12.3.1 Glycogen storage diseases 1985 Robin H. Lac

12.3.1 Glycogen storage diseases 1985 Robin H. Lachmann and Timothy M. Cox

CONTENTS 12.3.1 Glycogen storage diseases 1985 Robin H. Lachmann and Timothy M. Cox 12.3.2 Inborn errors of fructose metabolism 1993 Timothy M. Cox 12.3.3 Disorders of galactose, pentose, and
pyruvate metabolism 2003 Timothy M. Cox 12.3.1 Glycogen storage diseases Robin H. Lachmann and Timothy M. Cox ESSENTIALS Glycogen is a highly branched glucose polymer with a compact structure found predominantly in liver and muscle. Liver glycogen is important in the maintenance of euglycaemia during fasting; muscle glycogen is an immediate source of glucose for energy production during exercise. Genetic disorders affecting proteins that regulate glycogen synthesis and breakdown cause marked accumulation of glycogen in diverse tissues, and pathological glycogen often has an abnormal macromolecular structure. Depending on the enzyme system involved, diseases of glycogen metabolism principally affect liver and muscle. Clinical features are related to accumulation of glycogen in tissues and/or failure to release glucose. Glycogen storage is associated with organomegaly and tissue injury: this usually affects the liver and/or muscles, including the heart, but in severe cases other organs may be involved. Fasting hypoglycaemia occurs where hepatic breakdown of glycogen is impaired. Hyperlipidaemia, hyperlactataemia and hyperuricaemia leading to gout occur in those disorders with a major liver component, and poor metabolic control is associated with de- velopment of hepatic adenomas and frank liver cancers. Glycogen diseases that affect muscle usually present with rhabdomyolysis, ex- ercise intolerance, and muscle pain or weakness. Recently, several inherited multisystem disorders with neurodegeneration, such as polyglucosan body disease and Lafora’s disease, have been shown to result from abnormal glycogen structures in diverse cell types, including neurons. Formerly,

diseases of glycogen metabolism were diagnosed by showing excess storage of glycogen in the tissue of interest, accom- panied by reduced activity of particular glycogen-metabolizing en- zymes. Currently, where available, molecular analysis of genomic DNA is the preferred method for providing a definitive diagnosis. The mainstay of treatment of glycogen diseases affecting the liver is dietary, including pre-emptive management of hypoglycaemia that is readily provoked by fasting. In infants and children, continuous provision of carbohydrate by the nasogastric route may be required to maintain euglycaemia. Adults can usually be managed by a com- bination of frequent sugary snacks and the use of uncooked corn- starch as a slow-release source of glucose. Dietary interventions may also ameliorate some of the glycogen diseases that affect muscle, and weakness and pain after exertion can be improved by graduated exercise programmes in some patients. Introduction Maintenance of blood glucose is an essential homeostatic func- tion: profound hypoglycaemia causes encephalopathy and car- diac arrhythmias and is rapidly fatal if not treated promptly. Two processes are involved in maintaining normal blood glu- cose during periods of fasting: de novo synthesis of glucose (gluconeogenesis) and the release of glucose from carbohydrate stores (glycogenolysis). The body stores carbohydrate in the form of glycogen, a branched polymer of glucose. Glycogen stores in the liver are used to maintain normoglycaemia, but muscle also stores glycogen for its own use as an energy source during exer- cise. In this chapter, we will discuss the metabolism of glycogen and the inherited metabolic disorders which affect its synthesis and breakdown. Glycogen Glycogen allows for the compact storage of glucose in a form that has a minimal osmotic effect but which is readily accessible and meta- bolically active. The core of a glycogen molecule is a small protein, 12.3 Disorders of carbohydrate metabolism

SECTION 12 Metabolic disorders 1986 glycogenin. Branched chains of polymerized α-d-glucose units are covalently attached to this at their reducing termini (Fig. 12.3.1.1). The glucose molecules in glycogen chains are linked to each other by α-1,4 glycosidic bonds with α-1,6 bonds at the branch points (Fig. 12.3.1.1b). Glycogen molecules can contain up to 60 000 glucose molecules, have a molecular weight of several mil- lion daltons, and are visible to the electron microscope. The liver and muscle contain between 200 and 300 g of glycogen. The arbor- ization of the molecule, with large numbers of long outer chains that terminate in nonreducing glucose residues means that the en- zymes of glycogen degradation can rapidly release large quantities of glucose. Glycogen storage diseases (GSDs) can be caused by defects in glycogen synthesis or glycogen breakdown (Fig. 12.3.1.2). The stored glycogen may have a normal or an aberrant structure. Depending on the enzymatic defect, glycogen metabolism in the liver, muscle, or both tissues may be affected. Glycogen synthesis A glycogen molecule starts life with the autoglycosylation of a glycogenin molecule at a specific tyrosine residue. This primer molecule is then acted on by glycogen synthase which uses uridine diphosphoglucose molecules to form the α-1,4 linkages of the nas- cent sugar chain. The α-1,6 branch points required for the complex structure of glycogen are formed by ‘branching enzyme’ (amylo- (1,4 → 1,6) transglucosidase). It transfers a minimum of six α-1,4-linked glucose units from the distal ends of glycogen chains to a 1,6 pos- ition on the same or a neighbouring chain. Glycogen synthase is a highly regulated enzyme complex that exists in distinct isoforms in muscle and liver. Glycogen synthase is subject to phosphorylation control that inhibits its activity: the phos- phorylation of at least nine serine residues is brought about by pro- tein kinases and reversed by protein phosphatase I. This inhibition can be overcome by the allosteric activator, glucose 6-phosphate. (a) CH2OH CH2OH CH2OH CH2O CH2OH CH2OH O O O O O OH OH OH OH OH O O OH OH O O OH OH O O OH OH O O Glycogenin OH OH OH ...O O O OH OH ...O

CH2OH CH2OH (b) Fig. 12.3.1.1 (a) A cross-sectional view of glycogen, showing the core glycogenin protein surrounded by branches of glucose units, up to 60 000 of which can be contained within a glycogen granule. (b) Linear chains of glucose are formed by α-1,4 glycosidic bonds, with α-1,6 bonds at the branch points.

12.3.1 Glycogen storage diseases 1987 Regulation of glycogen synthase is important in maintaining blood glucose. Glucagon and adrenaline indirectly inhibit glycogen synthase by maintaining protein phosphatase I in its inactive con- figuration and promoting phosphorylation of glycogen synthase. Insulin stimulates glycogen synthase by activating protein phos- phatase I and promoting its dephosphorylation. Glycogen breakdown Two enzymes are involved in the breakdown of glycogen in the cyto- plasm: phosphorylase and debranching enzyme. Other enzymes are required to then produce free glucose. Phosphorylase sequentially removes glucose 1-phosphate units from the α-1,4-linked chains of glycogen. Debranching enzyme pos- sesses transferase and α-1,6-glucosidase activities. When phosphor- ylase has degraded glycogen chains to within four α-1,4-glucosyl units of an α-1,6 linkage, three glucose residues are transferred to the end of another chain by the glycosyltransferase activity. Debranching enzyme then hydrolyses the remaining α-1,6 bond to release free glucose using its amylo-1,6-glucosidase activity. Debranching en- zyme also cleaves the unique glucosyl–tyrosine linkage that anchors the terminal reducing glucose unit to glycogenin. The main product of glycogen breakdown in muscle and liver is glucose 1-phosphate. Glucose 1-phosphate is a key intermediate of glycolysis, gluconeogenesis, glycogenolysis, and the pentose phos- phate pathway, but cannot be transferred outside the cell. However, after conversion to glucose 6-phosphate by phosphoglucomutase, free glucose is formed by the action of glucose 6-phosphatase. Glucose 6-phosphatase exists as a multicomponent complex in the endoplasmic reticulum of hepatocytes and, to a lesser extent, in renal tubular cells—it is not found in muscle. The complex contains glu- cose 6-phosphatase, several proteins that facilitate the transport of glucose, glucose 6-phosphate, and phosphate, as well as other stabil- izing and regulatory units. Hepatic activity of glucose 6-phosphatase is the predominant metabolic source of blood glucose. In muscle, glucose 6-phosphate obtained from the breakdown of glycogen is used directly as an energy source via glycolysis. Glycolytic defects can also affect glycogen metabolism in muscle (e.g. phosphofructokinase-1 deficiency). Phosphorylase in liver and skeletal muscle is activated by phos- phorylation in response to hormonal or neural stimulation—a com- plex process that is mediated by the hepatic and muscle isoforms of phosphorylase kinases. Phosphorylase kinase is in turn regulated by protein kinase A (cAMP-dependent protein kinase), calcium and kinase activation of calmodulin, and protein phosphatases 1 and 2A. Another enzyme, acid α-1,4-glucosidase (otherwise known as acid maltase), also has an important role in the metabolism of glycogen, but in the lysosome not the cytoplasm. This lysosomal hydrolase is present in all cells except erythrocytes. It has no role in Glycogen synthase Branching enzyme UDP-glucose pyrophosphorylase Acid α-1,4 glucosidase (lysosomes) (cytosol) amylo 1,6-glucosidase Phosphorylase Debranching enzyme Phosphoglucomutase Phosphohexose isomerase Phosphofructokinase (glycolysis) Glucose 6-phosphatase Hexokinase/ glucokinase Glucose 1-phosphate Glucose 6-phosphate Fructose 6-phosphate Glucose 1-phosphate Glucose 6-phosphate Fructose 6-phosphate Fructose 1,6-diphosphate Fructose 1,6-diphosphate Phosphoglucomutase Phosphohexose isomerase Fructose diphosphatase (gluconeogenesis) Glycogenin primer Uridine diphosphoglucose GLYCOGEN GLYCOGEN SYNTHESIS BREAKDOWN GLUCOSE Fig. 12.3.1.2 The synthesis and degradation of glycogen.

SECTION 12 Metabolic disorders 1988 glycolysis, but hydrolyses the glycogen which is constantly entering the lysosome via autophagy. This pathway seems to be particularly important in muscle. Discovery and classification of glycogen storage diseases The study of patients with GSDs has played an essential part in elucidating the biochemical pathways described in the previous sections. In 1929, von Gierke described ‘hepatonephromegalia glykogenica’ with glycogen storage in the liver and kidney. Twenty years later, the husband and wife team of CF and GT Cori showed that this disease was due to deficiency of glucose- 6-phosphatase activity (GSD Ia). However, some patients with glycogen storage in the liver had normal glucose-6-phosphatase activity, and were later shown to have glucose-6-phosphate trans- porter defects (GSD Ib). Other patients were described who stored abnormal forms of glycogen (GSD IV), or who accumulated glycogen in muscle as well as (GSD III), or instead of (GSD V), liver, or where the primary site of glycogen storage was the lysosome rather than the cytoplasm (GSD II). More recently, the recognition of polyglucosan bodies has led to the description of new diseases which involve glycogen me- tabolism, as well as expanding the phenotype of classical GSD IV. A summary of GSDs, their enzymology, and principal features is given in Table 12.3.1.1. Although GSDs have traditionally been split into those that affect the liver and those that affect muscle, many are in reality multisystem disorders. The most important clinical features, however, remain fasting hypoglycaemia and Table 12.3.1.1 The glycogen storage disorders: genetic and enzymatic defects and principal clinical features GSD designation Gene Locus Common term/implicated protein Supplementary Clinical features 0 (L) 0 (M) GYS1 GYS2 12p12.1 19q13.33 Glycogen synthase Glycogen synthase Liver isozyme Muscle isozyme Hepatomegaly, hypoglycaemia Cardiomyopathy Ia Ib G6P6 SLC37A4 17q21.31 11q23.3 Von Gierke’s disease Glucose 6-phosphatase Glucose 6-phosphatase translocase Hypoglycaemia, hyperlacticaemia, hyperuricaemia, hypertriglyceridaemia Hepatomegaly, hepatic adenomas Renal failure GSD Ib also has neutropenia and colitis II GAA 17q25.3 Pompe’s disease Lysosomal (α-glucosidase) Cardiomyopathy (infantile form) Proximal myopathy, hypoventilation III AGL 1p21.2 Cori–Forbes disease (Limit dextrinosis) Debranching enzyme Hypoglycaemia, hepatomegaly, cardiomyopathy, myopathy IV GBE1 3p12.2 Andersen’s disease (Amylopectinosis) Branching enzyme Infantile liver failure. Cardiomyopathy, myopathy Adult polyglucosan body disease (neurogenic bladder, spastic paraparesis and peripheral neuropathy) V PYGM 11q12–q13.3 McCardle’s disease Glycogen phosphorylase (muscle) Exercise intolerance, rhabdomyolysis VI PYGL 14q22.1 Hers’ disease Glycogen phosphorylase (liver) Hypoglycaemia, hepatomegaly (very rare—Mennonite) VII PFKM 12q13.3 Tarui’s disease Phosphofructokinase (muscle) Exercise intolerance, rhabdomyolysis Haemolytic anaemia [VIII] N/A N/A [See Hers’ disease] N/A (obsolete) IX a1 IX a2 IX b IX c PHKA1 PHKA2 PHKB PHKG2 Xq12–q13.1 Xp22.13 16q12.1 16p12.2–11.2 Phosphorylase kinase α1 subunit Phosphorylase kinase α2 subunit Phosphorylase kinase β subunit Phosphorylase kinase γ subunit Muscle (regulatory) Liver (regulatory) Liver and muscle (regulatory) Liver (catalytic subunit) Exercise intolerance, rhabdomyolysis Hypoglycaemia, hepatomegaly Liver and muscle involvement Liver and testis X PGAM2 7p13 Phosphoglycerate mutase-2 Muscle isozyme XI LDHA 11p15.1 Lactate dehydrogenase A (M subunit) Muscle isozyme, desquamation XII ALDOA 16p11.2 Aldolase A (ubiquitous and muscle) Associated with haemolysis XIII ENO3 17p13.2 Enolase-β Extremely rare—muscle XIV PGM1 1p31.3 Phosphoglucomutase 1 Also disordered protein glycosylation (CDG1T) XV GLYG1 GLYG1 3q24 3q24 Glycogenin (absent glycogen) Glycogenin (abnormal glycogen - polyglucosan) Reduced or absent glycogen Polyglucosan body myopathy-2 (proximal) Cardiac and skeletal myopathy

12.3.1 Glycogen storage diseases 1989 myopathy and it can still be useful to distinguish between hepatic and muscle GSDs. The overall incidence of GSDs has been estimated at 1 in 20 000 with the commonest being GSD IX, followed by GSD I, II, and III. The clinical features of the commoner disorders are described in the following sections. Glycogen storage disease type I (von Gierke's disease) Biochemistry GSD I is due to glucose-6-phosphatase deficiency. GSD Ia is caused by defects in subunits of the endoplasmic reticular enzyme com- plex that enable production of glucose from glucose 6-phosphate. In GSD Ib, the endoplasmic reticular transmembrane protein glucose-6-phosphate translocase is deficient. In both forms, the production of glucose from both glycogenolytic and gluconeogenic pathways is blocked, resulting in profound fasting hypoglycaemia. Accompanying this, there is a build-up of glucose 6-phosphate. This is then metabolized by the pentose phosphate shunt, or transferred back into glycogen which is stored in the liver and, to a lesser extent, the kidney. The products of glucose-6-phosphate metabolism have an important role to play in the other metabolic consequences of GSD I: hyperlactataemia, hyperuricaemia, and hypertriglyceridaemia. The hypoglycaemia is somewhat mitigated by the fact that small quantities of free glucose can be liberated by the α-1,6-glucosidase activity of the secondary action of debranching enzyme. Residual production of glucose probably also occurs by lysosomal hydrolysis of glycogen. Lactic acidaemia results from stimulation of glycolysis at the level of phosphofructokinase by high concentrations of glucose 6- phosphate (and hence fructose 6-phosphate); lactate cannot be re- cycled in the liver to form new glucose and lactic acidosis results. Failure to dephosphorylate glucose 6-phosphate stimulates substrate cycling and increases the activity of the pentose phos- phate pathway, with enhanced production of the reduced form of nicotinamide-adenine dinucleotide phosphate (NADPH), ribose 5-phosphate, and purines. Degradation of purine nucleotides by AMP-deaminase and the coordinated action of xanthine oxidase on inosine phosphate and hypoxanthine leads to overproduction of uric acid in the liver. The deaminase is activated when the concentra- tion of free phosphate falls as a result of sequestration in sugar phos- phate esters. Lactate competes with urate for excretory pathways in the kidney and this also contributes to the hyperuricaemia. Enhanced flux through glycolysis and underutilization of gluconeogenic precursors leads to increased production of the re- duced form of nicotinamide-adenine dinucleotide (NADH) and NADPH, glycerol, and acetyl coenzyme A, and these in turn in- duce hypertriglyceridaemia. Malonyl coenzyme A, derived from acetyl coenzyme A, inhibits the carnitine acyltransferase system and blocks the oxidation of fatty acids; thus marked ketosis does not usu- ally develop. Clinical presentation Patients typically present in infancy with symptomatic hypogly- caemia and failure to thrive, accompanied by a swollen abdomen due to hepatomegaly. Hypoglycaemic encephalopathy is often ac- companied by seizures and can be fatal: recurrent episodes lead to permanent neurodisability. Children have impaired growth and increased subcutaneous fat deposition leading to a 'doll's face' appearance. With aggressive dietary management (see following subsection on 'Management'), the immediate life-threatening complications can be avoided. With improved survival, the chronic, multisystem complications of GSD I have emerged (Fig. 12.3.1.3). There is persistent hepatomegaly, with glycogen storage accom- panied by gross infiltration with fat. Cirrhosis and portal hyper- tension are, however, rare. Short stature, often combined with obesity, is common. The kidneys are enlarged by glycogen depos- ition. Progressive focal glomerulosclerosis and proximal tubular injury with a secondary Fanconi's syndrome may also occur. Short periods of fasting, or other metabolic stressors such as infection, provoke hypoglycaemia and lactic acidosis. In the longer term, poor metabolic control causes growth arrest; hyperuricaemia and gout; marked hypertriglyceridaemia (which can lead to acute pancreatitis) and hypercholesterolaemia with raised very low-density lipoprotein and normal

low-density lipoprotein cholesterol concentrations in the plasma; and prolonged bleeding time related to an acquired von Willebrand-like defect affecting the platelet. Hepatic adenomas are seen in adults. These can regress with improved metabolic control, but there is a risk of transformation to hepatocellular carcinoma, and all patients need to be carefully monitored with regular liver MRI. Patients with defects of the glucose-6-phosphate translocase system (type 1B) also have a neutropenia with impaired neutrophil migration and chemotaxis and are prone to recurrent bacterial in- fections. These patients are also at risk of developing granulomatous colitis with clinical features similar to ulcerative colitis. Partial deficiencies of the glucose-6-phosphatase system lead to variable clinical expression: in Japan, a milder form of GSD Ia oc- curs due to the common G727T mutation that is prevalent in that country. GSD I should be considered in patients presenting with glucagon-unresponsive hypoglycaemia with or without liver en- largement in adult life. Management Historically, GSD I (and the other GSDs presenting with hypogly- caemia in infancy) were associated with a very poor outcome. This has been transformed by the introduction of aggressive dietary man- agement aimed at maintaining a constant exogenous supply of glu- cose to meet basal requirements. Regular oral carbohydrate during the day and continuous overnight pump feeding with glucose, de- livered either by nasogastric or gastrostomy tube, clearly improves clinical and biochemical parameters. Subsequently, fasting tolerance has been improved with the use of uncooked cornstarch (obtained from the supermarket and suspended in water): this acts as a ‘slow- release’ form of glucose and, particularly in older patients, allows for more time between meals during the day and for some patients to discontinue overnight feeds. Modified cornstarches have now been produced with the aim of increasing fasting tolerance further, al- though it is not yet clear that they offer a significant benefit over shop-bought cornflour. Maintaining normoglycaemia requires a diet with about 65% of dietary energy as carbohydrate. Continuous glucose monitoring can be useful in adjusting doses of uncooked cornstarch and concentrations of overnight feeds. Regular dietetic

 review is important to minimize excessive weight gain and insulin resistance, and ensure the diet is nutritionally complete. Intercurrent illness can rapidly provoke hypoglycaemia and pa- tients with GSD I are given an ‘emergency regimen’ to use in times of metabolic stress. This consists of frequent oral glucose polymer. If for any reason patients can’t tolerate oral intake, 10% dextrose should be given intravenously at a rate of 2 ml/kg per hour. Hyperlipidaemia and hyperuricaemia need to be treated. Hyperfiltration or albuminuria indicates renal involvement and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should be introduced. Hypocitraturia may contribute to the increased incidence of nephrolithiasis and citrate supplementation may be useful. Iron supplementation is often needed. Osteopenia is common and calcium and vitamin D supplementation should be considered. Surveillance for hepatic adenomas is important. MRI with the use of intravenous contrast is the preferred method. About 70 to 80% of adult patients have been reported to have at least one lesion, and these progress in size or number in 50% of cases. The occurrence of adenomas seems to be related to metabolic control and in some cases improving biochemical parameters can lead to adenoma re- gression. Spontaneous regression is also seen (Fig. 12.3.1.4). The occurrence of hepatic adenomas is concerning because they can progress to hepatocellular carcinoma: predicting this pro- gression is difficult. Blood markers such as α-fetoprotein have not proved useful. A rapid increase in size or number of adenomas, changes in vascularization, and bleeding should lead to a multidis- ciplinary team review to discuss surgical intervention, including liver transplantation. Human granulocyte colony-stimulating factor is often required in patients with GSD Ib to increase the neutrophil count

and control mouth ulcers, recurrent infections, and inflammatory bowel disease. Long-term use of granulocyte colony-stimulating factor is associ- ated with a number of complications and should be supervised by a haematologist. Due to the dangers of fasting and the bleeding tendency associ- ated with GSD I, surgery must be managed carefully. Patients should be admitted the day before so that fasting can be covered with intra- venous glucose. Platelets should be available in case of postoperative haemorrhage. Epistaxis Acute pancreatitis Insulin resistance Splenomegaly (GSD Ib) Hypersplenism Neurology dependent on duration and severity of hypoglycaemia and acidosis Acute—coma Low IQ Seizures White matter parencyhmal loss Gross hepatomegaly in infancy —improves with metabolic control Hepatic steatosis Hepatic adenoma Hepatocellular carcinoma (rare) Pulmonary hypertension (rare) Diarrhoea Inflammatory bowel disease (GSD Ib) Chronic anaemia Platelet dysfunction Neutropenia Neutrophil dysfunction Mouth ulcers (GSD Ib) (GSD Ib) Gout Osteopenia Other Growth failure / delay Myopathy Polycystic ovaries Delayed puberty Nephromegaly Hyperfiltration in childhood Hypofiltration in adult life Tubulointerstitial disease Proteinuria Renal failure Renal calculi Fig. 12.3.1.3 Complications of GSD I.

 Pregnancy in women with GSD I is now relatively routine. With careful planning, close attention to glycaemic control, and increased carbohydrate requirements, especially in the second half of preg- nancy, and a well-managed labour, outcomes are good. With optimal medical management, patients with GSD I now lead relatively normal lives, but for some patients, good metabolic con- trol is never obtained. For these patients, liver transplantation offers a long-term ‘cure’ for many features of the disease. Where there is also end-stage renal failure, combined liver and renal transplant- ation can be performed. Glycogen storage disease type II
(Pompe’s disease) GSD II causes hypertrophic cardiomyopathy in infants and a pro- gressive skeletal myopathy in older patients. It is primarily classified as a lysosomal storage disorder and is discussed in Chapter 12.8. Glycogen storage disease type III
(Forbes–Cori disease) Biochemistry GSD III is due to deficiency of debrancher enzyme. This results in the storage of structurally abnormal glycogen, with short outer chains, called limit dextrin, in both liver and muscle. Although glycogenolysis is blocked, gluconeogenesis is unaffected and fasting hypoglycaemia is milder than that seen in GSD I and accompanied by ketosis rather than lactic acidosis. The sec- ondary metabolic consequences are mostly confined to a mild hyperlipidaemia. Clinical presentation GSD III affects both liver and muscle. Hypoglycaemia and the hep- atic consequences of storage dominate the clinical picture in chil- dren, with fasting hypoglycaemia and poor growth. The condition is less severe than GSD I and even in historic cohorts, most patients survived to adulthood. In adults, fasting tolerance improves and on the whole hypoglycaemia can be prevented with dietary management. Hepatic adenomas have only rarely been reported, although pa- tients can occasionally develop cirrhosis, and the kidneys are not affected. Patients do, however, develop muscle symptoms and complain of exercise intolerance, although rhabdomyolysis is not a recognized feature. Some patients develop a progressive, disabling myopathy with pronounced distal weakness and myopathic facies. Cardiac muscle is also involved and hypertrophic cardiomyopathy can result in arrhythmias or heart failure (Fig. 12.3.1.5). Management The management of hypoglycaemia in childhood is as in GSD I. In adult patients, it is important not to overtreat: with home glucose monitoring it is often possible to reduce the dietary content of com- plex carbohydrate. It has been suggested that the skeletal myopathy and cardiomy- opathy seen in GSD III is not solely due to glycogen storage and that energy deficit may also have a role to play. In theory, this might be addressed by providing

alternative sources of energy. Ketone bodies can be provided directly as d,l-3-OH butyrate or by use of a ketogenic diet. A high-protein diet should enhance gluconeogenesis. To date, there have been isolated case reports of improvements in cardiomyopathy and skeletal myopathy but no systematic studies of these approaches have been done. Although left ventricular hypertrophy occurs in many patients, its clinical significance is not clear. To date, there are very few case reports of heart failure or significant arrhythmia in adults. This may change as patients age and periodic echocardiography and ECG monitoring is probably prudent. The incidence of clinically significant hepatic fibrosis and cir- rhosis may also increase with age and liver imaging can be used to monitor this as well as the occurrence of hepatic adenomas. Fig. 12.3.1.4 Hepatic adenoma (white arrow) in left lobe of liver of a young woman with GSD Ia. Fig. 12.3.1.5 A 42-year-old woman with GSD III and myopathy. She has myopathic facies and a scoliosis.

SECTION 12 Metabolic disorders 1992 Polyglucosan body disease (glycogen storage diseases types IV, VII, XV, and 0) Biochemistry Polyglucosan body disease (PBD) is characterized by the storage of aggregates of abnormal polysaccharides which are less branched than normal glycogen. Polyglucosan has a fibrillar structure and, un- like glycogen is at least partially resistant to digestion with amylase. Polyglucosan is seen in the heart and parts of the brain as a product of normal ageing, but in PBD, aggregates occur at an earlier age and in a wide variety of different tissues. PBD is not a single genetic entity: more than seven different mo- lecular causes of polyglucosan body formation have been recognized to date. Some of these are known GSDs (glycogenin deficiency (GSD XV), branching enzyme deficiency (GSD IV), glycogen synthase de- ficiency (GSD 0), and phosphofructokinase deficiency (GSD VII)) but other involved proteins do not seem to have a direct role in glycogen metabolism (i.e. RBCK1, a ubiquitin ligase which regulates the NF-κB pathway and AMP-activated protein kinase (AMPK)). The biogenesis of polyglucosan bodies is not fully understood, but experimental work suggests that, at least in some cases, an imbal- ance between the activities of glycogen synthase and debranching enzyme may be important. Clinical presentation Branching enzyme deficiency (GSD IV) is the best characterized of the PBDs. The classical form of GSD IV presents with progres- sive liver failure in the first years of life. If these children are given liver transplants they go on to develop myopathy. Some patients present with isolated skeletal or cardiomyopathy. This can be of early onset, in which case it can progress quickly to respiratory failure and death, but other patients present as adults with slowly progressive disease. The term adult PBD refers to a form of branching-enzyme defi- ciency which presents between the ages of 40 and 60 with a com- bination of neurogenic bladder, spastic paraparesis, and peripheral neuropathy. Imaging shows leukodystrophy. Polyglucosan bodies are found throughout the central and peripheral nervous system. The condition is progressive and patients usually die within 20 years of diagnosis. The other causes of PBD are rarer and generally present as hyper- trophic cardiomyopathy with or without skeletal myopathy in chil- dren or adolescents. Glycogen storage disease type V
(McArdle disease) Biochemistry McArdle described a patient who suffered exercise-induced my- algia in whom lactate fell during ischaemic exercise rather than rising, suggesting a defect in glycogenolysis. Enzymology sub- sequently showed a deficiency of muscle phosphorylase activity. Patients are asymptomatic during low intensity, aerobic exer- cise, when muscle depends on fatty acid oxidation for energy, but during anaerobic exercise patients rely on glycolysis and develop symptoms. Clinical presentation Typically patients develop painful muscle cramps soon after the start of exercise. Continued high-intensity exercise leads to rhabdo- myolysis and acute kidney injury (which is normally fully revers- ible). However, if patients continue to exercise at lower intensities, symptoms resolve and they are able to continue. This ‘second wind’ phenomenon is

useful diagnostically and is due to the switch from glycolysis to alternative energy sources in aerobic exercise. Management No drug or dietary treatment has been shown to be effective in GSD V. There is some evidence that aerobic physical training is safe, and may improve exercise tolerance. This is probably due to an increased capacity for fatty acid oxidation. Treatment of rhabdomyolysis-induced acute kidney injury is the same as for other more common causes of rhabdomyolysis (see Chapter 21.5). Glycogen storage disease type IX Biochemistry GSD IX is due to deficiency of phosphorylase kinase. Phosphorylase kinase consists of four subunits, two of which have tissue-specific isoforms. The commonest form of GSD IX, and the commonest GSD, is X-linked and due to mutations in PHKA2. Clinical presentation GSD IXa is a hepatic GSD presenting early in life with hepatomegaly and fasting hypoglycaemia and ketosis. It is milder than GSD I and symptoms generally resolve in adulthood. Liver fibrosis has, how- ever, been reported as a long-term complication. The other forms of GSD IX are much rarer and can lead to muscle as well as liver disease. Management Management of hypoglycaemia is as for GSD I, but adult patients have normal fasting tolerance and do not need uncooked cornstarch. Diagnosis of glycogen storage disease Most patients with hepatic GSDs present with hypoglycaemia in early life. Historically, definitive diagnosis relied on demonstrating glycogen storage and assaying enzyme activity in the affected tissue: many adults with GSD I still bear the scars of liver biopsies performed in infancy. This was invasive and technically difficult, and has to a large extent been superseded by new techniques. In infants with suggestive symptoms, biochemical profiling, with measurements of glucose, lactate, and ketones, can suggest the correct diagnosis. In some cases (e.g. GSD III), this can be con- firmed by enzymology using leucocytes, but in GSD I, molecular genetic analysis is required as the enzymes are only expressed in liver (Table 12.3.1.2). Some patients present with hepatomegaly without biochemical features suggesting GSD. In these cases, histological examination re- veals glycogen storage. If frozen tissue has been kept, enzymology

---

Revision #1
Created 2026-01-22 16:37:35 UTC by Omar Ayman
Updated 2026-01-22 16:37:35 UTC by Omar Ayman