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Research Article

Investigation and Management of Glycogen Storage Disease Type VI

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ABSTRACT

Glycogen storage disease (GSD) type VI or Hers disease is a rare form of GSD which is caused by hepatic glycogen phosphorylase deficiency encoded by the glycogen phosphorylase L (PYGL) gene and inherited by autosomal recessive inheritance. PYGL gene mutations prevent liver glycogen phosphorylase (LGP) from breaking down glycogen effectively. Hers disease is a clinically and genetically heterogeneous group of disorders characterized by hepatomegaly, hypoglycemia, growth retardation and hyperlipidemia. The diagnosis of hepatic GSDs requires a proper and specific clinical history and examination. Determination of the mutation in the PYGL gene on chromosome number 14 provides a basis for the diagnostic test of this disease. Therapy for this disease needs very careful dietetic management with prospective surveillance for complications. Treatment with corn starch and a high protein diet is recommended in an effort to improve the clinical features of this disease.

Keywords: Glycogen storage disease, Hers disease, hepatomegaly, growth retardation, hyperlipidemia, hypoglycemia

INTRODUCTION

Glycogen storage disease type VI (GSD VI) defines a group of disorders that cause hepatomegaly and hypoglycemia with reduced liver phosphorylase activity[1]. It is an autosomal recessive inheritance of mutation on PYGL gene. Hers disease is the rarest form of GSD but it is probably the most under-diagnosed among the GSDs[2]. Hepatic glycogen phosphorylase (HGP) deficiency is predominantly the result of missense mutations that affects the enzyme activity[3]. The phosphorylase enzyme plays a vital role in the breakdown of glycogen into glucose. Hence the anomalies in the production of this enzyme means that the dysfunction of hepatocytes occur leading to the accumulation of glycogen within them (due to failure of glycogenolysis in liver) which results in the characteristic signs and symptoms of this infrequent congenital disorder. This paper will focus on the significant clinical features and management of hers disease.

Significant clinical features

In the liver, phosphorylase deficiency manifests primarily with hepatomegaly (liver enlargement) and growth retardation (short stature). Despite gross hepatomegaly, the affected individual seems to be asymptomatic[4]. In well treated individuals, the hepatic adenomas are rare[5]. Typically, it takes a benign course with remission of symptoms. Gradually, the phase changes from mild to moderate hypoglycemia (low blood sugar)[6]. In many cases, the body can adapt to low blood sugar levels and will be able to produce energy by other means. Therefore, the symptoms may go unnoticed for a long duration. The affected individuals may also have hyperlipidemia (elevated cholesterol and fats in the blood). Usually, the laboratory investigation of uric acid and lactic acid doesn't show any abnormalities[5]. The clinical features of GSD VI tend to improve with age[3]. Enlargement of the liver often disappears by puberty and the adult height is often normal. On the basis of the severity of the disease, a significant variation is seen in the clinical features.

Hepatomegaly associated with hers disease

Hepatomegaly (liver enlargement) is the cardinal presenting feature of GSD VI affecting the liver. It can represent intrinsic liver disease or may be the presenting physical finding of a generalized disorder. The appearance of a palpable liver does not always represent hepatomegaly. A liver edge greater than 3.5 cm in new borns and greater than 2 cm in children below the right costal margin represents an enlargement in the liver[8]. Excessive storage is one of the mechanisms that are known to cause hepatomegaly[9]. In GSD VI, inappropriate or excessive storage of glycogen occurs but it fails to release the glycogen normally for the metabolic reaction to take place, with time the stores of glycogen buildup in the liver causing hepatomegaly[5,9]. Failure of glycogenolysis in liver

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can result in hepatic glycogen accumulation. Glycogenolysis is the breakdown of glycogen to glucose-6-phosphate (G-6-P) and glycogen. The glycogen branches are catabolized by the sequential removal of glucose monomers by the glycogen phosphorylase. So, the deficiency of this enzyme involved in phosphorolysis leads to the failure of glycogenolysis in liver which results in hepatic glycogen accumulation leading to hepatomegaly. Good metabolic control improves the enlarged condition of the liver[5].

Hypoglycemia associated with hers disease

Hypoglycemia (low blood sugar) after a period of fasting is the hallmark of GSD VI[5]. Glycogen is most abundant in the liver; where it serves a buffer reservoir of glucose units for the maintenance of constant blood-glucose levels, and in muscle, where it can be rapidly broken down to provide energy for contraction. The preferred energy source of the brain is glucose. Thus, for the maintenance of human life a constant source of blood glucose is very much essential. Diet, degradation of glycogen and gluconeogenesis are the primary sources of blood glucose as dietary intake of glucose is sporadic and gluconeogenesis will not occur in rapid response to falling blood glucose levels. Glycogen serves as a means for storing glucose so as to mobilize it readily[10]. Hence, in GSD VI, the process of degradation of glycogen into glucose is being hindered leading to a fall in blood glucose levels and ultimately resulting in the condition known as hypoglycemia. Biochemically, patients have an increased risk of fasting hypoglycemia. In order to avoid damage to the brain, prevention of hypoglycemia by frequent meals is necessary[11].Treatment improves and reduces the frequency of hypoglycemia.

Growth retardation associated with hers disease

Growth retardation describes a growth rate below the appropriate growth velocity for age. Normal growth is affected by the interaction of genetic, nutritional, metabolic, and endocrine factors. A major proportion of the available carbohydrate is utilized by the central nervous system. The growth hormone (GH) secretion by the pituitary gland is stimulated by the growth hormone-releasing hormone (GHRH) from the hypothalamus. GH pulses when released into the systemic circulation, releases insulin-like growth factor (IGF)-1 at the site of the growing bone[12]. Growth retardation in hepatic GSD type VI can be explained as a part of the adaptation to the inability to maintain normal glucose homeostasis. Short stature is the normal expression of genetic potential (growth rate is normal) or it may be the result of a condition that causes growth failure with a lower-than-normal growth rate[13]. To a large extent growth potential is determined by polygenic inheritance. Short stature is improved with better metabolic control.

Hyperlipidemia associated with hers disease

Hyperlipidemia refers to the quantity of cholesterol (Chl) and/or triglyceride (TG) in plasma, higher than the upper limit of normality[14]. Usually the production and metabolic activity of TG and Chl occur in a state of dynamic balance. It will occur if Chl and/ or TG are synthesized excessively. When the function of liver is normal, the synthesis and metabolism of blood lipids can be automatically regulated by the human body according to the energy requirements[14]. Therefore, the liver plays a significant role in the synthesis and metabolic balance of TG and blood Chl level. In GSD VI, the dysfunction of liver due to glycogen accumulation leads to hyperlipidemia in which a high level of carbohydrate increases the TG level and thereby it increases the Chl level resulting in the condition known as hyperlipidemia.

Diagnostic testing

The diagnosis of hepatic GSDs require a careful clinical history and examination[15,16].The definite diagnosis finally is a combination of clinical presentation, specific constellation of biochemical abnormalities, determination of liver enzyme activity, and molecular genetic analysis.

Genetic or Molecular testing

Genetic/molecular testing can be performed to further confirm that there is mutation of the glycogen synthase gene. Currently, a definitive diagnosis can be provided by performing gene mutational analysis[17]. Molecular genetic testing involves clinical testing of sequence analysis and deletion/duplication analysis[18]. Now the preferred method for diagnosing GSD VI is by sequence analysis of PYGL in molecular genetic testing[18,19]. PYGL sequence analysis for GSD VI is often performed in females. The diagnosis of type VI glycogenosis can be improved by the mutation identification based on amplification of the PYGL coding sequence from blood DNA or RNA[20]. In DNA analysis, genomic DNA is extracted from peripheral blood leukocytes using standard procedures. PYGL gene on chromosome number 14 was amplified using polymerase chain reaction (PCR) from genomic DNA samples[21]. Recombinant-DNA technology has led to the detection of restriction-fragment-length-polymorphisms (RFLPs) which help to prenatally diagnose the informative fetuses at risk[22-24]. Biotinidase activity has been presented as a useful biomarker for liver GSDs. With the development in next-generation sequencing (NGS) technologies, mutation analysis has become the most preferred method for diagnosing GSDs. In this technology, a group of candidate genes can be sequenced simultaneously[15,16].

Liver biopsy

For GSD VI, molecular diagnosis is important because the disease is generally mild and definitive diagnostic tests require liver biopsy. By performing a liver biopsy, a definite diagnosis can be provided[17]. Definitive diagnosis requires the analysis of a fresh liver biopsy for the activity of phosphorylase enzyme in the presence and absence of its activator enzyme, phosphorylase kinase. It involves patient discomfort and risk, and test results vary with, patient dietary status, sample freshness and even the region of the liver from which the biopsy is derived[25]. Liver biopsies requiring very careful specimen handling can be avoided. It is reserved for those in whom the diagnosis cannot be confirmed by molecular genetic techniques.

Assay of enzyme activity

Assay of liver glycogen phosphorylase activity can be performed on RBCs, WBCs and hepatocytes[17,18]. By the direct assay of the enzyme in biopsies, the absence of enzyme activity in this disorder has been identified[11]. Molecular assay can provide reassurance that the

symptoms in an apparently affected child are not attributable to other causes of hepatomegaly and hypoglycemia. Despite deficient activity in liver cell, the diagnostic utility of molecular assay is limited because blood enzyme activity will be normal.[19]

Ultrasound

Due to possibility of increasing risk of hepatic adenoma with increasing age, annual liver ultrasound can be performed starting at age 5.

Physical examination

Height and weight measurements should be also assessed regularly to monitor growth[18,19]. Assess bone density periodically after complete growth to prevent from further complications like osteoporosis[18,19,30].

Carrier testing

Parental testing confirms the carrier status for the mutations in either one or both the parents. Carrier testing for at-risk relatives and prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the pathogenic variants in the family requires prior identification of the pathogenic variants in the family[18].

Blood tests

Intravenous glucose loading test (GLT) can be used for the differential diagnosis of hers disease. Blood cell enzymology is performed to reveal significant reductions in glycogen phosphorylase activity[3]. To assess metabolic control, blood glucose levels and blood ketones should be routinely monitored[18]. Performing fasting blood test is necessary to detect ketotic hypoglycaemia[19]. A hypoglycemia screen is performed to identify other relevant diagnoses such as persistent hypoglycemic hyperinsulinism of infants[26,27]. Overnight fast is generally well-tolerated in glycogen storage disease type VI because gluconeogenesis is preserved. Serum concentration testing of TG, Chl and liver transaminases are seemed to be mildly elevated[18,19]. In untreated glycogen storage disease patients, abnormal plasma concentrations of lactate, transaminases, uric acid, TG and cholesterol are usually reported[3].

Other diagnostic tests

Radiographic studies (for skeletal surveys) can be done which include CT or MRI scan of the affected region. Imaging studies to diagnose liver enlargement and ischemic forearm test are also carried out to diagnose this rare form of GSD[31].

Confirmation of a diagnosis of GSD VI is important because the differential diagnosis of hypoglycemia and hepatomegaly is considerable and includes other more severe disorders that should be excluded.

Management

Management of hers disease aims to suppress the secondary metabolic decompensating. The goal of the treatment is to prevent hypoglycemia and counter-regulation thereby reducing the secondary metabolic derangements[28]. Early and proper diagnosis of GSD VI is essential as dietary treatment with frequent high-starch feeds and raw cornstarch can prevent the progression of this disease[29]. The intake of sugars such as galactose, sucrose and fructose is restricted as it may worsen the metabolic derangements and liver enlargement in the GSD patient[30]. Management of hepatic phosphorylase deficiency is symptomatic and hypoglycemia is prevented by frequent feedings of a high-carbohydrate diet. In most patients, a late evening meal is not much beneficial. In an effort to achieve normal labs and normal growth, treatment with cornstarch and a high protein diet is recommended. It improves growth velocity and bone density in this condition, and reduces the frequency of hypoglycemia. In an attempt to maintain glucose concentrations above 70mg/dl, treatment is individualized[5].

Primary manifestations such as hepatomegaly and hypoglycemia may be prevented by the administration of uncooked starch and frequent small meals (one to three times a day) respectively[18]. The significant clinical features are rapidly ameliorated with the consumption of protein-rich meals (every four hours) and with the bedtime feeding of uncooked cornstarch in skimmed milk. High intake of protein provides the substrate for gluconeogenesis. To prevent early morning hypoglycemia, avoiding prolonged fasting and ingestion of a bedtime snack is recommended[17]. The secondary complications like growth retardation and osteoporosis can be improved with better metabolic control. Liver transplantation abolishes the biochemical abnormalities in rare cases[31]. New experimental treatment approaches, such as enzyme replacement and hepatic gene therapy or liver stem cell therapy have been explored using animal models[17].

Recently, a re-emergence has been there in the use of ketones in therapy, in the form of D, L-3-hydroxybutyrate salt and in some cases as medium chain triglyceride (MCT). Alternatively, a promising early data of efficacy is shown by waxy maize based starches[2]. Liver and kidney transplantation is indicated in severe refractory disease. Genetic counseling is beneficial for the affected individuals and their families. It is the process of providing individuals and families with information on the nature, inheritance, and implications of hers disease to help them make informed medical and personal decisions[18]. Other treatment is symptomatic and supportive. Some individuals do not require any treatment, but most have better growth and stamina with therapy[18]. Depending on the age of the patient, continuous gastric tube feeds can be included in therapy[30].

Complications of hers disease needs to be prospectively surveyed and managed[32]. Without multivitamin supplementation, it can be difficult for the affected individuals to get all essential nutrients, since the GSD diet is very prohibitive. To prevent osteoporosis, calcium and vitamin D3 supplementation is advisable[30]. In children with hers disease, administration of clonidine is another treatment modality for growth retardation. The effect of clonidine therapy on height is not known to cause any side effects[33]. To maintain the blood sugar level within a clinically safe range, diazoxide, which interferes with the release of insulin from islet cell, can be administered[11]. The patient should avoid excess simple sugars to prevent excessive hepatic glycogen deposition[19]. Avoid glucagon as rescue therapy for hypoglycemia as it's not effective for increasing blood glucose level in GSD VI. Similarly avoid

growth hormone for short stature as it may exacerbate ketosis. In this disease, a symptomatic care is appropriate[1]. Currently an individualized treatment is planned and provided based on the specific conditions and complications in order to improve the quality of life.

CONCLUSION

GSD VI is diagnosed using a combination of clinical symptoms, biochemical results, and pathology findings. A cross-disciplinary approach including intensive dietary treatment in order to achieve a better metabolic control and adequate medical therapy of the associated problems and complications is essential to reduce mortality, morbidity and improve the quality of life of the individual affected with GSD. Therapy requires a very careful dietetic management with prospectus surveillance for complications. Prognosis has been immensely improved by dietary treatment.

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