle GSD Type 0). Muscle glycogen synthase is ubiquitously expressed and encoded by *GYS1* gene, whereas *GYS2,* encoding for hepatic glycogen synthase, is only expressed in the liver. A recessively inherited stop mutation in *GYS1* has been reported in three siblings with muscle fatiguability and hypertrophic cardiomyopathy. Epilepsy was observed in the oldest child, who died of cardiac arrest at the age of 10 years. Glucose tolerance was investigated in the two younger siblings and was found to be normal [161].

Treatment

No specific treatment was reported apart from selective β_1-receptor blockade for cardiac protection.

Glycogen Storage Disease Type III (Debranching Enzyme Deficiency)

Eighty-five per cent of patients with GSD III have a generalised defect in which enzyme activity is deficient in liver, muscle, heart, leukocytes and cultured fibroblasts, and they have a syndrome that includes both hepatic and myopathic symptoms, and often cardiomyopathy (GSD IIIa) (► Section 6.1.2). Some adult forms present with a predominant myopathy.

AMP-activated Protein Kinase (AMPK) Deficiency

Clinical Presentation

Symptoms starts typically in late adolescence with ventricular pre-excitation (Wolff-Parkinson-White syndrome) predisposing to supraventricular arrhythmias. There is a progressive mild to severe cardiac hypertrophy and an increased risk of sudden cardiac death. The disorder is usually described as familial hypertrophic cardiomyopathy with Wolff-Parkinson-White syndrome. Although glycogen storage typically affects only the heart, a skeletal muscle involvement with myalgias or muscle weakness may also occur in some patients, and a skeletal muscle glycogenosis has been reported in a patient with exercise intolerance, high CK levels and a forearm exercise test showing a blunted lactate increase [162].

Metabolic Derangement

AMPK is a cellular energy sensor that is activated by exercise in muscle and an increase in the AMP/ATP ratio, stimulating fatty acid oxidation, glycolysis and glucose oxidation. This enzyme forms a heterotrimeric complex comprising a catalytic subunit (α) and two regulatory subunits (β and γ). Three isoforms of the gamma subunits are known (γ1, γ2 and γ3) with different tissue expression, and each contains four repeats of a structural module known as a cystathionine β–synthase (CBS) domain [163]. Pathological examinations of the hearts from affected patients revealed vacuoles containing polysaccharide.

Genetics

The *PRKAG2* gene coding for the γ-subunit of AMPK is located on chromosome 7q36. Mutations in the γ2-subunit of AMPK are transmitted as an autosomal dominant trait with full penetrance [164]. Interestingly, molecular analysis performed in babies who had died of cardiac congenital glycogenosis, which had been attributed to a heart-specific variant of phosphorylase b-kinase deficiency, revealed a recurrent activating mutation in *PRKAG2*. Therefore, it appears that the low PHK activities that were determined in the hearts of these patients were either artefacts or secondary to a down-regulation induced by AMPK dysfunction or cardiac glycogen deposition [165].

Diagnosis

The diagnosis, if clinically suspected, is based on ECG, heart biopsy and molecular genetics. The differential diagnosis includes Pompe, Danon (LAMP2) and Fabry diseases.

Treatment

Treatment requires a pacemaker/defibrillator, and a heart transplant.

6.3 Brain Glycogenoses

In the brain branching enzyme, glycogen synthase, debranching enzyme and phosphorylase are present in both astrocytes and neurons. In neurons, however, there is no glycogen synthesis, since glycogen synthase is directed toward glycogen degradation in the proteasome system by the laforin-malin complex. In astrocytes glycogen is degraded to supply energy during brief episodes of hypoglycaemia and hypoxia. Glycogenolysis in astrocytes produces lactate, which is exported by a monocarboxylic transporter to neurons, where it is oxidised in the mitochondria [166]. Brain GSDs present with adult neurodegeneration/epilepsy syndromes associated with accumulation of polyglucosan bodies. Polyglucosan deposition in the nervous system is characteristic of Lafora disease and adult polyglucosan body disease, but can also occur in normal ageing.

6.3.1 Lafora Disease (Neuronal Laforin/Malin Defects)

Clinical Presentation

Lafora disease is an autosomal recessive form of myoclonic epilepsy that typically manifests during adolescence and is characterised by tonic-clonic, myoclonic and absence seizures, or focal seizures frequently associated with visual symptoms. As the disease progresses, affected individuals develop a rapidly progressive dementia with visual loss, apraxia and aphasia, leading to a vegetative state and death within a decade of disease onset.

- **Metabolic Derangement**

The hallmark of Lafora disease is the presence of large inclusions (Lafora bodies) composed of abnormal glycogen molecules in the axons and dendrites of neurons, especially in the cerebral cortex, substantia nigra, thalamus, globus pallidus and dentate nucleus. Polyglucosan bodies are also seen in muscle, liver, heart, skin and retina, showing that Lafora disease is a generalised glycogenosis. The mechanisms by which accumulation of abnormally branched glycogen triggers neuronal apoptosis are undetermined [166, 167].

- **Genetics**

Lafora disease has been found associated with mutations in two genes: Epilepsy, Progressive Myoclonus 2a (*EPM2A*) and Epilepsy, Progressive Myoclonus 2b (*EPM2B*). *EPM2A* is mutated in about 50% of individuals and encodes laforin; *EPM2B* is mutated in 30-40% and encodes malin. These two mutations share an identical phenotype, as these two proteins operate through a common physiological pathway.

- **Diagnosis**

A skin biopsy will reveal the pathognomonic Lafora bodies in most patients. Mutation analysis will confirm the diagnosis.

- **Treatment**

No treatment is available.

6.3.2 Adult Polyglucosan Body Disease (Astrocytes Branching Enzyme Deficiency)

- **Clinical Presentation**

Adult polyglucosan body disease is a rare disorder characterised by slowly progressive gait disturbance, urinary incontinence, upper and lower motor neuron dysfunction, distal sensory loss and cerebellar dysfunction. Cognitive impairment occurs in about 50% of cases in the later stages of the disease. Several clinical variants, mimicking spinocerebellar ataxia, extrapyramidal disorders, or motor neuron disease, have been described [168-170] MRI may show atrophy of the cervical spine and diffuse confluent hyperintense periventricular and subcortical white matter signal abnormalities involving the pons, medulla, basal ganglia and dentate nuclei. Electrodiagnostic studies typically show sensorimotor axonal peripheral neuropathy, sometimes with demyelinating features.

- **Metabolic Derangement**

The pathological hallmark is the presence of large polyglucosan bodies in the peripheral nerves, cerebral white matter, basal ganglia, cerebellum and spinal cord. Axillary skin biopsy shows polyglucosan bodies in the myoepithelial cells of apocrine glands and may be helpful in confirming the diagnosis. The accumulation of this amylopectin-like polyglucosan is usually ascribed to the deficiency of glycogen branching enzyme (GBE).

- **Genetics**

Adult polyglucosan body disease is usually sporadic, although there are few familial cases with probable autosomal recessive inheritance, primarily in the Ashkenazi Jewish population. In patients from Ashkenazi Jewish families, genetic analysis has identified a homozygous missense mutation (Tyr329Ser) of the *GBE1* gene, but other *GBE1* mutations have also been found in other ethnic groups. There are also several reported cases in non-Jewish patients with normal GBE activity.

- **Diagnosis**

The diagnosis is usually made by sural nerve biopsy or on autopsy.

- **Treatment**

No treatment is available.

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