

A BEGINNERS' GUIDE TO CORI'S DISEASE

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ABSTRACT

Diseases that are related to the metabolism of Glycogen are called Glycogen Storage Diseases. These diseases are genetically inherited disorders that can be categorized into 10 subtypes depending on the deficiency or improper functioning of a particular enzyme. The deficiency of Glycogen debranching enzyme causes several malfunctions in the body that are particularly characterized under the reference of GSD type-III or Cori's disease or Forbe's disease. The main symptoms include hypoglycemia, hepatomegaly, weight loss etc. This disease can be significantly divided into four subtypes depending on the phenotypic variability of the gene. Types IIIa and IIIb are more common, other types include IIIc and IIId. Also, the extent or the severity of the disease can vary according to the type of tissues in which glycogen is deposited i.e., hepatic, cardiac, skeletal or gastrointestinal. The only possible way to control the disease is through proper intake of proteins, carbohydrates, and fats.

KEYWORDS: Diseases that are related to the proteins, carbohydrates, and fats.

Introduction to Glycogen Storage Diseases

Glycogen storage diseases (GSD's) are caused by the inherited metabolic disorder which results in the inefficiency of specific enzymes that are responsible for the metabolic anabolism or catabolism of the glycogen. This defect can be divided into either hepatic disorder such as hypoglycemia or neuromuscular disease and weakness. It was stated by Fernandes in 1995 that first clinical description of a patient with glycogen storage disease in a 7 years old child was stated by Van Creveld in the year 1928, the patient markedly had a large liver, obesity and small genitalia. Von Gierke was the first one to report (GSD 1) in 1929, the observation at necropsy of the accumulation of glycogen in the liver of two patient; since then there has been remarkable changes in the metabolic pathways of glycogen and has divided the glycogen storage disease in at least 12 types as shown in Table 1 (Ryman, 1974). Glycogen disorders either effect muscle or liver respectively or both of them (Ozen et al., 2000). Our focus will be on the GSD III which can be further subdivided into GSD IIIa which involves the both liver and muscle, and GSD IIIb involves solely the liver, these both disorders are caused by the deficiency of glycogen debranching enzyme which includes 4-alpha-glucanotranferase and amylo-1,6-glucosidase. The intensity of GSDs can result in being fatal in infancy or can cause mild disorder while the person lives a normal life. Either they will affect the single tissue or the multi system depending on the type

of disorder. These disorders are diagnosed by biochemical tests, clinical symptoms, pathology results which are followed by enzymatic studies thus finding out the enzyme deficiency in muscle, liver, skin fibroblasts and blood cells. GSDs can also be diagnosed by inferring the genetic variation, it is considered to be the Gold standard now days to confirm the diagnostic results. The benefits it has over the other diagnostic tests are that there is no more need for the invasive biopsy, fresh frozen tissues are not required as in the case of enzymatic studies, extremely careful handling is not required, DNA mutation analysis can also be useful for the parental diagnosis as in to study the inheritance of GSD (Chen, 2016).

Table 1: Glycogen Storage Diseases.

Type	Name	Enzyme Deficient	Clinical Features
0		Glycogen synthase	Hypoglycemia, hyperketonemia; early death
Ia	Von Gierke's disease	Glucose-6-phosphate	Glycogen accumulation in liver and renal tubule cells; hypoglycemia; ketosis; lactic acidemia; hyperlipidemia.
Ib		Endoplasmic Reticulum glucose 6-phosphate transporter	Neutropenia and impaired neutrophil function leading to infections (As type Ia)
II	Pompe's disease	Lysosomal $\alpha_1 \rightarrow 4$, $\alpha_1 \rightarrow 6$ glucosidase	Glycogen accumulation in lysosome; juvenile onset variant, muscle dystrophy, heart failure by age 2
IIIa	Limit dextrinosis, Forbe's or Cori's disease	Liver and muscle debranching enzyme	Fasting hypoglycemia; hepatomegaly in infancy; branched polysaccharide accumulation; muscle weakness
IIIb	Limit dextrinosis	Liver debranching enzyme	As type IIIa, but no muscle weakness
IV	Andersen's disease	Branching enzyme	Hepatosplenomegaly; accumulation of polysaccharide with few branch points; death from heart or liver failure before age 5.
V	McArdle's syndrome	Muscle phosphorylase	Poor exercise tolerance; muscle glycogen abnormally high (2.5%-4%); low blood lactate after exercise; hemolytic anemia
VI	Her's disease	Liver phosphorylase	Hepatomegaly; accumulation of glycogen in liver; mild hypoglycemia; generally good prognosis
VII	Tauri's disease	Muscle and erythrocyte phosphofructokinase 1	Poor exercise tolerance; muscle glycogen abnormally high (2.5%-4%); low blood lactate after exercise; hemolytic anemia
VIII		Liver phosphorylase kinase	Hepatomegaly; glycogen accumulation in liver; mild hypoglycemia, generally good prognosis.
IX		Liver and muscle phosphorylase kinase	Hepatomegaly; glycogen accumulation in liver; mild hypoglycemia, generally good prognosis.
X		cAMP-dependent protein kinase A	Hepatomegaly; glycogen accumulation in liver

Glycogen Metabolism

Glycogen is the main polypeptide used as the reserve carbohydrate especially humans and is analogous to starch reserve of plants. Glycogen is a polypeptide branched chain which is synthesized of alpha-1,4 glucose units and branching of 1, 6 linkages. Since, it has a higher molecular weight thus exerting minimal osmotic pressure in comparison to single unit. Due to its branching it is highly soluble and it becomes easier for the exo-enzymes to attack it and degrade it. All mammalian cells have the capacity to form and degrade the glycogen according to the needs, it is abundant in liver and muscles. As the chain of the glycogen grows by sequential addition of alpha-1,4 glucose units, branching is introduced by the breaking of segments of growing outer chains and creating 1,6 links. Elongation is achieved by the synthetase enzyme and branching enzyme. On contrary degradation is done by the enzyme phosphorylase which acts on the sequential chain of 1,4 linkage to give glucose 1-phosphate. This process is continued by the enzyme until it reaches the branch point where it loses the affinity to further degrade, this is known as limit dextrin of phosphorylase as shown in Fig 1(a). Now debranching can be done at the 1,6 linkages by the transferase followed by debranching enzyme which converts the 1,6 linked glucose to glucose units as

shown in Fig 1(b). Once the branch point is removed again phosphorylase can act to shorten the length until new branch point is encountered.

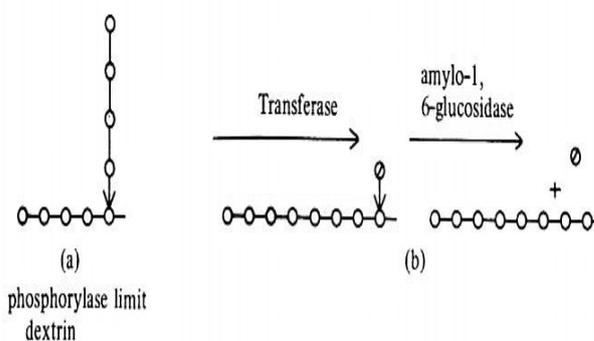


Figure 1: (a) Glycogen molecule after phosphorylase action. (b) Action of debranching enzyme.

The enzymes shown below in the Figure 2 are the ones whose absence, due to the genetic fault, leads to an abnormal accumulation of glycogen. At an average 12 glucose units are linked with 1,4 linkages sequentially till the branch point, but if there is a genetic flaw, for example type 3 glycogen storage disease, where the function of debranching enzyme is lost thus forming a

phosphorylase dextrin, where the outer chains of glycogen molecule will be very short. (Ryman, 1974).

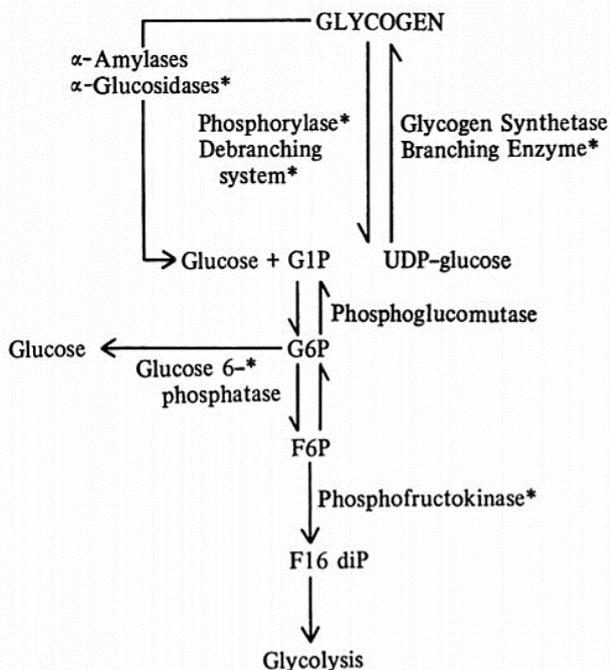


Figure 2: Enzymes involved in biosynthesis and oxidation of Glycogen.

glycogen debranching enzyme (GDE) which is encoded by the AGL gene present on chromosome 1p21 as mentioned in Figure 3. This disease can be subdivided in GSD IIIa, accounting for the 80% of patients who were reported to have glycogen disorder in both muscle and liver and GSD

IIIb accounting for 15% of glycogen disorder only in liver. Symptoms common are short stature, hepatomegaly, hypoglycemia and dyslipidemia. Only patients with type IIIa have myopathy or cardiomyopathy which can be frequently but not always, detected by elevated serum CK concentrations once the child is ambulating (Talente et al., 1994).

Liver can be affected in various ways by this GSD III. In childhood, hepatomegaly is identified where there is elevation of liver enzymes (ALT, AST) thus causing hepatocellular damage. Accumulation of glycogen and presence of periportal septal fibrosis thus showing enlarged liver or distention of hepatocytes (Coleman, et al. 1992). Hepatic involvement is considered mild and not really long lasting; condition improves with age whereas the major cause of concern is muscles disease. Muscle wasting is progressive slowly as the age increases, might get severe by the third or fourth decade of life. During early childhood the only manifestation is mild hypotonia delayed motor development (Sentner, et al. 2016). Although in some cases even the liver diseases are known to proliferate with increasing age for example liver cirrhosis, liver adenomas, some proving to be fatal (Labrune, et al. 1997). However, in some cases hepatic symptoms might not be seen until adulthood when the patient shows sign of neuromuscular disease. Clinical assays has shown that glycogen content is increased in 3 to 5 times in GSD type III and glycogen appears structurally abnormal, this marks as a differential factor among other GSD types, where there might be elevated glycogen content but does not have an abnormal glycogen structure (Mairie, et al. 1991). Selective enzyme deficiencies correlation with liver and muscle is not yet clearly understood. GDE levels has been studied in blood cells, western blotting has been used to study the absence of GDE protein in white blood cells, red blood cells, lymphoblastoid cells and in skin biopsy samples (Mairie, et al. 1986).

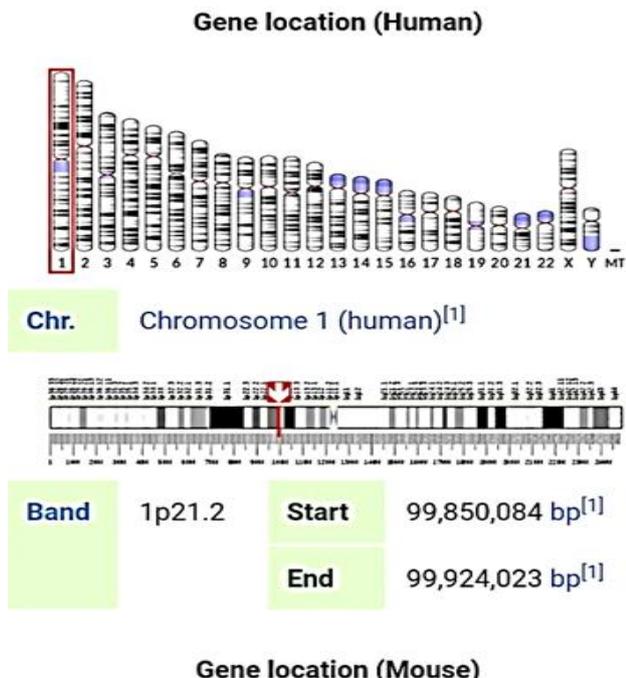


Figure 3 AGL gene locus in human and mouse genomic library.

Cori's Disease

Glycogen storage disease III also known as Cori disease, AGL deficiency, de-brancher enzyme deficiency, Forbes disease, limit dextrinosis, glycogen debrancher deficiency. This was first discovered in 1952 by Dr. Gilbert Forbes. This is caused by the deficiency in the

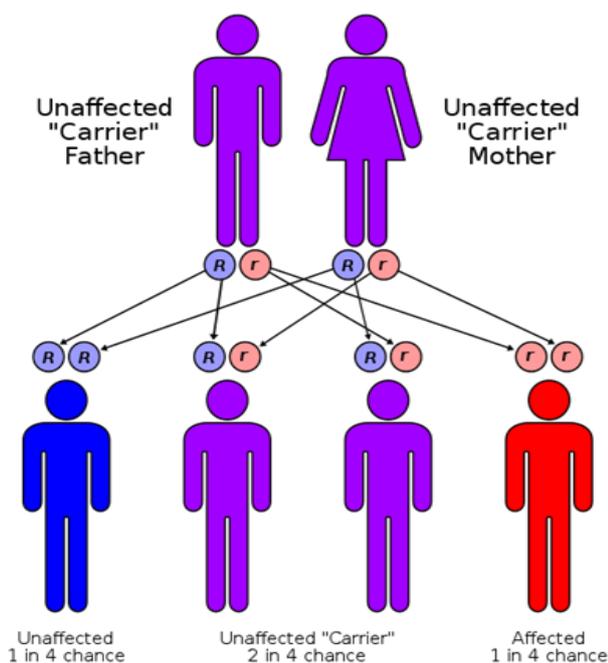


Figure 4: Inheritance pattern of Autosomal Recessive Disorder.

Treatment for GSD III is primarily dietary and is maintained by regulating the euglycemia. This can be done by taking frequent meals rich in carbohydrate content, cornstarch supplements either alone or along with gastric tube feedings. High protein diet is recommended for patients with myopathy along with hypoglycemia. Controlled diet can improve growth, development and metabolic parameters such as levels of triglycerides and cholesterol.

Enzyme Genetics

GSD type IIIa and IIIb are autosomal recessive allele disorders which means both copies of the gene in cell is mutated which each inherited from each of the parent. Individuals with one abnormal copy of the gene are known to be carriers for this disorder; usually the carriers are unaffected and don't showcase the signs and symptoms of this particular disorder. when both the parents have recessive gene for this disorder then each child has 25% risk for developing the disorder, 50% risk of acting as a carrier and 25% to not have this condition nor acting as a carrier and can be easily understood with the help of Figure 4.. Mutations are caused in the AGL gene which is present on the chromosome 1 in humans. As shown earlier in Figure 3 (Yang-Feng, et al. 1992). This genetic mutation is found to be 1 in 100,000 live births but the populations which are most prone to this genetic disorder is found to be Faroe Islands having the frequency of 1:22, occurs in the First Nation of Canada having the frequency of 1:18 (Rousseau, et al. 2015). This disorder is commonly found in Pakistan, Afghanistan, and India. Type IIIb is frequently found in the Jews of North Africa (Parwari, et al. 1997).

Most of the mutations occurring in AGL gene were found to be due to the non-protein production. Missense mutations and Frameshifts (due to insertion or deletion) can also occur within a gene. Overall, total 16 missense mutations along with 2:1 inframe deletions and insertions have been observed in the AGL gene analysis. Generally, the missense mutations found in patients suffering from GSDs lie outside the 3 main domains, specifically, (i) Transferase domain, (ii) Glucosidase domain and (iii) Carbohydrate-binding domains. These small amino acid changes can only affect the protein tertiary structure and its stability.

Allelic disorders are the key characterizing factors that mainly occur in GSDIII a and GSDIII b, with specifically causing two mutations in the 3rd exon i.e., strongly linked with GSD III b. Patients with GSD III a and GSD III d were observed to be free from any such mutation of exon 3. In GSD III b, second mutation can occur at any point in the gene. These mutations or changes can be diagnosed without the use of liver biopsy. Many second mutations were found to be similar in GSD III a and GSD III b patients, depicting that these mutations do not cause any affect to the subtype.

Other than exon 3 mutations and GSD III b, a small fraction of genotype/phenotype correlations also play a major role in confirming the particular type of the disease. However, it is impossible to predict the clinical representation of some mutations, because of some of the subjects being compound heterozygotes. Also, symptomatic variability has been reported in some cases having same genotype of the disease, thus ensuring that other physiological and genetic factors also affect the clinical representations. Thus, Glycogen Storage Disease, Type III is one of the highly heterogeneous disorders, with an average of somewhat >100 mutations until now (Goldstein, et al., 2010)

Population Genetics

In United States, The overall prevalence of Glycogen Storage Diseases is fewer than 1 in 40,000. The GSD-III mainly, occurs in about 1 in 100,000 live births (Gharbawy, 2017) However, in Israel, among all the glycogen storage diseases, the prevalence of GSD-III was 73%. It is more frequent in individuals belonging to North African society. Non-Ashkenazim cases were depicted to be 1 in 5420 (Levin *et al.*, 1967) while Jewish individuals had a frequency of 1 in 5400, while the carrier frequency comprised of 1 in 35 (Paravari *et al.*, 1997). While in Canadian Inuit population of Nunavik, the disease affected almost 1 in 2500 of the population.

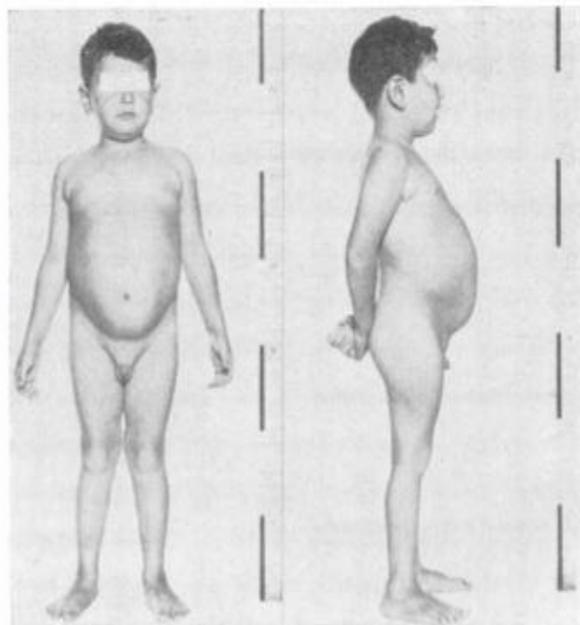


Figure 5: Boy with Type III GSD showing enlarged liver.

The highest prevalence of the disease, Cori's Disease, has been observed in the islands of Faroe. Two families were reported with GSD-III enzyme deficiency that leads to the hypothesis that the disease was inherited in an autosomal recessive order (Cohn et al., 1975). Later in 2001, five families were reported who had the symptoms of GSD-IIIa and same mutation in the AGL gene was observed which was homozygous to the founder effect. The results depicted that the prevalence of the disease is 1 in 3600 while 1 in 30 carrier frequencies was observed in a population of 45,000 individuals. Thus, the Faroese population was considered to be the most affected one worldwide (Santer et al., 2001).

Symptoms

Symptoms are least during the 4-6 years of life, most of the signs and symptoms improve with increasing age (mostly liver associated) or can become better with dietary management. Symptoms might become prominent after several years of life. Common symptoms observed in individuals having GSD-III were Enlarged liver (98%) with a low blood sugar level i.e., 53%. Also, the infected ones were more prone to infections (17%) when compared with normal ones. Other symptoms include protruding abdomen, as shown in Figure 5, with weak or flaccid muscles, short stature, and frequent nose bleed. While some of the symptoms are enlarged heart muscles usually in GSD type IIIa, there is slow rate of growth and development, delayed puberty and increased amount of fat in blood is present.

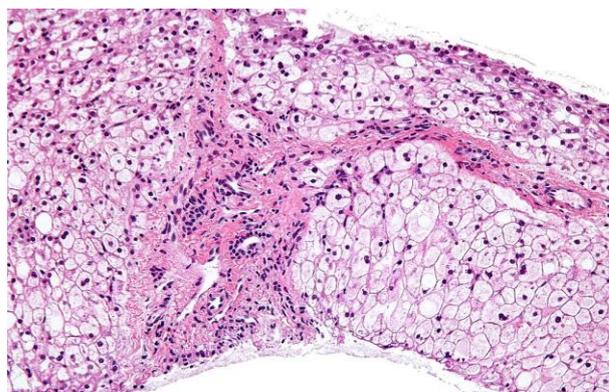


Figure 6: Micrograph of a GSD III patient observed through Liver biopsy.

Pathology

The Debranching enzyme along with Glycogen phosphorylase carries out the whole degradation of glycogen. The amount of the degraded glycogen determines the extent of the disease. A portion of Liver of a GSD-III patient has been shown in Figure 6. The debranching enzyme structure consists of three specific sites, out of which two perform independent catalysis. The improper activity of any of the two sites causes the dis-functioning of the enzyme (Shen, 002; Ozen, 2007) One catalytic site refers to 4- α -glucanotransferase activity, brings about the transfer of three glucose molecules at the end of the adjacent chain, while the other site refers to amylo-1,6-glucosidase activity that is responsible or carrying out the hydrolysis of glucose molecules present at the branch points.

Depending upon the tissue-specific expression, GSD can have variable phenotypes and can be categorized into four types (i) lack of both catalytic sites in liver and muscles causes Type IIIa that accounts for approximately 80% of the cases (Talente et al., 1994), while (ii) lack of both, glucosidase and transferase activity, in liver tissues causes IIIb (almost 15% of all the patients) (Shen et al., 1996). (iii) IIIc results due to the loss of glucosidase activity only while the loss of transferase activity resulted in the type III d.

Diagnosis

Glycogen storage diseases can be primarily predicted using the medical history of the family. Moreover, four major symptoms are considered that includes an enlarged liver, abnormal blood test reports, low glucose level in blood and lagging or retardation in growth. Several tests that confirm the prevalence of the disease are (i) Blood tests- for monitoring glucose level in blood and to keep a check of proper functioning of body muscles, (ii) Abdominal Ultrasound-to detect hepatomegaly, (iii) Tissue biopsy-For testing the amount of glycogen or enzymes present, (iv) Gene testing- For testing different mutations in enzymes. Gene testing can confirm the GSD. On the basis of several differences and similarities, GSDs can be differentially diagnosed as explained in Table 2.

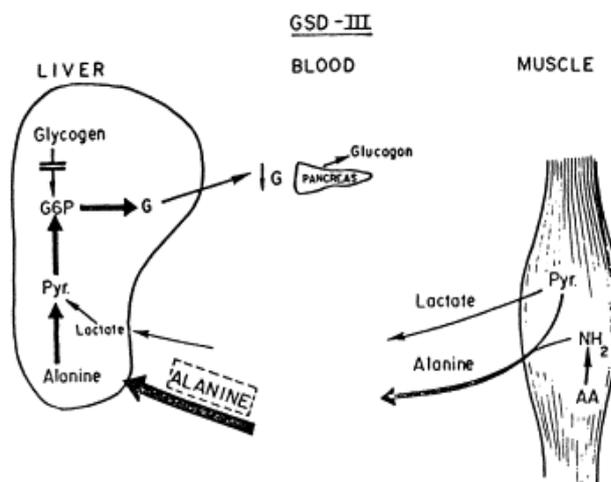
Table 2: Differential Diagnosis of GSD-III.

Disorder	Similarity with GSD-III	Distinguishing Features
GSD type 0	Fasting hypoglycemia and ketosis	Absence of hepatomegaly
GSD type 1	Hypoglycemia and Hyperlipidemia	Increased uric acid, increased lactate, lack of severe ketones, nephromegaly, and lack of muscle symptoms
GSD type II	Myopathy-elevated CK, AST, ALT levels.	AST usually higher than ALT, diaphragm involvement, proximal myopathy and lysosomal glycogen on histology
GSD type IV	Increased CK, myopathy	Hypotonia, amylopectin-like inclusions, muscle atrophy, dilated cardiomyopathy or neuronal involvement
GSD type V and VII	Muscle glycogen storage, increased CK	Dynamic symptoms of exertional muscle contractures and rhabdomyolysis
GSD VI	Hepatomegaly, elevated AST and ALT levels	Lack of muscle involvement, usually less severe clinically
GSD type IX	Hepatomegaly, elevated AST and ALT levels, hypoglycemia	X-linked form typically less severe clinically, other liver forms (Gamma2 variant and AR forms) can be more rapidly progressive, variability between and within different subtypes

Localization of the disease

Cardiac muscle involvement in GSD has been insignificant until 1968 when glycogen deposition was observed in the heart muscles (Pearson, 1968). However, the amount of glycogen deposited was considered ineffective as compared to the GSD-II (Pompe's disease). Miller et al., in 1972 described an unusual death of a 4-month infant, suffering with GSD-III (Kotb et al., 2004). Similarly, another case was reported in which a woman died suffering from the same phenotype of the disease. The autopsy (Olson et al., 1984) and biopsy were conducted and the results showed an excessive hypertrophy with glycogen in the heart muscles that lead to arrhythmia and atherosclerosis, which mainly occurs due to the onset of hyperlipidemia in cardiac muscles (Talente et al., 1994). The chances of stroke or cardiac failure can be depicted by conducting regular ECGs (Lee et al., 1997). Individuals with type III-a are recommended serial echocardiograms for every 12-24 months While in type III-b, hypertrophy has not been recognized yet (Kishnani et al., 2010).

In terms of Gastro-intestinal complications, Nutritional factors can be taken as a step towards the solution of the disease. GSD III involves the glycogen deposition that induces Hypoglycemia, Reduced bone-mineral density and myopathy. All these are minor problems that can be treated with dietary supplements and proper exercise. Patients with GSD III-a are mostly affected with myopathy. These patients require high amount of protein feedings. Proteins might be beneficial in three ways. (a) if they are intact with gluconeogenesis i.e., alanine as an alternate source of glucose during fasting (b) improved muscular functioning (c) can replace some carbohydrates (Slonim, 1984). Exercise is another important factor that is highly recommended for patients with GSD-IIIa (Kishnani et al., 2010). GSD-IIIb patients require corn-starch therapy only (Borowitz, 2008).

**Figure 7: GSD III in Hepatic Tissues.**

One of the possibilities lies is the deposition of glycogen in hepatic tissues. Errors caused by improper functioning of hepatic tissues, directly or indirectly, lead to death. Liver involvement in different Glycogen Storage diseases has been recognized much earlier in the history. It is particularly characterized by hepatocellular injuries and the hepatomegaly in childhood. Elevations in Aspartate Aminotransferase (AST) and Alanine transaminase (ALT) have also been observed in the early onset of the disease (Talente et al., 1994). It is mainly diagnosed using Liver biopsy techniques. The accumulation of abnormally short branched glycogen has been observed in the hepatic tissues (Portmann, 2007) that further causes Steatosis, Cirrhosis and Hepatocyte ballooning. The only solution to this error is organ allocation i.e., Liver Transplant (Labrune, 1997). As it is a genetic disorder, the chances of disease for the transplanted liver will minimize to zero (Kishnani et al., 2010).

Glycogen Storage Diseases in pregnant women have been reported to be escalating the risk factor for the fetus. During pregnancy, it is important to maintain normoglycemia (Kishnani et al, 2010). Major symptoms include polycystic ovaries with irregular periods in younger females (Lee et al., 1995). However, post-natal hypoglycemia was observed. The median ages for GSD-IIIa and GSD-IIIb were documented at 0.7 year and 1.0 year respectively. The symptoms observed in the child included hepatomegaly (98%), hypoglycemia (53%), infections (up to 17%) and failure to thrive (49%) (Christiaan et al., 2016). However, several measures should be taken in notice during pregnancy. These include avoidance of estrogen contraceptives, avoidance of hypoglycemia and a planned delivery (Kishnani et al., 2010).

Clinical manifestations in Musculoskeletal and Neuromuscular terms range from being asymptomatic to atrophy and different proximal/distal weaknesses. Motor delay is the main factor found in children aging from 3-22 years. A recent report confirmed 80% of children suffering from GSD III are subjected to 25% or lower average motor functioning (with respect to age). Hypotonia and mild weakness in GSD III patients can lead to congenital myopathy related to neuromuscular manifestations of the disease. While, musculoskeletal representation of the disease includes hypermobility at joints along with (i) hyperextension in knees and elbows, (ii) alignment due to anterior pelvic tilt and lumbar lordosis, (iii) slightly increased width of base support, (iv) valgum and recurvatum, (v) handfoot valgus and (vi) forefoot varus. Weaknesses either primary (related to debrancher enzyme deficiency) or secondary (related to changes in biomechanics) both affect the trunk and proximal and distal muscles that causes a decrease in gripping strength and ability to jump. Weaknesses significantly attributable to debrancher enzyme deficiency are mostly observed in adults. These distributions of weaknesses are highly variable in different individuals. The proximal weaknesses in individuals mostly occur in association with different hypertrophy or pseudo-trophy in some muscles. While the distal weaknesses along with atrophy suggest neuropathy. The muscle glycogen is very crucial for energy metabolism occurring in muscles, thus exercise intolerance is not recognized in this disease. General medical care should be given to the individuals depending on the variations in disease manifestations. Regular immunizations should be given to the children, that may prevent or inhibit the action of causative factors of the disease, as it will later on help minimizing the risk factor of hypoglycemia. Proper monitoring should be done related to Hepatitis B and C, as it may accelerate the risk of liver tumors in GSD III patients. The event of hypoglycemia in adults suffering from GSD III is relatively not common.

Medical Treatment and Prevention

As the disease is genetically transferred, it cannot be prevented; however it can be controlled if proper measures are taken. For Glycogen Storage Disease III, no medical therapy is available. Thus, it can be controlled or prevented by proper dietary treatment. Dietary management has been considered to be the cornerstone in this regard. Intake of high-protein content at day time (25% proteins, 45% carbohydrates and 30% fats) and proper supplementation of UCCS i.e., uncooked starch, before sleep plays an effective role in young patients with respect to retarded growth and metabolic control of the disease (Lucchiari et al., 2007) The protein content of 3-5 grams/kg of the body weight is recommended after every 3-4 hours. Fasting is greatly prohibited in this case. While, adults require a lower quantity of carbohydrates in their diet. The intake of protein should be 25% depending on the total calories taken. However, in adults with myopathies, it was proved to be very less effective. Proper monitoring of blood glucose level is a major part of a good dietary control.

Liver transplantations are recommended for the patients suffering with hepatocellular carcinoma.

Genetic Counseling, Prenatal Diagnosis and Screening

Along with other inborn mutations, proper genetic counseling should be provided to the families of the victims. GSD III or Cori's disease is a genetic disorder that is inherited to children via their parents. The parents of the infected children are then considered to be the victims. The risk of the recurrence of the disease to the parents is 25%. For the identification of the carriers proper DNA analysis are performed. In case of IIIb only two exons of the gene are sequenced. However, the mutations for IIIa phenotype are located on the whole length of the exon. Thus, a complete 35-exon gene undergoes sequencing and the carriers are depicted on the basis of the gene sequence obtained (Kishnani et al., 2010).

Prenatal diagnostics can be done using DNA polymorphic markers of the encoded gene, AGL gene (Shen et al., 1998). Also, it can be obtained by mutation analysis either on chorionic villus or amniocytes.

Future Advancements

Being genetically inherited, Glycogen Storage Diseases cannot be treated except for Gene Therapy techniques. However, several years of research have helped in monitoring and controlling the disease. First of all, researchers should make an effort in suppressing and preventing the amount of glycogen accumulation in the tissues. Secondly, Liver and Cardiac muscle involvement should be made lesser. Measures should be taken in decreasing the errors of abnormalities in specific pathways. Also, several other sources of energy should also be discovered that could meet the body demands properly. Medical labs must be well-equipped with

advanced methodologies that could help in the early diagnosis of the disease and could determine the severity of the disease (Kishnani et al., 2010).

CONCLUSION

Cori's disease is a rare genetic disorder. This disease is inherited in an autosomal recessive order. The major presenting symptom is hepatomegaly and bone weaknesses. Some patients show symptoms in early onset of the disease while some of its types are asymptomatic and are difficult to be diagnosed. This acute disease can progress into a chronic life-threatening disease causing different malfunctions in liver and other muscles of the body, including heart as well. To control such severity, proper in-time dietary and clinical treatments should be opted as soon as possible. Childhood immunizations should be properly monitored so as to minimize the risk of the disease. However, a vast room is available for more insights of the disease.

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