Glycogen storage disease types

ASSIGN BUSTER

Abstract

Glycogen storage diseases (GSD) are inherited metabolic disorders of glycogen metabolism. Different hormones, including insulin, glucagon, and cortisol regulate the relationship of glycolysis, gluconeogenesis and glycogen synthesis. The overall GSD incidence is estimated 1 case per 20 000-43 000 live births. There are over 12 types and they are classified based on the enzyme deficiency and the affected tissue. Disorders of glycogen degradation may affect primarily the liver, the muscle, or both. Type Ia involves the liver, kidney and intestine (and Ib also leukocytes), and the clinical manifestations are hepatomegaly, failure to thrive, hypoglycemia, hyperlactatemia, hyperuricemia and hyperlipidemia. Type IIIa involves both the liver and muscle, and IIIb solely the liver. The liver symptoms generally improve with age. Type II is a prototype of inborn lysosomal storage diseases and involves many organs but primarily the muscle. In this review glycogen storage disease types in which recent advances in diagnosis, pathogenesis or treatment have been highlighted

Introduction

Glycogen storage diseases (GSD) are a part of inherited disorders in the metabolism of glycogen. Postprandial periods show individuals to have a rise in blood glucose and suppression of endogenous glucose production. This exogenous glucose production is metabolized to pyruvate or stored as glycogen in the liver and skeletal muscle. Under aerobic conditions pyruvate is either converted to acetyl coenzyme A (acetyl-CoA), which then is metabolized under the mechanism of the citric acid cycle, producing water, carbon dioxide and ATP, or is used in the synthesis of fatty acids. Anaerobic

metabolism of pyruvate results in its conversion into lactate, which is highly significant in periods of hypoglycaemia in acting as an alternative fuel. This process is regulated by various hormones including, insulin, glucagon, and cortisol. Regulation of the relationship between glycolysis, gluconeogenesis and glycogen synthesis is also hormonally controlled. The overall synthesis of glycogen is summarised in Figure. 1. There are currently over 12 types of GSD and they are classified on the basis of the enzyme deficiency and the type of tissue involved. Although the disorder primarily affects the liver and skeletal muscles, interactions between kidney and the CNS resulting in characteristic symptoms of this disease have been recently observed. (Roach PJ 2002)

Glycogen Storage Disease type I

Glycogen storage disease type 1 is believed to be caused by a deficiency in the glucose-6- phospatase-α (G6Pase-α) complex. This is made up of a glucose-6-phosphate transporter (G6PT) which is able to translocate glucose-6-phosphate (G6P) into the lumen of the endoplasmic reticulum from the cytoplasm, and a G6Pase-α catalytic subunit (G6PC) which is responsible for the hydrolysis of endoluminal G6P to glucose and phosphate. It is the combined action of these two subunits which maintain blood glucose homeostasis between meals.

A deficiency of G6Pase-α results in type 1a and a deficiency in G6PT results in the presentation of GSD type 1b. Expression of G6Pase-α predominantly occurs in the liver, kidney and intestine Applegarth DA (2000), while expression of G6PT is unbound and ubiquitous. Detrimental mutations in either protein results in functional efficacy of the other protein to reduce

leading to the same metabolic phenotype, characterised by fasting hypoglycaemia, hepatomegaly, nephromegaly, hyperlipidaemia, hyperuricaemia, lacticacidaemia, and growth retardation. The hypoglycaemia seen in GSD type 1 patients is predominantly due to the lack of hepatic and/or renal gluconeogenesis and glycogenolysis. However in vivo kinetic studies have shown that extrahepatic and extrarenal tissue have an involvement in glucose homeostasis. Huidekoper HH et al. (2010) Current diagnostic methods include rapid qualitative enzyme chromatographic test for glucose-6-phosphate dehydrogenase deficiency, this rapid test for G6PD deficiency is a sensitive method for screening of G6PD deficiency requiring minimal training and equipment and enables rapid identification of G6PD-deficient persons. Tests are highly sensitive and give definitive diagnostic results. Tinley KE et al. (2010).

Currently therapy for GSD I patients consists primarily of nutritional support including frequent carbohydrate-rich meals. Janice YC and Brian CM (2007) However recent studies in murine GSD 1a models using adeno -associated virus expressing human G6Pase-α directed by G6Pase-α promoter/enhancer has shown promise as a suitable treatment of GSD1a patients, whereby complete normalization of hepatic glucose homeostasis can be achieved. (GHOSH A et al 2006) Hypoketotic hypoglycaemia and hypertriglyceridaemia are biochemical hallmarks of glycogen storage disease (GSD) 1. Increased malonyl coenzyme A production which compromises oxidation of long-chain fatty acids via carnitine palmitoyltransferase (CPT) 1 inhibition plays a crucial role in the pathogenesis of these complications, as medium chain triglycerides can be metabolised independent of CPT 1 a study carried out

using a medium chain triglyceride diet showed a reduction in the amount of carbohydrate and caloric intake required to maintain euglycaemia and led to improvement in growth and metabolic control in two prepubertal patients. DAS AM et al (2010)

Glycogen storage disease type II

GSD II, or Pompe disease, is primarily classified by the age of onset, rate of progression severity, and the organ involvement. Onset is generally apparent in the first month of life with symptoms of hypotonia, systemic muscle weakness, cardiomegaly and hypertrophic cardiomyopathy, feeding difficulties, respiratory distress, hearing loss, and general failure to thrive. Mellies, U et al (2009). The clinical presentation of GSD type 2 is heterogeneous, largely due to the varied residual enzyme activity, associated with mutations in chromosome 17q25. 2-q25. 3. It occurs due to the absence of the human lysosomal enzyme GAA and the metabolic processes in both normal (a) and Pompe's (b) is shown in a diagram below.

Profound muscle weakness in Pompe patients has for many years thought to be due to rupture of glycogen lysosomes however a current study has given evidence to an alternative pathogenesis. Failure of productive autophagy in muscle tissue is the predominant factor of weakness, in both patients with Pompe disease and GAA-knockout mouse models. The progressive accumulation of autophagic vesicles occurs in Type II-rich muscle fibre, this build up of autophagosomes disrupt contractile apparatus in muscle fibres, and furthermore this accumulation causes interference in enzyme replacement therapy, as it acts as a sink for recombinant enzyme, preventing efficient delivery to target lysosomes. Shea L and Raben N(2009).

Treatment predominantly involves enzyme replacement therapy, this has shown to significantly prolong survival, decrease cardiomegaly, and improve cardiac and skeletal muscle function. Kishnani PS, et al (2007). Recently a study carried out on the restoration of muscle functionality, was able to achieve complete genetic elimination of glycogen synthesis in GSD II mice, GAA and glycogen synthase 1 knockout mice were inter-crossed to generate a new double-KO model. Muscle atrophy observed in 11-month-old GSDII mice was less pronounced in GAA/GYS1-KO mice, resulting in improved exercise capacity. These double-KO mice exhibited profound reduction in the amount of glycogen present in the heart and skeletal muscles, complete correction of cardiomegaly, and a significant decrease in lysosomal swelling which caused autophagic build up. In addition correction of glucose homeostasis and insulin tolerance was also observed in the double-KO mice. Douillard-Guilloux G, et al. (2010)

Without treatment prognosis is death within the first year of life, and generally is a result of left ventricular outflow obstruction and ventilatory failure. Therefore early detection of this disease can prove to be vital in the treatment of this disease and highlights the reason for screening protocols, a study conducted in 2009 found 6 children out of 206088 which were then treated with alglucosidase alpha at 14 months, all infants had uniformly positive improvements to treatment Chien YH et al. (2009)

Glycogen storage disease type III

GSD III results from deficient glycogen debrancher enzyme activity, which has two independent catalytic activities; oligo-1, 4-1, 4- glucantransferase and amylo-1, 6-glucosidase. Both catalytic activities are required for normal

full debranching enzyme activity. Deficiency in the enzyme results in an excessive accumulation of abnormal glycogen, which is harmful for hepatocytes. Hepatomegaly, hypoglycemia, short stature, dyslipidemia, and in a few cases, slight mental retardation are seen in both subtypes. Muscle symptoms can start together with liver disorders or long after hepatic disorders or after liver symptoms disappeared in childhood. Currently a definitive diagnosis depends on either mutation analysis or liver and muscle glycogen debranching enzyme activity tests. Ozen H, (2007) A recent study aimed to establish an enzymologic diagnostic method for GSD IIIA by detecting muscular glycogen debranching enzyme activity. The study suggested that enzymologic methods for diagnosis had a power similar to that of gene analysis methods in the diagnosis of GSD-IIIA patients. The sensitivity and specificity of enzymologic diagnostic method and mutation detection were 91. 7% and 100% respectively. This suggests that the method is suitable for use in clinic as a first line diagnostic tool. Wang W. (2009)

Treatment for GSD III is primarily dietary and is aimed at maintaining normoglycemia. This is achieved by frequent meals high in carbohydrates and cornstarch supplements alone or with gastric tube feedings. For patients with myopathy, in addition to management of hypoglycemia, a high protein diet is recommended. Demo E et al (2007)