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Glycogen Storage Disease in Pediatric Population

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ABSTRACT

Introduction: The pathway of glycogen metabolism is regulated by many hormones such as insulin, glucagon, and corticosteroids. Glycogen storage diseases (GSD) most commonly affect muscles, liver, or both and occur in each 20000 to 43000 live birth. They are classified into 12 subtypes, but types I, II, and IX are the most common.
Methodology: We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, from January 2001, through February 2017. The following search terms were used: glycogen storage diseases, Von Gierke disease, Pompe's disease, Cori Disease, Forbes disease, Andersen's disease, McArdle disease, neonatal hypoglycemia, neonatal hepatomegaly.
Aim: In this review, we aim to study the genetic basis, diagnosis, presentation, and different management approach to various common types of glycogen storage diseases prevalent in pediatric population.
Conclusion: There are no cures for any type of glycogen storage diseases presently. Most treatments are designed to control signs and symptoms. The overall goals are primarily avoiding hypoglycemia, hyperlactatemia, hyperuricemia, and hyperlipidemia. Liver transplantation should be deliberated for patients with GSD type IV and for other progressive hepatic types of GSDs in order to avoid hepatic failure or malignancy. More research must be carried out to develop newer and more effective ways of management.

Keywords: neonatal hypoglycemia, glycogen storage diseases, Von Gierke disease, Pompe's disease, Cori Disease, Forbes disease, Andersen's disease, McArdle disease

INTRODUCTION

Inherited diseases that involve the glycogen metabolism pathway are called glycogen storage diseases (GSD). This pathway of glycogen metabolism is regulated by many hormones including insulin, glucagon, and corticosteroids. GSDs most likely affect muscles, the liver, or both. A GSD can occur in each 20000 to 43000 live births. GSDs are classified according to the enzyme defect, and there are about twelve subtypes. For example, type Ia can affect the liver, kidney, and/or intestines. Type Ib affects the same organs like type Ia, with addition to leukocytes. Both type Ia, and Ib present classically with failure to thrive, hypoglycemia, hepatomegaly, hyperlactatemia, hyperuricemia, and hyperlipidemia. Another example is type III, where type IIIa affects liver and muscles, and type IIIb affects only the liver. As patients age, liver symptoms improve gradually. Type IV is typically diagnosed in infants, and presents with failure to thrive and hepatomegaly, that gradually progresses to cirrhosis. Type I, III, and IX constitute about 80% of cases of GSD with liver involvement [1].

METHODOLOGY

- **Data Sources and Search terms**

We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 2001, through February 2017. The following search terms were used: glycogen storage diseases, Von Gierke disease, Pompe's disease, Cori Disease, Forbes disease, Andersen's disease, McArdle disease, neonatal hypoglycemia, neonatal hepatomegaly **The study was done after approval of ethical board of King Khalid university**.

- **Data Extraction**

Two reviewers have independently reviewed the studies, abstracted data, and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

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Glycogen storage disease type I

Glycogen storage disease type I (also known as Von Gierke disease, or Hepatorenal glycogenosis) is an autosomal recessive disease that occurs due to deficiency of the glucose-6 phosphatase (G6Pase) enzyme, causing disruption in both glycogenolysis and gluconeogenesis pathways. G6Pase is an important enzyme that provides glucose in cases of fasting, and mainly presents in the liver and the kidneys. Glycogen storage disease type 1 has four subtypes, and the classification is based on the defect in G6Pase. In type Ia, enzyme dysfunction is present inside the endoplasmic reticulum (ER), exactly in the catalytic subunit of the enzyme. On the other hand, type Ib affects transporters that move the substrate of the enzyme in and out the ER. The incidence of type I GSD in the Caucasian population varies between 1/100000 and 1/400000, with type Ia being the most common subtype. Ashkenazi Jews population has a higher incidence of the disease that reach 1/20000 [2].

1. GSD type Ia

In 1952, GSD type I and G6Pase deficiency was first reported by Cori, who was the first to discover an inherited enzyme disorder. It was found that chromosome 17 carries the gene responsible for G6Pase catalytic unit [3].

GSD type I presents early after delivery with hypoglycemia that does not respond to glucagon administration. Other symptoms may include tremors, irritability, hyperventilation, cyanosis, apnea, convulsions, paleness, sweating, cerebral edema, cerebral dysfunction, coma and/or death. Symptoms occur mainly in the morning and prior to feedings. Cases with late presentation can have doll-like facial appearance, lethargy, continuous hunger, failure to thrive, protuberant abdomen, thin extremities, and/or sleep problems. They also have more tendency for bleeding due to platelets dysfunction. During infections, patients usually have decreased appetite leading to more frequent attacks. Some cases will be complicated with anemia or rickets. When examining patients with GSD type I, hepatomegaly with abdominal protuberance may be present [4].

Laboratory findings include hypoglycemia, lactic acidosis, hyperlipidemia (most strikingly hypertriglyceridemia), hyperuricemia, hypercalciuria, and/or mildly elevated liver enzymes. Some cases reported also increased levels of biotindase in type Ia. Abdominal ultrasound may detect enlarged kidneys. Liver biopsy can show mosaic pattern with swollen, pale, steatotic, hepatocytes with hyperglycogenated nuclei. Liver biopsy and enzyme assays, and/or mutation analysis are required for definitive diagnosis [5].

The treatment depends mainly on preventing hypoglycemic attacks by continuous administration of glucose, with possible nocturnal intragastric feeding. These protocols can maintain acceptable glycemic level, which will cause significantly less metabolic consequences, and long-term sequelae. Kidneys' involvement is decreased with proper management and control of hypoglycemia. Any food including lactose, fructose, or sucrose must not be given. Only small amounts of fruits, vegetables, and milk are allowed. Compensatory vitamins and minerals should also be administrated. In cases of anemia, proper work-up should be done to detect and correct the underlying cause [6].

By controlling hypoglycemia, the severity of renal involvement may regress. Lactose, fructose and sucrose should be restricted except for fruits, vegetables and small amounts of milk products. Enough essential nutrients, vitamins and minerals should be given. If there is anemia, the causes must be evaluated and appropriate treatment should be started. In cases of hyperuricemia, allopurinol is indicated. In cases of acidosis, give bicarbonate or potassium. ACE inhibitors like captopril and Ramipril have been shown to decrease the rate of deterioration of kidneys and improve albuminuria. Lipids-lowering drugs are administrated in cases of resistant high triglyceride levels. Otherwise, there is an increasing risk of developing cholelithiasis and/or pancreatitis. In cases of irreversible damage, liver transplantation can be performed, and has been shown to improve biochemical abnormalities. However, this procedure's effect on kidneys has not been addressed yet. Renal transplantation can be performed but it will only improve renal functions [3].

2. GSD type Ib

GSD type Ib was originally reported in 1968, after in vitro recognition of normal G6Pase activity despite failure in vivo glucose liberation from G6P. Patients did have similar presentations to type Ia patients, with increased rates of infections, neutropenia, neutrophils dysfunction, and higher rates of inflammatory bowel disease. Generally, patients with GSD type Ib have an absolute neutrophil count of less than 1000 cells/mL. This neutropenia with increased infections will cause fever, diarrhea, and perioral and anal ulcers along with other manifestations related to decreased

immune response. Intestinal symptoms do not correlate in severity with the primary disease [7].

Treatment can be similar to GSD type Ia with diet modifications and continuous glucose supplementation. Considering neutropenia, and neutrophils dysfunction, granulocyte colony-stimulating factor (G-CSF) may be administrated. This protocol of dietary modifications and G-CSF therapy has been found to significantly decrease symptoms and improve prognosis. However, risks of long-term complications are still present. Examples of complications include: renal calculi, chronic kidney disease, inflammatory bowel disease, hepatic adenoma, and splenomegaly [8].

An important concern in treatment is the long-term difficulty in following treatment and the high rates of poor compliance. This will cause irreversible damage that will eventually require liver transplantation, which will improve biochemical disturbances, but neutropenia will still be present [9].

Glycogen storage disease type II

GSD type II (also known as Pompe's disease, alpha-1, 4-glucosidase deficiency) is a lysosomal storage disease that occurs due to decreased activity of acid maltase enzyme, which is coded by a gene present on chromosome 17. Clinical presentation of the disease differs among patients due to the variation in the enzyme dysfunction caused by different mutations [10].

GSD type II occurs in about 1/40000 of Caucasians, and has four subtypes. The classic infantile form of Pompe's disease presents with cardiomyopathy and muscular hypotonia. Juvenile and adult forms present mainly with skeletal muscle involvement. The severity of symptoms inversely correlates with the levels of active enzyme. Therefore, it is hypothesized that mutations causing the disease may be affecting production of degradation pathways rather than catalytic pathways [11].

If the enzyme is not present in all the tissues, the classic form of the disease occurs. In this case, liver is usually not enlarged unless heart failure occurs. Hypoglycemia and acidosis are usually not present, and patients die during their first year of life. When the enzyme is present but in little quantities, type two (the infantile) occurs with less severe cardiomyopathy with no obstruction of left ventricular outflow. Juvenile and adult forms occur later in life, with severity correlated with the onset of the disease rather than patients' age. Patients who have symptoms before age 15 years usually are at a higher risk of developing complications that require ventilator, wheelchair, and/or nutritional support. Other associated manifestations include Wolff-Parkinson-Syndrome and second degree atrioventricular block. Aneurysm development and rupture may also occur as a result of glycogen accumulation in smooth muscles of vessels. Some families can have members with disease in varying severity ranging from severe infantile to asymptomatic adult forms [12].

Laboratory abnormalities include elevated CK, aldolase, AST, ALT, and lactate dehydrogenase levels. CK is sensitive for the disease and can be found in more than 95% of patients. Enzyme levels can be measured to confirm the diagnosis [12].

Patients may benefit from a low-carbohydrate, low-protein diet. The use of recombinant alpha-glucosidase was first introduced in 2001 and was found to improve cardiac and muscles functions. The use of this modality was approved in 2006 for treatment of Pompe's disease. Other potential experimental treatments include the use of adeno-associated virus vector to provide genetic therapy [12].

Glycogen storage disease type III

GSD type III (also known as Cori disease, Forbes disease, Amylo-1,6-glucosidase deficiency; Glycogen debrancher deficiency) occurs from decreased activity of glycogen debranching enzyme resulting in accumulation of abnormal glycogen in hepatocytes causing damage. This enzyme is coded by a gene on chromosome 21, is available in several isoforms, and is responsible for two independent catalytic pathways: oligo-1,4-1,4-glucantransferase and amylo-1,6-glucosidase [13].

GSD type III occurs in 1/83000 live births in Europe, and 1/100000 live births in North America, and is responsible for about 24% of glycogen storage disease cases. GSD type III is most prevalent in Faroe Islands where it occurs in 1/3600 live births. This is thought to be due to a founder effect. Variable genotypes and phenotypes of the disease exist. However, genotype is not though to correlate with clinical manifestations [14].

GSD type III has three major subtypes. GSD IIIa involves the liver and muscles and alone accounts for about 80% of GSD III cases. On the other hand, GSD IIIb accounts for about 15% of cases and affects the liver only. GSD IIIc is the least common and occurs due to selective loss of glucosidase activity [15].

GSD type III classically presents with hepatomegaly, hypoglycemia, short stature, dyslipidemia, and/or mild intellectual disability.

Skeletal muscles involvement can start with liver involvement or later in life. In rare cases, there may be skeletal muscles involvement with the absence of hepatic symptoms. Hepatic symptoms decrease gradually as patients age, and usually disappear following puberty. Liver cirrhosis rarely occurs and hepatic cell carcinoma. Adults will mainly suffer from progressive muscle weakness with distal muscle wasting. Cardiac involvement occurs in most GSD IIIa patients and ranges from asymptomatic ventricular hypertrophy to symptomatic cardiomegaly [15].

Some patients may present in young patients with anatomical facial abnormalities like depression in the nasal bridge with a broad upturned nasal tip, bow-shaped lips with a thin vermillion border, and/or deep-set eyes). Some patients may suffer from recurring sinusitis or otitis media resistant to treatment. Laboratory abnormalities include elevations in LDS, AST, ALT, and ALP levels during childhood, with gradual decline until puberty. CK is usually elevated with muscle involvement. However, it sometimes can give false negative results thus can be used to rule out muscle involvement. No reliable tests are present to early detect liver cirrhosis and HCC [16].

Complications of GSD III include osteoporosis, which is associated with poor nutrition, lactic acidosis, and hypogonadism. Sometimes periportal fibrosis occurs leading to micronodular cirrhosis. In this case, biopsy will show hepatocytes distension due to accumulation of glycogen with fibrosis of periportal septa [17].

To diagnose GSD III, enzyme levels are measured in the liver and muscles. Sometimes mutation analysis can be used as a simple non-invasive method to establish a diagnosis. Other tissues like the heart, erythrocytes, or fibroblasts can also show decreased enzyme levels [14].

Treatment of GSD III mainly depends on dietary modifications to keep constant levels of normal glucose. To achieve this, diet with high carbohydrates should be supplied frequently alone or with adding gastric tube feedings. Patients with myopathy also require a diet with high protein content. In cases of irreversible damage to the liver, liver transplantation may be performed. However, this procedure may not provide improvement to cardiac damage [17].

Glycogen storage disease type IV

Glycogen storage disease type IV (also known as Amylopectinosis, Andersen's disease) is an inherited autosomal recessive disease that was first reported in 1956 by Andersen, and occurs due to a deficiency in the glycogen branching enzyme. The branching enzyme is coded by a gene located on chromosome 12, and its disease causes about 0.3% of glycogen storage diseases. GSD IV causes accumulation of abnormal glycogen leading to liver cirrhosis. In the absence of the branching enzyme, glycogen will not have branching causing the synthesis of a glycogen that has the structure of an amylopectin (polyglycosan). This abnormal glycogen can accumulate in hepatocytes, myocytes, and other tissues causing damage [18].

The presence of the enzyme in several tissues along with the presence of several isotypes of the enzyme, create a wide variation of clinical presentations of the disease that depend on the specific site of the mutation. The classic presentation of GSD IV is a previously normal patient with failure to thrive, hepatosplenomegaly and cirrhosis in the first 18 months of life, and death at about 5 years. In some mild cases, liver involvement is not severe or slowly-progressive. These cases will present with mild hepatosplenomegaly and liver enzymes elevation that may return to normal levels later with life [19].

When the enzyme is deficient in the liver and muscles, the disease will present with peripheral myopathy, cardiomyopathy, neuropathy, and/or liver cirrhosis, in young neonates or adults. The age of presentation is used to classify the presentation of neuromuscular symptoms into four subtypes. The fetal (perinatal) form can cause hydrops fetalis, polyhydramnios, arthrogryposis, and akinesia of the fetus. Cervical cystic hygroma can sometimes be present during pregnancy and represent a warning sign for prenatal diagnosis, which can be done using chronic villi sampling to determine enzyme activity. These cases are incompatible with life, and babies will die soon after birth. Babies present with severe hypotonia, hyporeflexia, cardiomyopathy, depressed respiration, neuronal involvement, no liver cirrhosis, and no heart failure. Childhood neuromuscular form causes cardiomyopathy and presents with exercise intolerance, exertional dyspnea and congestive heart failure in advanced cases. Some cases may only involve muscles with normal creatine kinase levels. The adults form usually presents as an isolated myopathy, with symptoms starting later in life and resembling muscular dystrophies. Patients will have progressive proximal weakness with waking difficulties. Other presentations of the disease include pyramidal tetraparesis, peripheral neuropathy, early neurogenic bladder, extrapyramidal symptoms,

seizures, and/or cognitive decline leading to dementia [20]. Enzyme levels in erythrocytes can be measured to confirm the diagnosis. Biopsy of affected tissues will show amylopectin-like inclusions. MRI can be used and will show white matter abnormalities. Liver biopsy can show acid Schiff positive hepatocytes and inclusions from abnormal glycogen. Liver transplantation is the only available effective modality of treatment in cases of GSD IV with liver damage. However, it would not provide improvement to muscles involvement [21].

Glycogen storage disease type V

Glycogen storage disease subtypes V (also known as McArdle disease) occurs due to deficiency in muscle glycogen phosphorylase enzyme due to mutations in the encoding gene on chromosome 13. The disease usually presents in young adults with muscle cramps with exercise. Severe exercise can cause rhabdomyolysis leading to myoglobinuria and possibly, acute renal failure [22].

CONCLUSION

Currently, there are no cures for any GSD, and as we have seen above, most treatments are designed to control signs and symptoms. The overall goals are primarily avoiding hypoglycemia, hyperlactatemia, hyperuricemia, and hyperlipidemia. Liver transplantation should be deliberated for patients with GSD type IV and for other progressive hepatic types of GSDs in order to avoid hepatic failure or malignancy. More research must be carried out to develop newer and more effective ways of management, such as screening and gene therapy.

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