End-Stage Liver Disease in the Setting of Type IIIa Glycogen Storage Disease

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Abstract

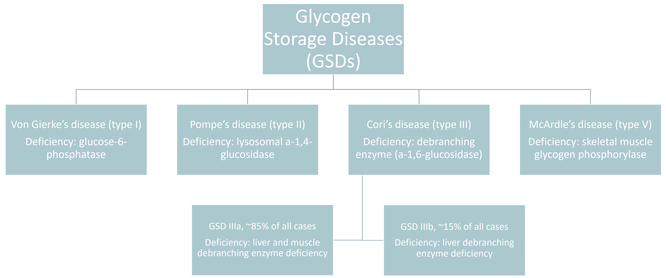
- Glycogen storage diseases (GSD) are genetic defects in glycogen metabolism and utilization.
- Features frequently associated specifically with GSD type IIIa are attributed to defective glycogenolysis and clinically present as hepatomegaly, transaminitis, hypoglycemia, myopathic changes and elevated creatinine kinase[1].
- Systemic therapy in this patient population includes high-protein feedings and snacks[2].
- Although exceedingly rare, reports exist of GSD IIIa progressing to cirrhosis secondary to abnormally structured glycogen causing hepatocyte damage.
- This case highlights the management of GSD IIIa, the importance of therapeutic adherence and the management multifactorial induced cirrhosis.

Introduction

- GSDs are rare inborn errors of metabolism involving the inability to store or metabolize glycogen to glucose in the body. Time of clinical onset for each GSD depends on the enzyme deficiency and the extent of the body's adaptive processes to overcome the failure to metabolize or store glycogen[3].
- All GSDs have hallmark findings on biopsy, GSD type III can be confirmed on biopsy with findings of micronodular cirrhosis with associated hepatocyte distention and periportal fibrosis, both findings attributed to glycogen accumulation[3].
- In type IIIa GSD the branched glycogen polymer is unable to be cleaved at branching points due to nonfunctional or reduced glycogen debranching enzymes (GDE). Type IIIa is seen with a completely nonfunctional GDE enzyme, signifying defective glycogenolysis with intact gluconeogenesis process[4].
- Dietary management of patients with ketotic GSDs includes providing a constant and alternate fuel for gluconeogenesis by means of exogenous glucose and protein supplementation. Specifically, high-protein and ketogenic diets have been recommended and demonstrated to improve myopathies, lower serum creatinine kinase and improve prealbumin and other protein markers[4].

Case Presentation

- This case presents a 35-year-old female with pertinent past medical history of GSD IIIa diagnosed at 18 months of age after developing hepatomegaly.
- Diet therapy including high-protein and frequent small meals with corn starch supplementation was recommended to prevent further clinical manifestations of GSD IIIa.
- Due to unfavorable social determinants of health including economic instability, our patient went on to develop decompensated cirrhosis and required an orthotopic liver transplant (OLT) at 15-years-old.
- Post OLT there was a 16-year period of loss to follow up, resulting in this patient presenting to our Emergency Department with grade III hepatic encephalopathy, jaundice and hematemesis. Her initial physical exam was significant for grade III hepatic encephalopathy, scleral icterus, jaundice and spider angiomas.
- Initial work-up was significant for labs demonstrating previous hep C infection, oliguric AKI, hyperammonemia, liver function test significant for cholestatic and hepatocellular involvement and a MELD-Na of 35.
- Imaging obtained with coarsened liver echotexture and nodular contour consistent with OLT cirrhosis, this finding confirmed by liver biopsy. Changes consistent with portal hypertension including grade II esophageal varices and portal gastropathy were present on endoscopy.
- Admission complicated by hepatorenal syndrome, oliguria and encephalopathy. After medical optimization retransplant was performed and she was discharged on Tacrolimus and Cellcept.



Discussion

- Patients with GSD IIIa typically follow a benign course in the setting of adequate lifestyle modifications with clinical resolution of symptoms including hepatomegaly after puberty[5].
- Diagnosis of GSD IIIa classically occurs in childhood given the clinical presentations of hepatomegaly, failure to thrive, fasting hypoglycemia, cardiac hypertrophy and muscle weakness[6].
- Recommended dietary restrictions include high protein, combination of cornstarch and consuming complex carbohydrates, limited consumption of simple sugars and multivitamin supplementation[7].
- As it pertains to this patient, her GSD IIIa disease course was complicated by hepatocellular failure progressing to require liver transplant at 15-years-old. Her further loss of follow-up and environmental factors contributed to requirement for re-transplant.
- Although GSD IIIa typically has a favorable prognosis, the course is unable to be predicted given the multifactorial organ system involvement and social and environmental factors.

Conclusions/ Future recommendations

- Given the multisystem effects of GSD, a multidisciplinary team-based management is optimal and should encompass a trained clinician, metabolic disease specialist, geneticist with addition of specialists pertaining to the compromised organ systems.
- Targeted management includes awareness of multisystem involvement including glycogen deposition in cardiac muscle, peripheral neuropathy due to the debrancher deficiency, liver dysfunction due to glycogen deposition, and muscle weakness. Special consideration must be taken for obstetric patients given requirement of high-risk obstetrician follow-up[8].
- Close monitoring of the synthetic function of the liver is indicated,. Although there is low possibility of recurrence of primarily liver disease in the OLT, consideration must remain as a secondary disease process may compromise the liver and require repeat retransplant.
- Therapies undergoing investigation include small molecule therapies such as the mTOR inhibitor Rapamycin, which may reduce organ and muscle glycogen accumulation[9].

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References

1. Ozen H. Glycogen storage diseases: new perspectives. World J Gastroenterol. 2007 May 14;13(18):2541-53. doi: 10.3748/wjg.v13.i18.2541. PMID: 17552001; PMCID: PMC4146814.
2. Mayorandan, S., Meyer, U., Hartmann, H. *et al.* Glycogen storage disease type III: modified Atkins diet improves myopathy. *Orphanet J Rare Dis* **9**, 196 (2014). https://doi.org/10.1186/s13023-014-0196-3
3. Stone WL, Basit H, Adil A. Glycogen Storage Disease. [Updated 2022 Jun 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459277/
4. Ross KM, Ferrecchia IA, Dahlberg KR, et al. Dietary Management of the Glycogen Storage Diseases: Evolution of Treatment and Ongoing Controversies. Adv Nutr. 2020 Mar 1;11(2):439-446. doi: 10.1093/advances/nmz092. PMID: 31665208; PMCID: PMC7442342.
5. Kishnani, P., Austin, SL, Arn, P., *et al.* Glycogen Storage Disease Type III diagnosis and management guidelines. Genet Med. 2010 July; 12: 446-463. doi: https://doi.org/10.1097/GIM.0b013e3181e655b6
6. Schreuder, A., Rossi, A, Grunert, S et al. Glycogen Storage Disease Type III. Gene Reviews. 2010 March 9. University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK26372/
7. Mayorandan, S, Meyer, U, Hartmann, H, et al. Glycogen storage disease type III: modified Atkins diet improves myopathy. Orphanet Journal of Rare Diseases. 2014 Nov 28; 9 (196). https://doi.org/10.1186/s13023-014-0196-3
8. Kishnani, P, Austin, S, Arn, Pamela, et al. Glycogen storage disease type III diagnosis and management guidelines. ACMG Practice guidelines
9. Yi H, Brooks ED, Thurberg BL, Fyfe JC, Kishnani PS, Sun B. Correction of glycogen storage disease type III with rapamycin in a canine model. J Mol Med (Berl). 2014 Jun;92(6):641-50. doi: 10.1007/s00109-014-1127-4. Epub 2014 Feb 8. PMID: 24509886