زانکۆی سەلاحەدین - هەولێر
Salahaddin University-Erbil

Glycogen Storage Diseases

Submitted to the Chemistry Department-College of Education – Salahaddin University in partial fulfillment of the requirements for the degree of (BSc.) in chemistry

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Abstract

The glycogen storage diseases (GSDs) are a group of inherited metabolic disorders that result from a defect in any one of several enzymes required for either glycogen synthesis or glycogen degradation. The GSDs can be divided into those with hepatic involvement, which present as hypoglycemia, and those which are associated with neuromuscular disease and weakness. The severity of the GSDs ranges from those that are fatal in infancy if untreated to mild disorders with a normal lifespan. The diagnosis, treatment, and prognosis for the common types of GSDs are reviewed.

Diabetes mellitus is the most common metabolic disease in humans and is rising in prevalence in many places in the world, including China, where it has recently been reported as affecting 9.7% of the population. Neurological abnormalities in diabetic patients are common and involve both the central and peripheral nervous system.

Keywords: Glycogen storage disease, hypoglycemia, myopathy, review, cardiomyopathy, hepatic adenoma, Diabetes mellitus

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1. Chapter One

1.1. Introduction

The glycogen storage diseases (GSDs) are a group of inherited metabolic disorders that result from a defect in any one of several enzymes required for either glycogen synthesis or glycogen degradation. Broadly speaking, the GSDs can be divided into those with hepatic involvement, which present as hypoglycemia, and those which are associated with neuromuscular disease and weakness (Table 1). [Cantú-Reyna, C.; Santos-Guzmán, J.; Cruz-Camino, 2019]

The severity of the GSDs ranges from those that are fatal in infancy if untreated to mild disorders with a normal lifespan. While some forms of GSD affect a single tissue type (for example, skeletal muscle in McArdle disease), others affect multiple systems. The GSDs have traditionally been diagnosed using a combination of clinical symptoms, biochemical results, and pathology findings. Standard studies performed by the pathologist include muscle or liver histology findings in combination with electron microscopy and enzyme studies. Depending on the specific GSD, enzyme deficiency may be detected in liver, muscle, skin fibroblasts, and, rarely, blood cells. Within the last decade, DNA mutation analysis has become the primary method for diagnosing glycogen storage disease. While such testing was initially performed to complement enzymatic activity studies and clarify ambiguous results, such testing is now becoming the gold standard to confirm a suspected diagnosis. The benefits of such testing are numerous and include the following:

• Molecular analysis obviates the need for invasive biopsy.

• Unlike enzyme studies which may require a significant amount of fresh frozen tissue, DNA-based

testing does not usually require extremely careful handling of sensitive specimens.

• DNA mutation analysis can be used for prenatal diagnosis. [Champe P.C. and Harvey R.A.,2014]

Table 1
Summary of the glycogenoses

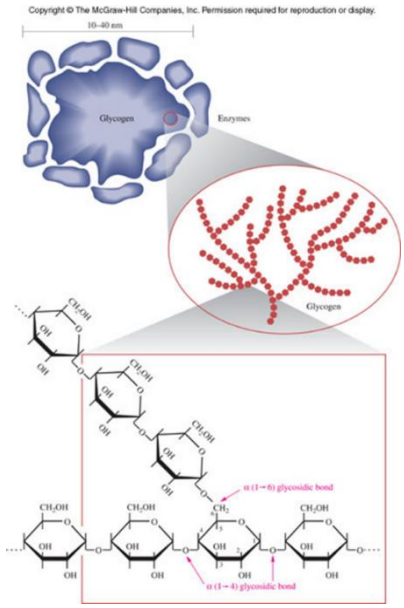
GSD Type	OMIM# (Online Mendelian Inheritance in Man)[1]	Enzyme/Protein Deficiency	Gene	Chromosome Location	Mode of Inheritance	Main Presentation: Hepatic vs. Neuro-muscular?
GSD Ia	232200	Glucose-6-phosphatase-α catalytic subunit	*G6PC*	17q21.31	Autosomal recessive	Hepatic
GSD Ib	232220	Glucose-6-phosphate transporter	*SLC37A4*	11q23.3	Autosomal recessive	Hepatic
GSD II	232300	α-1,4 glucosidase	*GAA*	17q25.3	Autosomal recessive	Neuro-muscular

Table 2
Presentation of hepatic glycogen storage disease

Type	Enzyme	Presenting Symptoms
I	Glucose-6-Phosphatase	Hypoglycemia FTT /developmental delay Hepatomegaly
III	Debranching	Hepatomegaly Hypoglycemia Hepatitis
VI	Phosphorylase	Hepatomegaly Ketotic Hypoglycemia

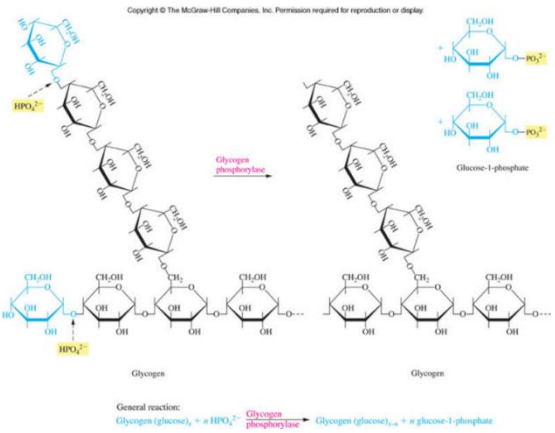
1.2.Structure of Glycogen

Glycogen is a highly branched α(1→4) and α(1→6) polymer of glucose Exists as granules found in cytoplasm of liver and muscle cells



1.3. Action of Glycogen Phosphorylase

Glycogen phosphorylase breaks up glycogen into glucose subunits (see also figure below): (α-1,4 glycogen chain)n + Pi ⇌ (α-1,4 glycogen chain)n-1 + α-D-glucose-1-phosphateGlycogen is left with one fewer glucose molecule, and the free glucose molecule is in the form of glucose-1-phosphate. In order to be used for metabolism, it must be converted to glucose-6-phosphate by the enzyme phosphoglucomutase. Although the reaction is reversible in vitro, within the cell the enzyme only works in the forward direction as shown below because the concentration of inorganic phosphate is much higher than that of glucose-1-phosphate. .[Livanova NB, Chebotareva NA, Eronina TB, Kurganov BI (October 2012)]



1.4.Diabetes mellitus

Diabetes mellitus refers to a group of diseases that affect how the body uses blood sugar (glucose). Glucose is an important source of energy for the cells that make up the muscles and tissues. It's also the brain's main source of fuel.

The main cause of diabetes varies by type. But no matter what type of diabetes you have, it can lead to excess sugar in the blood. Too much sugar in the blood can lead to serious health problems.

Chronic diabetes conditions include type 1 diabetes and type 2 diabetes. Potentially reversible diabetes conditions include prediabetes and gestational diabetes. Prediabetes happens when blood sugar levels are higher than normal. But the blood sugar levels aren't high enough to be called diabetes. And prediabetes can lead to diabetes unless steps are taken to prevent it. Gestational diabetes happens during pregnancy. But it may go away after the baby is born. [Ferri. FF,2022]

1.4.1.Type 1 diabetes

Once known as juvenile diabetes or insulin-dependent diabetes, is a chronic condition. In this condition, the pancreas makes little or no insulin. Insulin is a hormone the body uses to allow sugar (glucose) to enter cells to produce energy.

Different factors, such as genetics and some viruses, may cause type 1 diabetes. Although type 1 diabetes usually appears during childhood or adolescence, it can develop in adults.

Even after a lot of research, type 1 diabetes has no cure. Treatment is directed toward managing the amount of sugar in the blood using insulin, diet and lifestyle to prevent complications. [Papadakis, MA . et al,2022]

1.4.2.Causes of type 1 diabetes

Type 1 diabetes is an autoimmune condition, where the immune system (the body's natural defence against infection and illness) mistakes the cells in your pancreas as harmful and attacks them. Without insulin, your body will break down its own fat and muscle, resulting in weight loss. This can lead to a serious short-term condition called diabetic ketoacidosis. This is when the bloodstream becomes acidic, you develop dangerous levels of ketones in your blood stream and become severely dehydrated. This results in the body being unable to produce insulin, which is required to move glucose out of the blood and into your cells to be used for energy. [Papadakis, MA .2022]

1.4.3.Symptoms of type 1 diabetes

The symptoms of type 1 diabetes should disappear when you start taking insulin and you get the condition under control.

The main symptoms of diabetes are:

- feeling very thirsty
- urinating more frequently than usual, particularly at night
- feeling very tired
- weight loss and loss of muscle bulk
- itchiness around the genital area, or regular bouts of thrush (a yeast infection)
- blurred vision caused by the lens of your eye changing shape[Papadakis, MA.2022]

1.4.2. Type 2 diabetes

Type 2 diabetes is an impairment in the way the body regulates and uses sugar (glucose) as a fuel. This long-term (chronic) condition results in too much sugar circulating in the bloodstream. Eventually, high blood sugar levels can lead to disorders of the circulatory, nervous and immune systems.

In type 2 diabetes, there are primarily two interrelated problems at work. Your pancreas does not produce enough insulin — a hormone that regulates the movement of sugar into your cells — and cells respond poorly to insulin and take in less sugar.

Type 2 diabetes used to be known as adult-onset diabetes, but both type 1 and type 2 diabetes can begin during childhood and adulthood. Type 2 is more common in older adults, but the increase in the number of children with obesity has led to more cases of type 2 diabetes in younger people.

There's no cure for type 2 diabetes, but losing weight, eating well and exercising can help you manage the disease. If diet and exercise aren't enough to manage your blood sugar, you may also need diabetes medications or insulin therapy. [Feldman, et al. M.,2022]

1.4.2.1.Symptoms of type 2 diabetes

The symptoms of diabetes include feeling very thirsty, passing more urine than usual, and feeling tired all the time. The symptoms occur because some or all of the glucose stays in your blood and isn't used as fuel for energy. Your body tries to get rid of the excess glucose in your urine.

The main symptoms of type 2 diabetes are:

- urinating more often than usual, particularly at night
- feeling very thirsty
- feeling very tired

- unexplained weight loss
- itchiness around the genital area, or regular bouts of thrush (a yeast infection)
- cuts or wounds that heal slowly
- blurred vision – caused by the lens of the eye becoming dry [Papadakis, MA. 2022]

1.4.2.2.Causes of type 2 diabetes

Type 2 diabetes occurs when the pancreas doesn't produce enough insulin to maintain a normal blood glucose level, or the body is unable to use the insulin that is produced (insulin resistance). The pancreas is a large gland behind the stomach that produces the hormone insulin. Insulin moves glucose from your blood into your cells, where it's converted into energy.In type 2 diabetes, there are several reasons why the pancreas doesn't produce enough insulin. [Papadakis .MA 2022]

1.5_ Overview of glycogen metabolism and glucose homeostasis

Glucose is the preferred energy source of the brain. Thus, a constant source of blood glucose is essential for human life. Blood glucose can be obtained from three primary sources: diet, degradation of glycogen, and gluconeogenesis. Because dietary intake of glucose (and glucose precursors) is sporadic and gluconeogenesis cannot occur in rapid response to falling blood glucose levels, glycogen serves as a means for storing glucose in a form that can be readily mobilized

Glycogen is a branched-chain homopolysaccharide synthesized from _-D-glucose molecules. . In the absence of dietary glucose, liver glycogen is rapidly broken down to glucose and released into the blood; similarly, skeletal muscle glycogen is degraded and used to generate ATP for muscle contraction. When glycogen stores are depleted, gluconeogenesis can occur in specific tissues, allowing synthesis of glucose de novo using amino acids from protein along with lactate from both the kidney and muscles. [Champe P.C. and Harvey R.A.,2013)

1.6. Glycogen storage disease type I

Glycogen storage disease type I, also known as von Gierke disease, is an inborn error of metabolism due to deficiency of the glucose-6-phosphatase complex. This multi component complex, referred to at the G6Pase system, or G6Pase-α, was hypothesized by Arion et al. to consist of four separate proteins, including the G6Pase-α catalytic subunit (G6PC), the glucose-6-phosphate transporter (G6PT), an inorganic phosphate transporter, and a glucose transporter There are at least two known forms of GSD type I: GSD Types Ia and Ib; these are due to defects in the G6PC and G6PT, respectively. The existence of a third and fourth type, GSD Types Ic and Id, have been largely debated since they do not differ from GSD Type Ib clinically, enzymatically, or genetically. Approximately 80% of GSD Type I cases are of the Type Ia variety and result from mutations in the G6PC gene which encodes the glucose-6-phosphatase-α catalytic subunit (G6PC =OMIM 613742). Almost all other remaining cases (GSD Type Ib) are due to mutations in the SLC37A4 gene encoding the glucose-6-phosphate transporter (G6PT =OMIM 602671). 6.[Veiga.da-Cunha, Gerin. Chen, (2018),]

1.6.1.Glycogen storage disease type Ia

GSD Ia (OMIM 232200) was the first inborn error of metabolism proven to be caused by an enzyme deficiency. In 1952, Gerty and Carl Cori demonstrated deficiency of glucose-6-phosphatase activity in liver homogenate from five patients with a clinical diagnosis of von Gierke disease In two of these cases, which were fatal, there was virtual absence of enzyme activity. The glucose-6-phosphatase-catalytic subunit is expressed in the liver, kidneys, and intestinal mucosa. It is the key enzyme in homeostatic regulation of blood glucose levels, and GSD type Ia has the distinction of being the only glycogen storage disease to be both a disorder of glycogenolysis and gluconeogenesis. [Harper, Harper, PS 2014, p. 187] **Name of authors not book??????**

1.6.2.Clinical presentation

Affected individuals usually present in the first year of life with severe fasting hypoglycemia, hepatomegaly, failure to thrive, growth retardation, and developmental delay. Other common findings related to hypoglycemia include sweating, irritability, muscle weakness, drowsiness, and seizures. Symptoms usually become apparent as infants are weaned from frequent feeds. In addition to severe fasting hypoglycemia, biochemical studies reveal hyperlactatemia, hyperuricemia, and hypertriglyceridemia. Children often experience bruising and epistaxis due to impaired platelet function, and normochromic anemia may be present. Children with GSD type Ia develop a markedly protuberant abdomen due to massive stores of liver glycogen. The spleen, however, remains normal in size and cirrhosis does not develop. Other physical findings include truncal obesity, doll-like facies, short stature, and hypotrophic muscles. With optimal metabolic control, the hepatomegaly improves and growth normalizes. Complications including hepatic adenomas, osteoporosis, focal segmental glomerulosclerosis, and a small fiber neuropathy used to be common in the 2nd and 3rd decades of life, but the frequency of these complications has markedly decreased with improvements in therapy and good metabolic control, [Wang, D.Q Carreras, C.T. Fiske L.M. (2012)]

1.6.3.Genetics

GSD Type Ia has a disease incidence of approximately 1 in 100,000 births and a carrier rate of approximately 1 in 150. The disorder is found in ethnic groups from all over the world, and the disease is more common in people of Ashkenazi Jewish, Mormon, Mexican, and Chinese heritage. The disorder is associated with mutations in the G6PC gene on chromosome 17q21 which encodes the glucose-6-phosphatase-α catalytic subunit. GSD Ia has classic autosomal recessive inheritance. G6PC spans 12.6 kilobases and is composed of five exons which encode for a hydrophobic, endoplasmic reticulum (ER)-associated glycoprotein [Ekstein, J. Rubin, B.Y . Anderson S.L. (2013),]

1.6.4.Pathology

While liver biopsies are no longer required for diagnosing this condition, glycogen filled hepatocytes with prominent steatosis are seen in GSD type Ia. Unlike other forms of GSD, however, fibrosis and cirrhosis do not occur. Hepatocellular carcinoma appears to arise from inflammatory adenomas, and chromosomal alterations have been described in the cancerous lesions with proto-oncogene activation leading to dysregulation of insulin-glucagon-growth hormone signaling [Kishnani, P.S. Chuang, T.P. Bali, D. (2019),].

1.7.Glycogen storage disease type II – Pompe disease

Glycogen storage disease type II (acid maltase deficiency, or Pompe disease) (OMIM 232300) is caused by a deficiency of α -1,4 glucosidase, an enzyme required for the degradation of lysosomal glycogen The disorder was initially described by Johannes Pompe in 1932 [J. Pompe (2012)]. It is the only form of GSD to be classified as a lysosomal storage disorder. Pompe disease is purely a neuromuscular form of GSD which does not present with metabolic abnormalities because the lysosomal enzyme defect lies outside of intermediary metabolism. Instead, storage of glycogen occurs mainly in skeletal muscle and leads to loss of muscle function. [Hers, H.G. (2013)].

1.7.1.Clinical presentation

Pompe disease has a broad clinical spectrum with variable age of onset, severity of symptoms, and rate of disease progression. The disorder encompasses a continuum of phenotypes ranging from a rapidly progressive infantile form to a slowly progressive late-onset form. In general, however, Pompe disease is classified into three different subtypes, including infantile, juvenile, and adult forms. There is clinical correlation with the amount of α-1,4-glucosidase expression: residual enzyme activity is found in the adult form, while enzyme activity is completely absent in the severe infantile form. It is important to note that mental development and blood glucose concentrations are normal in all forms of Pompe disease.

The classic infantile form is the most severe. Affected infants present shortly after birth with profound hypotonia, muscle weakness, and hyporeflexia. An enlarged tongue and hypertrophic cardiomyopathy are characteristic. Diagnosis may be based on typicalEKGfindings which include largeQRScomplexes and shortened PR intervals [P.S. Kishnani, R.D. Steiner, D. Bali, et al (2016)]. The liver is normal in size. Sensorineural hearing loss is also prevalent and a less recognized feature [Hermans, M.M. van Leenen, D. Kroos M.A., (2014). Huie, M.L. Chen, A.S. Tsujino, S. (2014)].

1.7.2.Genetics

The incidence of Pompe disease is estimated to be approximately 1 in 40,000 to 1 in 50,000. The disorder can be found in ethnically diverse populations, including European Caucasians, Hispanics, and Asians, and several mutations are more common in some populations due to founder effects. For more information, the reader is referred to the Pompe Disease Mutation Database at www.pompecenter.nl/.α-1,4-glucosidase is encoded by the GAA gene located on the long arm of chromosome 17 at 17q25.3 The gene is composed of 20 exons and over 350 different mutations have been reported . Of note, while most mutations will be picked up by gene sequencing, at least 11 different gross deletions and one gross insertion have been reported which would not be detectable using this method [Cooper, D.N. Ball, E.V. 2012.]. Prenatal diagnosis is possible via enzyme assay or DNA analysis of chorionic villi obtained between 10–12 weeks gestation. There appears to be genotype-phenotype correlation, with specific mutations associated with infantile, juvenile, and adult-onset disease. Severe mutations which lead to complete loss of enzyme activity are associated with severe, infantile Pompe disease, while mutations which allow partial enzyme expression are associated with adult-onset disease. One very common mutation in intron 1 of the GAA gene, defined as c. -32-13 T>G, has been found in almost two-thirds of patients with adult-onset disease.This particular mutation affects pre-mRNA splicing but allows for correct splicing approximately 10% of the time. Affected individuals who are compound

heterozygotes for this particular mutation plus a null allele show approximately 5% of normal enzyme activity [Kroos, M.A. Pomponio, R.J. (2017).].

1.7.3.Pathology

The site of glycogen accumulation is different for all three forms of Pompe disease. Furthermore, the amount varies greatly in different organs and even in different muscles [Fernandes, J.2012]. Histological examination of muscle will reveal large glycogen-filled vacuoles as well as freely dispersed glycogen outside the lysosomes. As lysosomes accumulate with glycogen, cell function becomes impaired. Mutation analysis is now the preferred method of diagnosis. Enzymatic studies can be performed, however, on muscle tissue or fibroblasts. It is imperative that α-1,4-glucosidase, also known as acid maltase due to its optimum pH lying between 4.0 and 4.5, be differentiated from neutral maltase found in the cytoplasm. Acid maltase is initially an inactive enzyme that is transported to the prelysosomal and lysosomal compartment via the mannose-6-phosphate receptor The enzyme is eventually processed into a fully active form that normally degrades glycogen that enters lysosomes via autophagy. Deficiency of enzyme causes glycogen to overload the lysosomal system and leads to progressive and irreversible cellular damage.

4.Glycogenoses types III and IV – disorders of abnormally structured glycogen

Glycogenoses types III and IV are clinically heterogeneous disorders caused by buildup of abnormally structured glycogen in the liver and muscle.

1.8. GSD type III – Cori disease

Glycogen storage disease type III (Cori disease or Forbes disease) (OMIM 232400) was initially discovered in 1952 when a patient being followed by Dr. Gilbert Forbes was found to have excessive amounts of abnormally structured glycogen in liver and muscle tissue. Type III GSD varies widely in clinical presentation and can be divided into two

types: type IIIa, with both hepatic and muscle involvement, and type IIIb, which primarily presents with liver disease [Kishnani, P.S. Austin, S.L. Arn P. (2012).]. Both GSD IIIa and GSD IIIb result from an enzyme deficiency in the glycogen debranching enzyme (GDE). This enzyme is encoded by the AGL gene located on chromosome 1p21.

1.8.1.Clinical presentation

GSD type III is a phenotypically heterogeneous disorder with a wide clinical spectrum. While patients with GSD type IIIb mainly present with hepatic findings, affected individuals with type IIIa have both liver and muscle involvement. For. both IIIa and IIIb, liver disease predominates in infancy and early childhood including hepatomegaly, hypoglycemia, hyperlipidemia, and growth retardation. For those with type IIIa GSD, there is additional variable skeletal and/or cardiac myopathy which often, though not always, may be detected via elevated serum CK concentrations once children are ambulating. Mild hypotonia and delayed motor development are usually the only manifestation during early childhood. By late childhood and adolescence, decreased stamina and pain with exertion can be noted. Muscle wasting is slowly progressive in adulthood and may be severe by the 3rd or 4th decade of life Although ventricular hypertrophy is a frequent finding, symptomatic cardiomyopathy leading to death is relatively rare. Unlike muscle disease which is a progressive process, the hypertrophic cardiomyopathy is reversible and appears to be due to excessive storage of glycogen. With a diet restricting intake of simple sugars, the hypertrophic cardiomyopathy can resolve and cardiac function normalize. [Demo, E. Frush, D. Gottfried, M. (2017).].

1.8.2. Genetics

GSD Types IIIa and IIIb are autosomal recessive allelic disorders caused by mutations in the AGL gene on the short arm of chromosome 1.The incidence of GSD III is estimated to be 1 in 100,000 live births, but high risk populations have been identified. Unusually high rates of GSD IIIa occur in the First Nation of Canada and on the Faroe

Islands where there are carrier frequencies of 1: 18 and 1 : 22, respectively . GSD IIIa is also more common on the Indian subcontinent (India, Pakistan, Afghanistan). Type IIIb accounts for 15% of all GSD III, and it is unusually frequent in Jews of Northern Africa (carrier frequency of 1: 35) . To date, at least 140 different pathogenic AGL mutations have been reported [Cooper, D.N. Ball, E.V. Stenson, P.D. 2012].

1.8.3. Pathology

The encoded enzyme, glycogen debranching enzyme (GDE), together with glycogen phosphorylase, is responsible for the complete degradation of glycogen. GDE has a presumed glycogen binding site at the carboxy terminal end, as well as two separate sites responsible for independent catalytic activities. These activities include 4-α-glucano transferase activity (1,4-α-D-glucan 1,4-α-D-glucan 4-α -D glycosyltransferase activity) responsible for the transfer of three glucose units to the outer end of an adjacent chain, and an amylo-1,6-glucosidase activity responsible for hydrolysis of branch point glucose residues. The variable phenotype seen in GSD type III is partly explained by differences in tissue-specific expression. When the enzyme is deficient in both liver and muscle, GSD type IIIa results; in contrast, when AGL is deficient only in the liver and enzyme activity is retained in muscle, then GSD type IIIb results. Rare cases have also been reported where only one of two GDE catalytic activities is lost [Van Hoof F. and Hers, H.G. (2017). Sugie, H. Fukuda, T. Ito, (2012).]. When there is loss of only glucosidase activity, the patient is classified as having GSD Type IIIc, and when there is only loss of transferase activity, the patient is classified as having GSD type IIId.

2.Chapter Two

2.1.Diagnosis for type I

The diagnosis of GSD is based on clinical signs and/or symptoms related to hypoglycemia and hepatomegaly. Laboratory parameters such as increased lactate level (in GSD type I), 1-elevated level of serum cholesterol and triglycerides and

hypertransaminasemia are helpful in diagnosis establishment. The key point is to differentiate between GSD type I and so-called ketotic types (III/VI/IX). Symptoms in GSD I typically present earlier (in the first few months of life) with severe fasting hypoglycemia within 3–4 h after feeding. Hypoglycemia is usually less severe in patients with GSD III/VI/IX due to the intact process of gluconeogenesis [Clayton PT. (2003)].

2-Blood lactate levels increase rapidly in GSD I as blood glucose (BG) concentrations decrease to levels that normally trigger a counter-regulatory response (< 70 mg/dl or 4 mmol/l) and are markedly increased when BG levels decrease to < 40–50 mg/dl or 2.2–2.8 mmol/l).

3-Blood β-hydroxybutyrate levels increase only modestly in GSD I, in contrast to marked hyperketonemia with fasting hypoglycemia characteristic of GSD 0, III, VI, and IX [Fernandes J, Pikaar NA. (2012)].

2.2.Diagnosis for type I I

1-An enlarged liver

2- low blood sugar with high levels of ketones test

3-transaminases test

4-lipids and creatine kinase test

is indicative of GSD-III.

5- Uric acid and fasting lactic acid levels test

are usually normal. In GSD-IIIb creatine kinase can be normal.

6-Molecular genetic testing for mutations in the AGL gene can be used to confirm the diagnosis. Nowadays

7-, liver and muscle biopsies are uncommon. In many countries besides the United States,

8-studies in blood cells and skin fibroblasts are clinically available to confirm GDE deficiency. [.Endo, Y Horinishi, A . Vorgerd, M. 2014]

2.3. Diagnosis for type III

diagnosis of GSD III A diagnosis of GSD III is based on: (i) demonstration of excessive and structurally abnormal glycogen accumulation with shorter outer branches and deficient debranching enzyme activity in frozen liver and/or muscle biopsy samples or (ii) identification of pathogenic mutations in the AGL gene on both alleles. [Shen, JJ . Chen YT. 2012]

3.Chapter three

3.1. Treatment for type I

Dietary treatment has immensely improved prognosis. The aim of treatment is to prevent hypoglycemia and counter-regulation thereby minimizing the secondary metabolic derangements. Therapy may consist of continuous gastric tube feeds or uncooked cornstarch may be used depending on the age of the child and patient/family preferences.

3.2Treatment for type II

Treatment guidelines for patients withGSDIb are similar to those forGSDIa with the addition of therapy for the neutropenia and GSD enterocolitis. Recombinant human granulocyte-colony-stimulating factor (GCSF), a cytokine cells into mature neutrophils, should be used to treat neutropenia if infections, severe mouth ulcers, or that induces proliferation and differentiation of bone marrow precursor chronic diarrhea are occurring. The GSD Ib population has been prone to untoward effects (massive splenomegaly, splenic sequestration, splenic rupture, and portal hypertension) with

GCSF therapy. Therefore, a starting dose of 2.5 micrograms/kg/day is recommended, and the lowest dose that controls infections should be used [Kishani, P.S. Austin, S.L. Abdenur, J.E. (2014)].

3.3.Treatment for type III

While glycogenolysis is impaired inGSDIII, gluconeogenesis is intact allowing lactate, amino acids, and glycerol (from fatty acid oxidation) to be used to maintain blood glucose concentrations. Protein is used as the primary source of energy in GSD type III since it also can be used directly by the muscles and has been associated with improvement in the myopathy. A diet with 3-4 grams/kg of protein is recommended through dietary therapy which is dosed to maintain blood glucose concentrations above 70 mg/dL and beta-OH-butyrate concentrations less than 0.3 mmol/L. The frequency of cornstarch doses varies with age. In infancy, frequent cornstarch administration may be required with therapy similar to that used inGSDtype I.With older children and adults, cornstarch frequently is only required 2-3 times per day, and sometimes it is only administered prior to bedtime. For patients with moderate to severe hypertrophic cardiomyopathy, a high-protein nocturnal enteral therapy may be beneficial. Intake of simple sugars is limited to 5 grams per meal to minimize postprandial hyperinsulinemia and avoid over-storage of glycogen protein and supplements [Kishnani, P.S. Austin, Arn P. S.L. (2014)].

3.4.Relation between glycogen storage disease and diabetes

Glycogen storage disease type Ia is a genetic disorder that is associated with persistent fasting hypoglycemia and the inability to produce endogenous glucose. The development of diabetes with glycogen storage disease is exceedingly rare. The underlying pathogenesis for developing diabetes in these patients is unclear, and there are no guidelines for treatment. [Rajas, Labrune, F. 2013]

3.5.Conclusion

The glycogen storage diseases represent a clinically heterogeneous group of disorders that usually become apparent in early infancy and reflect the consequences of a deficiency of enzymes essential for the normal synthesis and degradation of glycogen. The symptomatology depends primarily on the organs that are involved in the enzymatic defect. Most diseases with primarily hepatic involvement manifest abnormalities in glucose homeostasis, whereas those types with enzyme deficiency in muscle present with muscle weakness, cramps and frequently myoglobinuria. In the former group, most of the physical findings and metabolic alterations can be explained on the basis of the primary defect in maintenance of a normal blood glucose. Most of these diseases appear to be inherited as autosomal recessives and many of them become less severe as the child gets older. Although the specific type of glycogen storage disease may be indicated by the clinical presentation and the results of certain functional tests, conclusive diagnosis can be established only by enzyme assay of the involved tissue.

3.6. Recommendation Of Glycogen Storage Disease

GSDs type 0, IV, VI, IX and XI with liver involvement may have a similar clinical presentation. However, these diseases exhibit a phenotypic continuum, and even in the mildest forms, regular monitoring and dietary adjustments are necessary to restrain disease progression and complications. Some cases may exhibit a clinical burden with severe organ complications. Building a proper knowledge among physicians about these rare conditions is crucial to improve prognosis and quality of life of patients, especially those affected by the most severe forms. Further studies are needed to outline the genotype–phenotype correlation and define personalized therapies and management.

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