Glycogen Storage Disease Type IV: A Case Report

Mohamed Sellouti[*,1], **Hakim El Yajouri**[*], **Abdelilah Radi**[*], **Abdelhakim Ourrai**[*], **Amale Hassani**[*], **Rachid Abilkassem**[*] **and Aomar Agadr**[*]

[*]Department of Pediatrics, Mohammed V Military Teaching Hospital, Rabat.

ABSTRACT Glycogen storage disease (GSD) IV is a rare autosomal recessive inherited disorder caused by mutations in the gene coding for glycogen branching enzyme(GBE). The clinical spectrum is wide-ranging from isolated non-progressive hepatopathy, neuromuscular disorders with variable age of onset, to the adult polyglucosan body disease. We report a five-month-old female patient with GSD who presented with conjunctival jaundice and hepatomegaly. A liver biopsy showed the presence of material with histochemical and ultrastructural characteristics consistent with amylopectin. Measurement of glycogen quantity in the red blood cells showed increased storage of glycogen. Biochemical analysis demonstrated severely reduced branching enzyme activity.

KEYWORDS Glycogen storage disease, glycogen branching enzyme, liver transplantation

Introduction

Glycogen storage disease(GSD) IV is an autosomal recessive metabolic disorder caused by mutations in the glycogen branching enzyme gene (GBE1). The glycogen branching enzyme is vital for glycogen synthesis, and when deficient results in the accumulation of amylopectin-like configurations of glycogen in the liver, heart, muscle, nervous system and skin[1]. GBE1 is located at chromosome 3p14 and encodes for a 702 amino-acid protein [2,3,4,5]. GSD IV usually presents in the first year of life with features of hepatic failure and portal hypertension, normally causing death by the age of 2 to 4(3). We report the first case of GSD IV in Morocco.

Case report

A five-month-old female child was admitted for progressive abdominal distention and hemorrhagic syndrome. There is the story of his brother's death in acute liver failure. The infant weight 4.3kg (25th-50th percentile), measured 58 cm (50th-75th

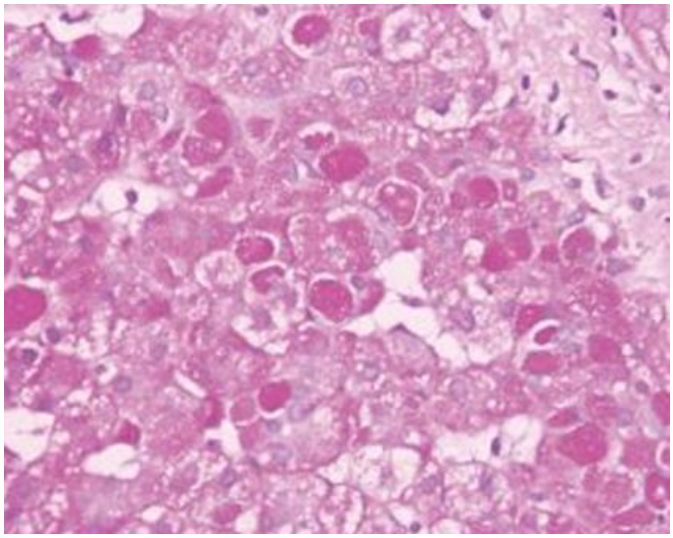

Figure 1: Liver biopsy revealed marked intracytoplasmic glycogen deposits and PAS test positive.

DOI:10.5455/IJMRCR.Glycogen-Storage-Disease-Type-IV
First Received: February 28, 2020
Accepted: March 14, 2020
Manuscript Associate Editor: Ivan Inkov (BG)

[1]Departement of Pediatrics, Mohammed V Military Teaching Hospital, Faculty of Medicine and Pharmacy, Rabat Morocco, Tel:00212660627466;
Email:msellouti@gmail.com

percentile) and had a head circumference of 44 cm (50th-75th percentile). On clinical exam, the patient was afebrile, with blood pressure at 75/46 mm Hg, and heart rate at 77 beats/min. The abdominal was distended. The liver was palpable by a handbreadth below the rib, and the spleen was palpable 2 cm below the left costal margin in the middle mid-clavicular line. On neurological exam, he had a severe bilateral facial weakness, severe hypotonia, and minimal spontaneous movement.

Biological assays showed hyperleukocytosis at 18900/mm3 (59% lymphocytes and neutrophils at 41%), hemoglobin at 11.3g /dl, red blood cells at 4.1 106 / mm3, VGM at 70.2 μ3, 21.9 μg TCMH, 31.9% MCHC, and platelet count at 529 103 / mm3. Hepatic cytolysis with SGOT at 363UI/l and SGPT at 223IU/l.Total and direct bilirubin level respectively at 108 and 83 μmol / l, alkaline phosphatase at 290 IU / l, a prothrombin level at 32%; kaolin cephalin time at 30 seconds (control at 25 seconds); blood glucose level at 4.9 mmol / l, a cholesterolemia at four mmol / l; hypertriglyceridemia at 3.45 mmol / l, urea at 4.2 mmol and creatininimia at 71 μmol / l. Serological markers for hepatitis A virus, hepatitis B virus, hepatitis C virus, toxoplasma, rubella virus, cytomegalovirus, and herpes simplex virus were all negative. Abdominal ultrasound showed hepatosplenomegaly with periportal thickening and ascites. Transthoracic echocardiogram revealed no abnormal findings.

A liver biopsy was performed revealing a ballooning of the hepatocytes with abundant granular cytoplasm which showed positive staining with periodic acid-Schiff "PAS" & reclearing with diastase enzyme. Portal areas showed marked fibrosis with evidence of early micronodular cirrhosis. The picture is consistent with cirrhosis complicating type IV glycogen storage disease. Fatty changes, nuclear hyperglycogenation & fibrosis were graded 0-3, according to Gogus et al. (6). Biochemical analysis was performed and demonstrated severely reduced branching enzyme activity in liver tissue (1 μmol/min/g tissue; range 32 ± 10 μmol/min/g). A diagnosis of glycogen storage disease, type IV, was confirmed. This patient is waiting for orthotopic liver transplantation.

Discussion

GSD IV or Andersen disease is a rare autosomal recessive disorder caused by a deficiency in the glycogen branching enzyme, encoded by the GBE1 gene. GSD IV is estimated to occur 1/600,000–1/800,000. Classically, five clinical subtypes have been recognized. However, the widely heterogeneous presentations, varying in the age of onset and affected organ systems, do not all fit well into these subtypes [7]. GSD IV shows heterogeneous clinical courses. The most common and classical form of GSD IV is the classic hepatic form, non-progressive hepatic form, neonatal neuromuscular form and adult polyglucosan body disease, which presents with myopathy or cardiomyopathy symptoms[8]. The severity of GSD IV phenotypes has been correlated to residual glycogen-branching enzyme activity, with null mutations leading to severe perinatal and congenital subtypes. However, it remains mostly unclear how milder, biallelic mutations relate to organ involvement and disease progression[9].

The human GBE1 gene is located on chromosome 3p12 and consists of 16 exons [10]. GBE1 mutation analysis that has been performed in patients suggests a genotype-phenotype correlation, along with null mutations such as deletions, insertions, or nonsense mutations that are associated with a more severe clinical phenotype [8,3,11]. More than 40 different mutations in the glycogen branching enzyme gene have been described.

The pathogenesis of tissue damage, especially liver cirrhosis, is not understood: an irritating role of the abnormal polysaccharide, causing fibrosis, was proposed by Anderson[12], but remains hypothetical[13]. A higher concentration of the abnormal polysaccharide in the liver or the greater vulnerability of this organ to its toxic effects may explain why hepatic damage usually dominates the clinical picture. Cirrhosis is seen routinely, even in patients in whom hepatic symptoms have not yet manifested[14].

GBE assays in various tissues (liver, skeletal, muscles, nerve tissues, cultured skin fibroblasts) help to confirm the diagnosis of GSD-IV. Also, the accumulations of amylopectin-like glycogen can be shown in the liver, skeletal and heart muscles, and other tissue. These materials react with PAS staining and are partially resistant to diastase digestion. In the EM study, most patients demonstrate fibrillar aggregations that are typical of amylopectin.

No specific treatment has been shown to alter the natural course of the disease. Supportive treatment is helpful before liver transplantation

Patients with the classic hepatic form of GSD-IV are candidates for liver transplantation. After the liver transplantation, there are some reports that various extra-hepatic manifestations, as well as hepatic function, have no progressed or improved because a donor liver has corrected the hepatic disease and may be a source of the deficient enzyme because of systemic microchimerism(15,16).

Acknowledgement

We would like to acknowledge the teamwork of the Metabolic and Genetic Disorders Unit- Faculty of Medicine Rabat University Mohamed V, where the laboratory work of this study has been done.

Disclosure Statement

There were no financial support or relationships between the authors and any organization or professional bodies that could pose conflict of interests.

Competing Interests

Written informed consent has been obtained from the patient for publication of this case report and any accompanying images.

References

1. Willot S, Marchand V, Rasquin A, Alvarez F, Martin SR. Systemic progression of type IV glycogen storage disease after liver transplantation. J Pediatr Gastroenterol Nutr 2010; 51: 661–664.

2. Akman HO, Karadimas C, Gyftodimou Y, Grigoriadou M, Kokotas, Konstantinidou A et al. Prenatal diagnosis of glycogen storage disorder type IV. Prenat Diagn 2006; 26: 951–955.

3. Moses SW, Pavari R. The variable presentations of glycogen storage disease type IV: a review of clinical, enzymatic and molecular studies. Curr Mol Med 2002; 2: 177–188.

4. Asserto A, van Diggelen OP, Diogo L, Morava E, Cassandrini D, Carreira I et al. Null mutations and lethal congenital form of glycogen storage disease type IV. BBRC 2007; 361: 445–450.

5. L'hermine-Coulomb A, Beuzen F, Bouvier R, Rolland MO, Froissart R, Menez F et al. Fetal type IV glycogen storage disease: clinical, enzymatic and genetic data of a pure muscular form with variable and early antenatal manifestations in the same family. Am J Med Genet 2005; 139A: 118–122.

6. Gogus S, Kocak N, Ciliv G, Karabulut E, Akcoren Z, Kale G, et al. (2002): Histologic features of the liver in type Ia glycogen storage disease: comparative study between different age groups and consecutive biopsies. Pediatr Dev Pathol; 5:299-304.

7. Burrow TA, Hopkin RJ, Bove KE et al. (2006) Non-lethal congenital hypotonia due to glycogen storage disease type IV. Am J Med Genet A 140:878–882

8. Bruno C, Cassandrini D, Assereto S, Akman HO, Minetti C, Di Mauro S. Neuromuscular forms of glycogen branching enzyme deficiency. Acta Myol 2007; 26:75-8

9. Magoulas PL, El-Hattab AW (2013) Glycogen storage disease type IV. In: Pagon RA, Adam MP, Bird TD, Dolan CR, Fong CT, Smith RJ et al. (eds) GeneReviews. University of Washington, Seattle. https://www.ncbi.nlm.nih.gov/books/NBK115333/. Retrieved 1 Dec 2017

10. Thon VJ, Khalil M, Cannon JF. Isolation of human glycogen branching enzyme cDNAs by screening complementation in yeast. J Biol Chem 1993;268:7509-13.

11. Shin YS. Glycogen storage disease: clinical, biochemical, and molecular heterogeneity. Semin Pediatr Neurol 2006;13:115-20

12. Anderson DH. Familial cirrhosis of the liver with storage of abnormal glycogen. Lab invest 1956;5 11-20

13. Ishirata, Uchino F, Adachi H . Type IV glycogenosis-a-study of two cases. Acta Path Jap 1975;25: 613-33

14. Servidei S, Riepe RE, Lanston C, Tani LY, Bricker JT, Crisp-Lindgren N, Travers H, Amstrong D, DiMauro S. Severe cardiomyopathy in branching enzyme deficiency. J Pediatr 1987;111:51-6.

15. Selby R, Starzl TE, Yunis EY, Brown BI, Kendal RS, Tzankis A. Liver transplantation for type IV glycogen storage disease.N Engl J Med 1991;324:39-42.

16. Starzl TE, Demetris AJ Trucco M, Ricordi C, Ildstad S, Terasaki PI, Murase N, Kendal RS, Kocova M, Rudert WA. Chemerism after liver transplantation for type IV glycogen storage disease and type I gaucher's disease. N Engl J Med 1993;328 :745-9.