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TEACHING FILES (GRAND ROUNDS)

GLYCOGEN STORAGE DISEASE - TYPE 3

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Clinical Problem:

A 9-month-old female child was referred for asymptomatic hepatomegaly detected by the local physician. Her birth history was normal and she had achieved milestones as per her age. The child had no family history of jaundice and had received all doses for Hepatitis B vaccine. On examination, weight was 6.5 kg (Less than 3rd centile as per WHO growth charts), height was 66 cm (Less than 3rd centile as per WHO growth charts) and she had hepatomegaly with a liver span of 13 cm. Other examination findings were normal. On investigation, serum bilirubin was 1.2 mg/dl, SGOT was 144 IU/L, SGPT was 160 IU/L, total proteins were 6.3 gm/dl, albumin was 4.2 gm/dl, GGTP was 98 IU/L, alkaline phosphatase was 320 IU/L, cholesterol was 201 mg/dl (Normal range: 100-220 mg/dl) and triglycerides were 607 mg/dl (Normal Range: 30-100 mg/dl). Prothrombin time was 15 sec and INR was 1.2. Complete blood count was normal. Venous blood gas (VBG) showed ph of 7.4 and bicarbonate of 23.4 meq/L. Serum lactate was 2.2 mmol/L. CPK was 24 U/L. Serum uric acid was 3.5 mg/dl. Ultrasound abdomen showed hepatomegaly with coarse echotexture. There was no splenomegaly or nephromegaly. Doppler of the portal system was normal. Ophthalmological evaluation were normal. Histological examination of liver biopsy was suggestive of glycogen storage disease (GSD) Type 3 in view of fibrotic septae with plant like appearance and ballooned hepatocytes. Genetic testing showed the patient to be homozygous for C.1081C>T in exon 8 and C.1883A>G in exon 14 in AGL gene suggestive of GSD type 3.

How to diagnose and manage glycogen storage disease?

Discussion:

- GSDs are a group of metabolic disorders that are inherited, caused by deficiency in enzymes that are needed for either glycogen synthesis or glycogen degradation. There is a very broad spectrum on how GSDs present – they can either affect a single tissue type like the muscles or can involve multiple systems.[1] The GSDs have historically been diagnosed by a combination of pathology findings, biochemical results and clinical symptoms. Findings from muscle or liver histology and enzyme deficiency studies are relied upon. The main technique for diagnosing glycogen storage disease over the past ten years is DNA mutation analysis.[1] Common types of GSD are depicted in Table 1.[2,3,4,5,6] Other phosphokinase deficiency diseases range from GSD type VIa to VIII to IX. The GSD Type III is caused by a deficiency of glycogen debranching enzyme (GDE) which is located on chromosome 1p21.[6] It has a variable presentation depending upon the severity which makes diagnosis difficult. In GSD III often presenting features are hepatomegaly, growth retardation, hypoglycemia, hyperlipidemia, transaminase elevation. In GSD IIIa individuals have deficient GDE enzyme activity in both liver and muscle, whereas those with GSD IIIb have enzyme deficiency limited to the liver.[6] Thus in Individuals with GSD IIIa along with hepatic manifestations they, may have variable myopathy and ventricular hypertrophy or cardiomyopathy. Muscle weakness in GSDIII can be both proximal and distal along with hypoglycemia or hepatomegaly but does not affect respiratory muscles.[6] Hypoglycemia is a feared symptom, however it is not as frequent in GSD type I. In GSD III there may be elevated creatine kinase, ketosis on fasting but normal lactate and uric acid.[7] Hence these patients need regular monitoring of blood glucose (preprandial), liver function studies, lipid profile, lactate, creatine kinase and cardiac functions. Presence of myopathy may be evaluated using electromyogram and nerve conduction studies. Liver (and or muscle) histology in GSD III demonstrate a vacuolar accumulation of non-membrane bound glycogen primarily located in cytoplasm, which is Periodic Acid Schiff (PAS) positive and diastase sensitive. Lipid vacuoles are less frequent in GSD III than in GSD I, presence of fibrosis, ranging from minimal periportal fibrosis to micronodular cirrhosis is noted in GSD III not in GSD I. For definitive diagnosis either molecular genetics or enzymatic testing is necessary.[6]

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Table 1. Common types of GSD[2,3,4,5,6]

Type of GSD	Deficiency of enzyme	Treatment	Outcomes
Type 0	glycogen synthethase deficiency	Symptoms are alleviated by frequent protein-rich meals and night time feedings of uncooked cornflour (UCCS)	Liver not enlarged
Type I - Von Gierke Disease (subtypes Ia, Ib, Ic, Id)	Glucose-6-phosphatase	Treatment: frequent oral glucose/cornstarch; avoidance of fructose and galactose.	Increased Glycogen in liver and kidneys, increased blood lactate, increased triglycerides, increased uric acid. Liver and Kidney enlarged
Type II - Pompe's Disease	Lysosomal acid a-1,4-glucosidase (acid maltase)	Enzyme replacement therapy (ERT) is currently the most reliable treatment.	Cardiomyopathy, hypotonia, exercise intolerance and systemic findings lead to early death.
Type III - Cori's Disease (subtypes-IIIa, IIIb, IIIC, IIId)	Debranching enzymes (a-1,6-glucosidase and 4-a-d-glucanotransferase).	Treatment focussed on diet , with the goal of maintaining normoglycemia. Frequent carbohydrate-rich meals along with proteins and cornflour supplements, either alone or in conjunction with gastric tube feedings.	Milder symptoms as compared to Von Gierke but normal blood lactate levels. Can lead to cardiomyopathy based on the subtype.
Type IV - Anderson's Disease	Branching enzyme.	Liver transplantation is the only treatment option for individuals	Hepatosplenomegaly and failure to thrive are the most common symptoms in early infancy. Infantile cirrhosis, muscular weakness, hypotonia, cardiomyopathy and early childhood death are among the other findings.
Type V – Mc Ardles disease	Skeletal muscle glycogen phosphorylase (myophosphorylase).	Painful muscle cramps, myoglobinuria (red urine) with strenuous exercise and arrhythmia from electrolyte abnormalities.	Liver is not involved, so Blood glucose levels typically unaffected.
Type VI - Her's Disease	Liver glycogen phosphorylase	Mostly a mild manifestation, so no treatment required. Avoid prolonged periods of fasting.	Gross hepatomegaly; patient is largely asymptomatic without hypoglycemia.

GSD III being multisystem disorder needs a multidisciplinary team for its best management by experienced physician along with occupational therapist, genetic counsellor, metabolic dietitian along with emotional and psychological support provided to patients and their families.[6] Prevention of hypoglycemia in infants and young child with GSD is the initial focus of management. Small frequent feeding and avoidance of fasting is the initial step. Bed time snack, corn starch and/continuous enteral feedings may be needed for overnight fast.[6] High carbohydrate intake is avoided. Cornstarch is given with a typical starting dose of 1 g/kg enterally to prevent hypoglycemia. Recommended protein intake is 3 g/kg (25% of total calorie intake); additional protein supplementation may be required. Vitamin D and calcium supplementation might also be indicated. The last resort of liver transplantation is only reserved for patients with severe hepatic dysfunction or cirrhosis.[6,7] Because gluconeogenesis is intact in GSD III, sucrose, fructose, lactose are not restricted as they are for individuals with GSD I.[6] Liver ultrasound is done every 6-12 months in children and 12-24 months in adults to evaluate the liver size, structure or complications like hepatic cirrhosis with manifestations of portal hypertension, adenomas, if any, liver MRI as needed. Yearly measurements of serum calcium and 25(OH)-vitamin are advised due to associated risk of osteoporosis, regular monitoring of growth parameters are necessary on follow up.[6,7] Routine evaluation of cardiac status with ECG and echocardiogram is recommended in GSD IIIa at the time of diagnosis and then 1-2 yearly until there is abnormality in echo or if there is clinical symptoms of cardiac involvement. For GSD IIIb evaluation

of cardiac status at the time of diagnosis, later on every 5 yearly is reasonable.[7] The long-term results for GSD patients primarily hinge on effective dietary management tailored to each specific GSD type and patient adherence to these protocols.[8] The identification of biallelic pathogenic variants in AGL confirms the diagnosis of GSD III in a proband. Once the AGL pathogenic variants in an affected family member have been identified, prenatal testing for a high-risk pregnancy and preimplantation genetic testing for GSD III are options.[7]

Compliance with ethical standards

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Conflict of Interest: None

References:

1. Chen MA, Weinstein DA. Glycogen storage diseases: Diagnosis, treatment and outcome. Translational Science of Rare Diseases. 2016;1(1):45-72.
2. Ozen H. Glycogen storage diseases: new perspectives. World J Gastroenterol. 2007 May 14;13(18):2541-53.
3. Morales A, Anilkumar AC. Glycogen Storage Disease Type II. [Updated 2022 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470558/
4. Magoulas PL, El-Hattab AW. Glycogen Storage Disease Type IV. 2013 Jan 3 [Updated 2019 Aug 1]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK115333/
5. Labrador E, Weinstein DA. Glycogen Storage Disease Type VI. 2009 Apr 23 [Updated 2019 Nov 27]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK5941/
6. Kishnani PS, Austin SL, Arn P, Bali DS, Boney A, Case LE, et al. Glycogen Storage Disease Type III diagnosis and management guidelines. Genet Med. 2010 Jul 1;12(7):446-63.
7. Schreuder AB, Rossi A, Grünert SC, et al. Glycogen Storage Disease Type III. 2010 Mar 9 [Updated 2022 Jan 6]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK26372/
8. Szymańska E, Lipiński P, Rokicki D, Książyk J, Tylki-Szymańska A. Over 20-Year Follow-up of Patients with Hepatic Glycogen Storage Diseases: Single-Center Experience. Diagnostics (Basel). 2020 May 13;10(5):297.