Genetic and Glycogen Storage Diseases

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Article information	*Abstract*
	Glycogen storage diseases are a group of inborn error of metabolism and characterized by accumulation of glycogen in various tissues. The overall incidence of glycogen storage diseases is estimated 1 per 20,000-43,000 live births. There are twelve distinct diseases that are commonly considered to be glycogen storage diseases and classified based on enzyme deficiency and affected tissue. We searched all review articles and books in the national and international databases which considered as inherited metabolic disorders and the genetic associations of these disorders. A large number of enzymes intervene in the synthesis and degradation of glycogen which is regulated by hormones. Several hormones, including insulin, glucagon and cortisol regulate the relationship between glycolysis, glycogenosis, and glycogen synthesis. These diseases are divided into three major groups: disorders that affected liver, disorders that affected muscle and those which are generalized. Glycogen storage diseases are called by a Roman numerical that reflects the historical sequence of their discovery by an enzyme defect or by the author's name of the first description.

Introduction

All glycogen storage diseases are considered as inherited metabolic disorders. A metabolic disorder is a disease that interferes with the metabolism. Metabolism is the process by which the food we eat is broken down and converted into energy. Glucose is a simple sugar and is a form of carbohydrate. The sugar found in many foods and is the main source of energy for our body. Glycogen is form of glucose storage in our body. The main place to store glycogen is liver and musclecellsare. A large number of enzymes involved in glycogen synthesis and degradation that are regulated by hormones (figure 1). Glycogen storage diseases are a group of hereditary genetic disturbances in the body that cause glycogen to be improperly formed or drainage. The disturbance by the accumulation of abnormal amount sortypes of glycogen is found. These disorders are characterized by the accumulation of glycogen. These disorders are characterized by a variety of abnormal glycogen.

Materials and Methods

We searched all review Articles and books in the national and international databases which considered as inherited metabolic disorders and the genetic associations of this disorders.

Glycogen storage diseases (GSDs): Glycogen is a storage form of glucose in muscle and liver, and is a polymer that acts as an energy source. In GSDs, due to enzyme deficiency, glycogen accumulates in liver, skeletal muscle, and heart.

Glucose-6-Phosphatase deficiency, von Gierke disease (GSDI): There is a specific enzyme in the liver and kidney but not in the muscle tissue that called glucose-6-phosphatase (G6Pase). This enzyme separates a group of phosphate from glucose-6-phosphate (G6P). Therefore the intracellular glucose can be released in to the bloodstream. This stage is the last stage in the liver leads to enhanced glucose of the blood.

GSDIb caused by deficiency of the endoplasmic reticulum glucose-6-phosphate (G6P) translocase and about one in five GSDI patients has type Ib [1].

Both GSD Ia and Ib are autosomal recessive disorders. The gene encoding G6Pase (G6PC) was located on chromosome 17q21 and up to now more than75 different mutations have been identified [2, 3]. Subsequently, the gene encoding the G6P transporter (G6PT) was located on

Chromosome 11q23 and more than 65 different mutations have been reported [4]. Clinical presentations of this disease are hepatomegaly, hypoglycemia, short stature, lactatemia, hyperlipidemia that accrue because of deficiency of this hepatic enzyme [5]. Von Gierke disease is diagnosed through various tests; especially blood tests will reveal low blood sugar and lactic acid. Abdominal sonography can be assessed the size of liver and kidney. To confirm the diagnosis, a biopsy of the liver performed and functions of glucose-6-phosphatase enzyme can be investigated. Its treatment is continuous feeding to keep blood glucose levels stable [5]. Treatment consisted of frequent carbohydrate enriched meals during day and night.
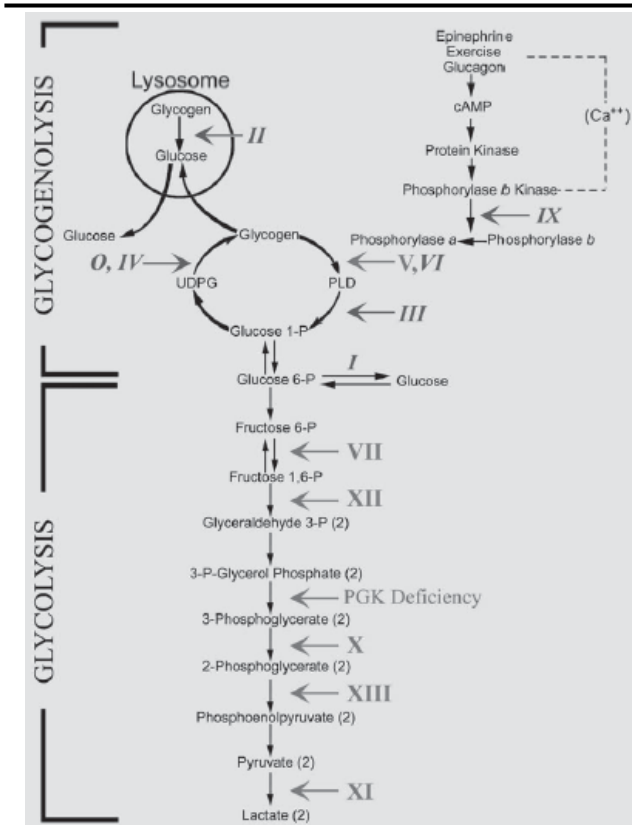
Figure 1. View of glycogen metabolism and glycolysis

Glycogen Debranching Enzyme (GDE) Deficiency (GSD III also known as Cori or Forbes disease): The disease is caused by a defect in the debranching enzyme, amylo-1,6-glucosidase. This disease is an autosomal recessive disorder due to deficiency of GDE which causes storage of glycogen in liver. The gene of GDE is located on chromosome 1p21 and at least 48 different mutations in the GDE gene have been reported [6].

Hepatomegaly, hypoglycemia, short stature, and hyperlipidemia predominate in children, and this presentation may be indistinguishable from GSDI. With increasing age, the symptoms improve in most patients with GSD III and may disappear around puberty [7].

Diagnosis is based on DNA investigations in leukocytes combined with enzyme studies in leukocytes, erythrocytes and/or fibroblasts. Prenatal diagnosis is possibleby identifying mutations in the GDE gene if these mutations are already known. If the mutations are unknown, polymorphic markers may be helpful in informative families. Dietary treatment prevents hypoglycemia and improves hyperlipidemia.

Glycogen Branching Enzyme (GBE) Deficiency or GSDIV: Glycogen storage disease type IV (GSDIV), also known as Andersen disease or amylopectinosis, is an autosomal recessive disorder caused by a deficiency of glycogen branching enzyme (GBE) result in the accumulation of amylopectin-like compact glycogen molecule with fewer branching points and longer outer chains. Patients present in early childhood with hepatomegaly and liver cirrhosis [8]. The GBE gene has

been located on chromosome3p14. Three important point mutations, F257L, R515C and R524X were found in patients with the classical progressive liver cirrhosis form. The only effective therapeutic approach at present for GSDIV patients with the classic progressive liver disease is Liver transplantation.

Glycogen Phosphorylase Deficiency or GSD VI also known as Hers disease: Glycogen storage disease type VI (GSDVI) is an autosomal recessive disorder due to deficiency of the liver isoform of glycogen phosphorylase. Phosphorylase breaks the straight chains of glycogen down to glucose-1-phosphate. Glucose-1-phosphate in turn is converted into glucose-6-phosphate and then into free glucose. Three isoforms of phosphorylase are known and encoded by three different genes. The gene encoding the liver isoform, PYGL, is on chromosome 14q21. The mutations of this gene have been reported [9]. The main clinical symptoms are hepatomegaly, short stature, hypoglycemia, and growth retardation. Hepatomegaly decreases with increasing age and usually disappears around puberty [10]. Patients are clinically indistinguishable from those with liver GSD type IX.

Phosphorylase Kinase (PHK) Deficiency or GSD IX: Glycogen storage disease type IX is the most frequent glycogen storage disease. Six different subtypes are distinguished according to the clinical presentation and mode of inheritance: [1] X-linked liver glycogenosis (XLG or GSD IXa); [2] combined liver and muscle PHK deficiency (GSD IXb); [3] autosomal liver PHK deficiency (GSD IXc); [4]X-linked muscle glycogenosis (GSD IXd); [5] autosomal muscle PHK deficiency (GSD IXe); and [6] heart PHK deficiency (GSD IXf) with the mode of inheritance not clear yet [9, 11], but probably due to AMP kinase mutations [12].

PHK is a decahexameric protein composed of four subunits, α, β, γ, and δ. Two different isoforms of the α subunit, αL for liver and αM for muscle, are encoded by two different geneson the X chromosome, PHKA2 and PHKA1 respectively. The PHKA2 gene has been located on chromosome Xp22. The β subunit encoded by PHKB. The PHKB gene has been mapped to chromosome 16p12-q13. Two different isoforms of the γ subunit are γM for muscle and γT for testis/liver. The γM and γT isoforms encoded by PKHG1 and PKHG2, respectively. The PKHG2 gene has beenlocated on chromosome 16p12. Three isoforms of calmodulin (CALM1, CALM2, and CALM3) are encoded by autosomal genes [9, 13].

Clinical presentations are hepatomegaly, short stature (myopathy), hypoglycemia, growth retardation, elevated liver transaminases, and hypercholesterolemia . Diagnosis is based on clinical findings that obtained by measuring the enzymatic activity of phosphorylase kinase in liver, muscle and erythrocytes. It can be confirmed by molecular investigations [14].

Glycogen Synthase (GS) Deficiency or GSD 0: this defect leads to decreased rather than increased liver glycogen. The gene that encodes Glycogen Synthase is GYS2 and located on chromosome 12p. Several mutations of this gene are known. The main clinical

symptom of GSD 0 is hypoglycemia which appears in infancy or early childhood [15, 16].

The muscle glycogenoses: Muscle mainly uses fatty acids at rest. During submaximal exercise, it uses the energy from glucose that is mainly derived from liver glycogen. In contrast, the main source of energy during very heavy exercise is followed by an aerobic glycolysis derived from muscle glycogen breakdown. Enzymatic defects in this pathway may affect muscle function.

Myophosphorylase deficiency or McArdel disease or GSD V: Glycogen Storage Disease Type V is described by McArdle in 1951. GSD V is an autosomal recessive disorder due to muscle phosphorylase deficiency and initially affects the muscles. There are three isoforms of glycogen phosphorylase: brain/heart, muscle, and liver. GSD V is caused by deficient myophosphorylase activity and this gene (PYGM) is located on chromosome 11q13 [17]. Clinical variants of this disease are fatal infantile myopathy characterized in a few cases, and fixed weakness in older patients. The number of known mutations has rapidly increased to over 40. The most common mutation is the R49X mutation in Caucasians, which accounts for 63% of alleles in U.S. patients and 81% of the alleles in British patients [18, 19]. This mutation, however, has never been reported in Japan, where a single codon deletion 708.709 appears to dominant. Clinical manifestations are myalgia, exercise intolerance, and weaknesse and there is no corelation between genotype and phenotype. Patients with the same genotype may have different clinical presentations. In a study of patients with GSD V for associated insertion/deletion polymorphism in the angiotensin converting enzyme (ACE) discovered a good correlation between clinical severity and number of ACE genes that were deleted [20]. Like most muscle glycogenoses, serum creatine kinase (CK) is increased in McArdle patients. After carnitine palmitoyl transferase II (CPTII) deficiency, McArdle disease is the second most common cause of recurrent myoglobinuria in adults [21].

Glycogen storage disease type VII: GSDVII is caused by phosphofructokinase (PFK) deficiency and first described by Tarui. Phosphofructokinase is a tetrameric enzyme that is controlled by three autosomal genes. The gene that encodes the muscle subunit (PFK-M) is located on chromosome 12; a gene that encodes the liver subunit (PFK-L) is located on chromosome 21, and a gene that encodes the platelet subunit (PFK-P) on chromosome 10. Mature human muscle expresses only the M subunit and contains exclusively the M homo tetramer (M4), whereas erythrocytes, which contain both the M and L subunits, contain five isozymes: M4 and L4 (two homo tetramers), M1L3; M2L2; M3L1 (three hybrid forms). The diagnosis of PFK deficiency is based on the combination of muscle symptoms and hemolytic anemia. Other clinical presentions of GSDVII are multisystem involvement (seizures, corneal opacifications, cortical blindness, or cardiomyopathy) [22].

Phosphoglycerate mutase (PGAM) deficiency or glycogen storage disease type X: GSD X is an autosomal recessive disorder. PGAM is a dimeric enzyme that different tissues contain various proportions of a brain isozyme (BB), a muscle isozyme (MM), and the hybrid isoform (MB). *PGAMM* gene that encodes the M subunit is located on chromosome 7. Clinical manifestations of this disease are exercise intolerance and cramps.

Aldolase A deficiency or glycogen storage disease type XII: GSD XII is an autosomal recessive disorder. Aldolase exists in three isoforms: Aldolase A, Aldolase B, and Aldolase C. Erythrocytes and skeleton muscle contain mainly the aldolase A. Aldolase A gene (ALDOA) is located on chromosome 16. The only reported patient with aldolase A was a four and half year old boy with predominantly myopathic symptoms [23].

β-Enolase deficiency or glycogen storage disease type XIII: GSD XIII is an autosomal recessive disorder and caused by β-Enolase deficiency. β -Enolase is a dimeric enzyme formed from three subunits, α, β, and γ, encoded by different genes. ENO3, The gene encoding β-enolase, is located on chromosome 17. GSD XIII is still represented by a single patient; a 47-year-old Italian man affected with exercise intolerance and myalgias, and chronically elevated serum creatine kinase [24].

Muscle glycogen storage disease type 0 or glycogen synthase deficiency: GSD 0 is a disease characterized by a deficiency in the glycogen synthase enzyme. There are two versions: the muscle version involves GYS1 and the liver version involves GYS2 (Wikipedia). Recently, a study described GSD 0 in a child with hypertrophic cardiomyopathy and myopathy due to stop mutation in the GYS1 gene.

The generalized glycogenoses and related disorders

Acid maltase deficiency or glycogen storage disease type II or Pompe disease: GSDII is a lysosomal storage disorders that primarily affect the muscles. GSDII is caused by α-glucosidase or acid maltase deficiency in the lysosome membrane of muscle cells. Due to deficiency of the enzyme, glycogenaccumulatesin the lysosomeinall tissues, but specifically in the heart and muscle, resulting in muscle weakness. GSDII causes an increase in transaminase (ASAT, ALAT) and creatinekinase levels. The gene (GAA) that encodes the acid maltase is located on 17q25 chromosome. More than 80 mutations have been identified in the GAA. Prenatal diagnosis is possible by enzyme assay or DNA analysis of chorionic villi.

This disorder that occurs by the defect in a single enzyme manifests as three different clinical phenotypes: infantile, juvenile, and adult. The infantile form is generalized and usually fatal at age 1. The symptoms can include hypotonia and larged tongue [25]. The juvenile form starts either in infancy or in childhood, causes proximal, truncal, and respiratory muscle weakness. Myopathy deteriorates gradually leading to respiratory failure and death in the second or third decade of life. The adult form is also confined to muscle and mimics other myopathies with a long latent period. Decreased muscle strength and weakness develop in the third or fourth decade. Cardiac involvement is mild or absent. For diagnosis, blood tests will be done and also to assess

muscle disease exists, various factors will be examine such as levels of serum creatine kinase (CK).

Glycogen storage disease type IIb or danon disease: GSDIIb or pseudo-Pompe disease is caused by deficiency of LAMP-2 (lysosomal-associated membrane protein 2). In persons with Danon disease the LAMP2 gene is mutated and normal LAMP2 protein is no longer made. Danon disease is an X-linked dominant lysosomal storage disease.The gene that encodes LAMP2 is located on the long arm of the X chromosome (Xq28). It started after the first decade of life and is extremely rare and involves the skeletal and cardiac muscle. Acid maltase activity is normal and some patients have mental retardation. Asan exception, hemizygous women are also involved and show first symptoms of disease later in life [26].

Lafora disease: Lafora disease (LD), also called Lafora progressive myoclonic epilepsy or MELF, is characterized by the presence of inclusion bodies, known as Lafora bodies, within neurons and the cells of the heart, muscle ,liver, and skin. Major problems include seizures, dementia, and myoclonus. Patients develop the first symptoms during adolescence and the course is rapidly progressive. The pathologic hallmark of the disease is based on the demonstration of Lafora bodies (round, basophilic, PAS-positive inclusion bodies) within the cerebral cortex, substantianigra, globuspallidus, and thalamus. Lafora disease is an autosomal recessive disorder, caused by mutations in one of two known genes (EPM2A, EPM2B). Linkage and haplo type analyses exclude both loci. The EPM2A gene is located on chromosome 6q24 and about 30 pathogenic mutations have been identified. The protein encoded by EPM2A is laforin and play a role in the cascade of phosphorylation/dephosphorylation reactions that control glycogen synthesis and degradation. The EPM2B (NHLRC1) gene is located on chromosome 6p22.3 and encodes the protein malin. Recent studies suggest that another gene involves in the disease [27].

Conclusion

Genetic disorders that caused effects in enzymes of GSD are identifiable molecular genetics advances. Better understanding of these enzymatic disorders lead to develop effective nutritional therapies for this patient.

The lack of neonatal screening precludes reliable estimates of the incidence. According to studies in the Europe and United States, incidence glycogen storage diseases estimated 1 per 20,000-25,000 births. GSD type I with 24.6%, type II with 15.3%, type III with 24.2%, type IV with 3.3%, type V(2.4%), common glycogenosis (type VI) with 30% and type VII with 0.2% of patients with GSD are included.

Prenatal and postnatal diagnosis can be helpful to diagnosis and treatment of these diseases. Because most of these disorders are inherited as an autosomal recessive, consanguineous marriages can be increase incidence of this disease in families which have the defective allele of gene. We need to inform the parents before and after birth, marriage and family when the patient is felt to prevent the birth of children [28]. In addition, many studies have shown that proper diet can be effective in the treatment process of metabolic disease and there is a clear influence of environment on genetics [29-31].

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