Glycogen storage disease

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Abstract

Glycogen storage disorders are a group of inborn errors of metabolism characterized by accumulation of glycogen in various tissues. This accumulation is the histological hallmark of these disorders although the phenotype shows variable overlap. Hepatomegaly, hypoglycaemia, elevated lactate and urate with or without neutrophil dysfunction is the classical presentation for the commonest disorders namely GSD types I a, 1b and III. Elevated creatine kinase, weakness, hypertrophic cardiomyopathy with or without rhabdomyolysis represents the commonest muscle subtypes with the best known ones being GSD II, III and V. Control of glucose deficiency by added calories, tube feeding or modified cornstarch is frequently the mainstay of treatment. Supportive therapies are needed to establish near normality. Potential curative therapies are enzyme replacement therapies by mode of liver transplantation, bone marrow transplantation or use of recombinant enzyme.

Keywords bone marrow transplantation; cornstarch; enzyme replacement therapy; GSD or glycogen storage disease; hypertrophic cardiomyopathy; inborn error of glycogen metabolism; liver transplantation; rhabdomyolysis

Introduction

Glycogen storage diseases are a group of disorders characterized by the accumulation of glycogen in various tissues. Glycogen is a branched chain polymer of glucose and is normally present in muscle and liver. When there is excessive storage of glycogen in these tissues due to enzyme deficiencies it manifests with clinical symptoms and signs associated with these two main storage areas. It is helpful to divide glycogen storage disorders into those affecting primarily the liver and those affecting muscle. This division is clinically useful as long as it is remembered that there is some overlap and some other tissues and organs are also affected.

The disorders were numbered as they were discovered and initially it was assumed that they would be similar in their pathology and that the most severe variants would be discovered first followed by milder variants. Over time it has become clear that they don't share the same pathology and there are some conceptual differences and for that reason many of these disorders were renamed on a few occasions causing even more confusion. With this caveat in mind it is still useful for the generalist to remember that the lower numbered disorders usually do represent the more severe end of the spectrum and generally fasting tolerance time increases as the numbers increase. For example Glycogen storage Disorder type 1 is usually associated with severe fasting intolerance with fasting times as short as 45 min compared to case affected by Glycogen storage disease type IX who may have completely normal fasting times and frequently being diagnosed by the finding of incidental hepatomegaly. Due to new advances in molecular diagnosis more and more services are now offering sequencing for all Glycogen storage disorders genes in a single diagnostic run.

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Glycogen storage disease type I

Type I glycogen storage disease (GSD-I) is the commonest most severe childhood form and typically presents in early infancy. First report of patients was by von Gierke in 1929, when he described enlarged liver and kidneys containing excessive amount of glycogen seen at autopsy. GSD-I is inherited as an autosomal recessive condition and although there are no accurate estimates of the incidence for GSD-I, for the GSDs as a group it is approximately 1 in 20 000 infants.

Pathophysiology

Deficiency of hepatic glucose-6-phosphatase enzyme was found in the initial patients with GSD-I (MIM 232200). Glucose-6-phosphatase catalyses the final step of both gluconeogenesis and glycogen breakdown. It operates inside the lumen of the endoplasmic reticulum and must cross the endoplasmic membrane to be effective. In 1959 a subgroup of patients without the classical glucose-6-phosphatase defect was described and later the defect in the transport of glucose-6-phosphate was demonstrated. Thus the name glycogen-storage disease type Ia (GSD-Ia) designates the true enzyme defect, and glycogen storage disease type Ib (GSD-Ib) designates the transport defect. GSD-Ic and GSD-Id disease subtypes had also been proposed caused by an abnormal inorganic phosphate transport, however most of the described patients were later found to have mutations in the gene encoding the glucose 6-phosphate translocase and therefore also belong to the GSD-Ib group (MIM 232220).

Clinical and biochemical features

In GSD-I, the liver is unable to generate free glucose in response to neuroendocrine stimuli caused by hypoglycemia. The defect also results in an accumulation of glucose-6-phosphate that enters glycolysis, which results in increased lactate production.

Children with of GSD-I may be identified in the neonatal period with hypoglycemia and lactic acidosis but it is more common for the patients to first present at 3–4 months of age with hepatomegaly and/or hypoglycaemic seizures. GSD-I patients typically have doll-like facies (due to fat deposits in the cheeks), short stature during childhood and protuberant abdomen due to liver enlargement. Whilst the kidneys are also commonly enlarged there is no increase in the size of other organs.

The characteristic features of GSD-I is a fasting lactic acidosis and a short glycaemic fasting tolerance, which may be less than 2 h, however the latter improves with age. The presence of hyperuricaemia is caused by both decreased renal clearance and

increased production of urate. Hyperlipidaemia occurs as a result of increased synthesis of triglycerides, VLDL, and LDL and decreased peripheral lipolysis. Patients are at an increased risk of pancreatitis due to hypertriglyceridaemia.

Patients with GSD-Ib also have neutropenia and neutrophil dysfunction leading to recurrent bacterial infections. Although diarrhoea is frequently seen in both GSD I types, the majority of GSD-Ib patients suffer from a type of inflammatory bowel disease similar to Crohn's disease. Both GSD-Ia and GSD-Ib patients have abnormal platelet aggregation and have tendency for excessive bleeding. Although patients have very significant hepatomegaly, and there is a universal distension of hepatocytes by glycogen and fat on histology, there is usually no marked elevation in liver transaminases.

The long-term complications, which are observed mostly in adult patients following poor metabolic control, include gout, multiple liver adenomas, hepatocellular carcinoma, insulin resistance and progressive renal disease. With early diagnosis, active surveillance and appropriate modern clinical management it is thought that most of the complications can be prevented.

The diagnosis of type I glycogen storage disease can be suspected on the basis of clinical presentation and abnormal lactate and lipid values. Previously, a definitive diagnosis required a liver biopsy to demonstrate a deficiency. Gene mutational analysis now allows noninvasive way of diagnosing most of type Ia and Ib patients.

Treatment and prognosis

The mainstay of treatment in GSD-I is maintenance of normal blood glucose concentrations. Normoglycaemia can be achieved using a combination of continuous nasogastric tube feeding, uncooked cornstarch and regular oral feeds. Most of the metabolic abnormalities improve with better glycaemic control. Nasogastric tube feeds should be started at the time of diagnosis and may consist of modified formula feeds or glucose polymer to provide 8–10 mg/kg per minute of glucose in an infant and 5–7 mg/kg per minute in an older child. Uncooked cornstarch acts as a slow-release form of glucose and can be administered in slowly increasing doses in infants. Dietary intake of fructose and galactose is usually restricted because these sugars cannot be converted to free glucose. Allopurinol is used to help reduce the levels of uric acid and potassium citrate to try and limit the effects of high lactate that contributes to nepfrocalcinosis. Hyperlipidaemia can be managed with lipid-lowering drugs such as HMG-CoA reductase inhibitors and fibrates. Microalbuminuria is an early indicator of renal dysfunction and can be treated with low doses of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB). In type Ib glycogen storage disease granulocyte colony-stimulating factor is used to correct the neutropenia and neutrophil function. In the past, many young patients with type I glycogen storage disease died, and the prognosis was guarded for those who survived. With the prevention of hypoglycemia, growth and metabolic parameters improve. In patients with extremely low fasting tolerance, severe immune compromise and compromised quality of life the option of liver or bone marrow transplantation can be considered. Overall much better prognosis can be given to the patients with GSD I, although longer follow up is required to gain a more accurate data.

Glycogen storage disease type II

Glycogen storage disease II or also called Pompe or acid maltase deficiency is deficiency of acid alpha glycosidase (MIM 232300) and maps to chromosome 17. It was described by Pompe in 1932 and the infantile form is distinctly different from the later onset form of the disease. The prevalence of the infantile form is around 1/138 000 and the later onset form around 1/57 000.

Pathophysiology

In this disease there is intra-lysosomal accumulation of normal glycogen due to abnormality of the hydrolase exporting glycogen from the lysosomes. As the lysosomes only contribute about 3% to energy metabolism hypoglycaemia is not a feature of this disease but it is the destruction and accumulation inside the lysosomes causing cell injury and loss of normal function. This primarily affects muscle metabolism and in the infantile form cardiac muscle is involved distinguishing it from the later onset form where cardiac muscle is unaffected.

Clinical and biochemical features

This is a classical proximal myopathy with or without cardiac involvement with presentation from birth to late adulthood. The great variability depends to some extend on the functional ability of the enzyme to degrade and storage the excessive glycogen. The infantile form presents with cardiomegaly, recurrent respiratory infections, weakness and delayed motor milestones. The finding of a large heart and elevated creatine kinase should prompt a clinician to look for this rare disorder as early treatment is essential. Enlarged tongue and wood grain consistency of the muscles can also be found in most cases but detection of these subtle signs require experience, which given the rarity of the condition is not easy for the generalist to acquire. In older children the inability to jump, climb stairs or diaphragmatic weakness will also present as motor delay, frequent falls, clumsiness, waddling gait or obstructive sleep apnoea. In the adolescents and adults primarily weakness and sleep disturbance due to nocturnal hypercapnia will be the main symptoms and should be distinguished from the other more common proximal myopathies.

On muscle biopsy a vacuolated myopathy picture can be noticed but with specific staining it becomes clear that the excessive glycogen is intra-lysosomal. Measuring the defective enzyme in white cells or on a dried bloodspot with supported mutational analysis confirms the diagnosis.

Treatment and prognosis

Early treatment with enzyme replacement therapy has the best outcome but this very expensive and not curative. Both mortality and morbidity is altered by early enzyme replacement therapy and improvements in quality of life and survival has been widely reported. Enzyme replacement therapy (alglucosidase alpha) has been available since 2006 and is best administered in expert centres for rare disorders. Without treatment the infantile form is associated with early death and the later onset form with significant morbidity and mortality. Both forms are at increased risk of death during anaesthesia and this is particularly true for the infantile form where arrhythmias are frequently uncovered.

Supportive therapy for infections and assisted ventilation and wheelchair use is common in older patients. Other new