The Pharmaceutical and Chemical Journal, 2017, 4(5):8-12

Available online www.tpcj.org

Research Article

ISSN: 2349-7092
CODEN(USA): PCJHBA

Glycogen Storage Disease Type IV: A Case Report

Tahia H. Saleem[1], Hamdy N. Eltalawy[2], Ahmed El-Abd Ahmed[3], Nagla H. Abu-faddan[4], Yasser Gamal[5], Mohammed H. Hassan[6]*

Medical Biochemistry and Molecular Biology dept.[1,6] Neuropsychiatry dept.[2] Pediatric dept.[3,4] Pathology dept.[5] Assuit faculty of medicine[1,2,4,5] Qena faculty of medicine-South Valley University[3,6]
Corresponding author: *To whom correspondence should be addressed:
Dr. Mohammed H. Hassan, Lecturer of Biochemistry and Molecular Biology, Qena Faculty of Medicine, South Valley University, Qena, Egypt. Mohammedhosnyhassaan@yahoo.com

Abstract Glycogen storage disease type IV (GSD-IV) "Andersen's disease" is an autosomal recessive disorder due to a deficiency of glycogen branching enzyme (GBE)**.** We report a four years old female patient with glycogen storage disease type-IV who exhibited an abdominal distension and failure to thrive since the age of 9 months. The patient showed hepatosplenomegaly and hypotonia of both upper and lower limbs proximally. The laboratory findings showed fasting hypoglycemia, raised liver enzymes, moderate hypochromic microcytic anemia, hyperlactatemia with raised total creatine phosphokinase & lactate dehydrogenase. The light microscopic findings of the liver biopsy specimen were consistent with GSD-IV. This study focuses on evaluation of the detailed clinical, biochemical and histopathological findings that found in a pediatric patient with GSD-IV.

Keywords GSD; *GBE1*; Neuromuscular affection

Introduction

Glycogen storage disease type IV (GSD-IV or Andersen's disease) is an autosomal recessive disorder due to a deficiency of glycogen branching enzyme (GBE), MIM232500. The branching enzyme catalyses the last step in glycogen biosynthesis by attaching short glucosyl branches in α-1,6-glycosidic linkages to the linear chains of nascent glycogen and the deficiency results in the accumulation of abnormal glycogen, with fewer branching points, and amylopectin-like polyglucosans in different tissues to various degrees [1].

Glycogen storage disease type IV is rare, accounting for approximately 3% of the glycogen storage diseases with an overall incidence of approximately 1:600,000-1:800,000 [2].

Many variants of GSD-IV with different tissue involvement and variable clinical manifestations have been reported. Typically, the presentation in childhood with liver involvement often leading to cirrhosis, with death by 5 years of age; some patients, however, have mild liver disease without progression and can reach adulthood without liver transplantation. In multiple system involvement, the deficiency of the enzyme was detected in muscle, spleen and the liver. This includes myopathy with or without cardiomyopathy and neuropathy. The age of onset ranges from neonatal to the adult age [1].

Case report

A female child, 4 years of age from Sohag governorate, Egypt. The condition started from the age of 9 months when the mother noticed a progressive abdominal distension with failure to thrive, then sought medical advice. The

patient then admitted in the pediatric department of Sohag university hospital, Egypt, for doing the diagnostic workup. There is a history of episodic cold sweats, irritability, tachypnea & lethargy (hypoglycemic symptoms) that was sometimes accompanied by convulsions. There was no history of fever, jaundice, change in the color of urine or stool or history of bleeding tendency. She was born at full term without any complications and the newborn screening test results were normal. The maternal perinatal history was unremarkable for infections, previous blood transfusion or intravenous drug use. Family history was negative for jaundice, early infantile death, neurodegenerative, metabolic or liver disease .There was a positive consanguinity among her parents "Third degree". There was a history of normal mental with delayed motor milestones in the form of head support that occur at 8 months of age, sitting alone happened at one year of age, standing supported was at two years of age and walking with support occur at four years of age .

Physical examination revealed a body weight of 11 kg (below 3rd percentile) and a height of 82 cm (far below the 3rd percentile), head circumference were 45.5 cm, chest circumference was 49 cm, abdominal circumference 61 cm. She had mild tachypnea and a doll face. There was abdominal distention (fig.1), with hepatomegaly 8 cm below the costal margin, firm in consistency, smooth surface, rounded border & not tender and splenomegaly 6 cm below the costal margin with no other palpable organs. No icterus, lymphadenopathy or ascites. There was delayed a physical development with normal mental development.

Neurological examination revealed: wasting of the proximal muscles of both upper and lower limbs; (deltoid, supraspinatus, infraspinatus muscles, glutei muscles and quadriceps muscle). There was hypotonia of both upper and lower limbs proximally. Shoulders showed telescoping sign and pelvic girdle showed frog like position with normal muscle tone distally. Muscle power in proximal upper limbs was 3, distally was 4b-5. In proximal lower limbs it was 3-4a, distally it was 5. Deep reflexes were preserved in both upper and lower limbs. Flexor planters were responding bilaterally.

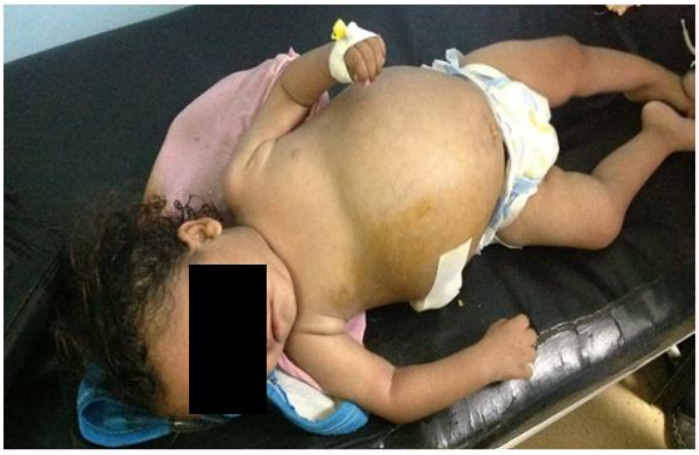

Figure 1: 4 years old female with GSD type-IV showing marked abdominal distension

Laboratory findings showed: Fasting blood sugar: 25 mg/dl. (N: 70 – 110), ALT: 145 IU/L. (N: 0 – 41), AST: 444 IU/L. (N: 0 – 39), ALP: 204 IU/L. (N: 40 – 129), Total bilirubin: 1.1 mg/dl. (Reference range, up to 1.0), Direct bilirubin: 0.7 mg/dl. (Reference range, up to 0.25), Albumin: 3.5 g/dl. (Reference range, 3.4 – 5.5), Total proteins: 6.4 g/dl. (Reference range, 4.9 – 8.9), PT: 12.6 Sec. – PC: 86.6% - INR: 1.08. (Control: 11.9 Sec. – 100% - 1.0). Cholesterol: 218 mg/dl. (Reference range, <200). Triglycerides: 186 mg/dl. (Reference range, <200). Uric acid: 4.7 mg/dl. (Reference range, M: 3-7 &F: 2.5-6). Urine analysis: normal. Creatine phosphokinase- total: 856 U\L, (Reference range, 26-192). Lactate dehydrogenase: 987 U\L, (Reference range, 81-234). Complete blood picture: WBCs: 8.80 $X10^3$/µl (GRA%=56, MON%=9.8 &LYM%=30). RBCs: 3.74 $X10^6$/µl (Hb: 9.2 g/dl, MCV: 73.4). PLT: 374 $X10^3$/µl. Reticulocytic count= 2.1%.

The hepatitis antibody panel (hepatitis B and C, cytomegalovirus, and Epstein-Barr virus) were negative. Lactate: 12.5 mg/dl, (control range: 1-3). Biotinidase: 10.26 U\L, (control range: 7.15- 10.44). Glucose -6- phosphatase activity in biopsied liver tissue homogenate: 7.142 unit per mg tissue proteins (control range: 7.08- 11.42).

Imaging studies for the case revealed: **Abdominal ultrasound** reveals: markedly enlarged liver, homogenous echopattern, smooth surface, no focal lesions, portal vein is not dilated, with diffuse hepatic pathology. Moderately enlarged spleen. No free intraperitoneal fluid collection. **Nerve conduction velocity:** showed normal distal latency, motor conduction velocity and amplitude. **Electromyography:** showed stunted motor unit potential with marked polyphasia and early recruitment with full interference pattern of the proximal muscles, a picture of myopathic pattern. **Echocardiography:** shows thick pericardium with mild pericardial effusion with ejection fraction=67%.
Electroencephalogram "EEG": Normal

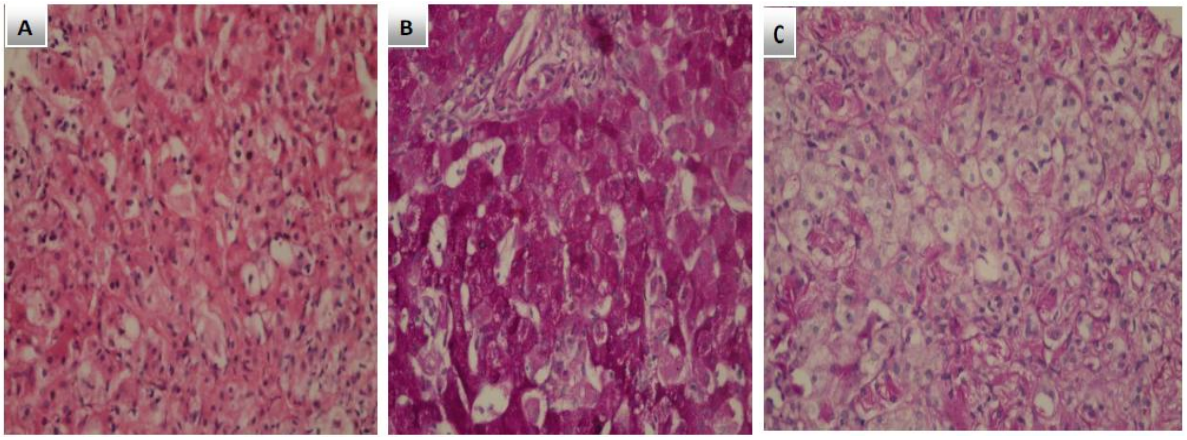

Figure 2: Liver biopsy shows hepatocytes with abundant granular cytoplasm and severe fibrosis merging into cirrhosis. The hepatocytes are distended with PAS diastase sensitive like material. (A: H & E stain X 400; B: PAS stain X 400; C: PAS with diastase X 400)

Histopathological examination: of a percutaneous needle biopsy of the liver revealed: 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. 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* [(3)],** were 2, 3, 3 respectively **(fig.2).** A diagnosis of glycogen storage disease, type IV, was rendered.
Finally muscle biopsy was sent to a private laboratory and the result was the presence of **positive mutation for *GBE1*** (gene coding for glycogen branching enzyme) that confirm the diagnosis.

Discussion

Glycogen storage disease type IV "GSD-IV" exhibits extensive clinical heterogeneity with respect to age of onset, as well as variability in pattern and extent of organ and tissue involvement. The most common form (the classic form) is characterized by hepatosplenomegaly with progression to lethal hepatic cirrhosis in the first few years of life, failure to thrive, and death by 5 years of age [4]. Additionally, the neuromuscular form of GSD-IV is quite variable and may be subclassified into several different phenotypes. Congenital and early infantile phenotypes, presenting with hypotonia, skeletal muscle atrophy, and possibly cardiac and hepatic involvement, with varying degrees of severity and prognosis, have also been described [5-11].
Regarding the clinical data of this case; it was found that the condition was started from the age of 9 months. There was a delayed physical with normal mental development associated with marked abdominal distension, hepatosplenomegaly without jaundice or ascites. There was hypotonia and muscle wasting of both upper and lower limbs proximally. These findings are in agreement with a study by Li *et al* [12] who reported a French Canadian male with GSD-IV presented at 10 months of age with hypotonia, myopathy, and hepatomegaly and a study by Lee *et al* [13] who reported a 15-month old female child with GSD-IV with failure to thrive, progressive abdominal distension and hepatosplenomegaly that stated from the age of 9 months. But our finding are in disagreement with Bao *et al* [6] who reported 3years and 8months Jewish female with GSD-IV who presented at 12 months of age with failure to thrive, hepatomegaly but there was no clinical evidence of muscle, cardiac, or neurological involvement

and Sahoo *et al* [4] who reported a 10 month old male infant with GSD-IV with massive hepatomegaly with no hypotonia, muscle wasting but with normal growth. This difference could be explained by the extensive clinical heterogeneity with respect to the age of onset, as well as variability in pattern and extent of organ and tissue involvement regarding GSD-IV.

As for the laboratory findings for this case; there was fasting hypoglycemia, raised liver enzymes, moderate hypochromic microcytic anemia, hyperlactatemia with raised total creatine phosphokinase & lactate dehydrogenase. There was normal glucose-6-phosphatase activity in the liver tissue to exclude GSD type-I. These findings are in agreement with a study by Sahoo *et al* [4] who reported the laboratory results of a 10 month old male infant with GSD-IV with a total bilirubin level of 0.5 mg/ dL (9 mmol/L); aspartate aminotransferase, 956 U/L (reference range, 0–50 U/L); alanine aminotransferase, 287 U/L (reference range, 0–45U/L) and alkaline phosphatase, 321 U/L (reference range, 170–580 U/L). Urine was negative for reducing substances. Results for prothrombin time, total protein, albumin and cholesterol were all within normal limits. The hepatitis antibody panel (hepatitis B and C, cytomegalovirus, and Epstein-Barr virus) was negative. In disagreement with him, he found normal lactate dehydrogenase level and normal complete blood picture that could be explained by the absence of liver cirrhosis and myopathy in his case. Also our case study is in agreement with a study by Lee *et al* [13] who reported the laboratory results of a 15-month old female child with GSD-IV in which hemoglobin level was 9.0 gm\dl, total bilirubin: 2 mg\dl, direct bilirubin: 0.8 mg\dl, total protein: 5.8 gm\dl, albumin: 3.3 gm\dl, aspartate aminotransferase: 477 U\L, alanine aminotransferase: 210 U\L, alkaline phosphatase: 879 U\L, lactate dehydrogenase: 810 U\L. Serological tests for hepatitis B and hepatitis C were non-reactive. In disagreement with him he found impaired prothrombin time and concentration that could be explained by the difference in the degree of severity of liver cirrhosis of the affected GSD-IV patient.

Regarding the histopathological result of this case; ballooning of the hepatocytes with abundant granular cytoplasm that showed positive staining with periodic acid-schiff "PAS" & reclearing with diastase enzyme. Portal areas showed marked fibrosis with evidence of early micronodular cirrhosis. These findings are in agreement with Sahoo *et al* [4] who reported the histopathological findings of liver biopsy of a 10 month old male infant with GSD-IV in the form of loss of normal hepatic architecture, bridging fibrosis, and micronodule formation. Many scattered hepatocytes showed glassy refractile cytoplasmic inclusions, which stained positively with periodic acid–Schiff and were generally sensitive to diastase digestion. Also this study is in agreement with a study by Lee *et al* [13] who reported the histopathological findings of liver biopsy of a 15-month old female child with GSD-IV in the form of cirrhotic pattern with disarrayed lobular architecture and severe hepatic parenchymal cell loss replaced by fibrosis. The hepatocytes showed distended cytoplasm with clear materials that were shown to be positive by Periodic acid-Schiff (PAS) reaction.

There is no specific treatment for GSD IV although maintenance of normoglycaemia and adequate nutrition may improve liver function and muscle strength and improve long-term outcome for growth in some patients. Liver transplantation is an effective treatment for patients with progressive liver disease. The majority of patients will die in childhood either due to liver failure or severe cardiomyopathy and associated neurological dysfunction. There seem to be a milder subgroups with non progressive liver disease or adult onset neurological disease and normal survival is expected in this subgroup [14].

Conclusion

This child is still living up till now.

Acknowledgment

We would like to acknowledge the team work of the Metabolic and Genetic Disorders Unit- Faculty of Medicine-Assiut University-Egypt, where the laboratory work of this study has been done.

References

1. Aksu, T., Colak, A. and Tufekcioglu,O.(2012): Cardiac Involvement in Glycogen Storage Disease Type IV: Two Cases and the Two Ends of a Spectrum. Case Reports in Medicine. Hindawi Publishing Corporation. Article ID 764286; 1-4.
2. Magoulas PL., El-Hattab AW., Roy A., Bali DS., Finegold MJ. and Craigen WJ. (2012): Diffuse reticuloendothelial system involvement in type IV glycogen storage disease with a novel GBE1 mutation: a case report and review. Hum Pathol; 43:943–51.
3. 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.
4. Sahoo S., Blumberg K., Sengupta E. and Hart J. (2002): Type-IV glycogen storage disease. Arch Pathol Lab Med; 126: 630-631.
5. Moses SW, Parvari R. (2002): The variable presentations of glycogen storage disease type IV: a review of clinical, enzymatic and molecular studies. Curr Mol Med 2:177–188.
6. Bao Y, Kishnani P, Wu JY and Chen YT. (1996): Hepatic and neuromuscular forms of glycogen storage disease type IVcaused bymutations in the same glycogen-branching enzyme gene. J Clin Invest 97:941–948.
7. Tay SK, Akman HO, Chung WK et al. (2004): Fatal infantile neuromuscular presentation of glycogen storage disease type IV. Neuromuscul Disord 14:253–260.
8. Shin YS. (2006): Glycogen storage disease: clinical, biochemical, and molecular heterogeneity. Semin Pediatr Neurol 13:115–120.
9. Sindern E, Ziemssen F, Ziemssen T et al. (2003): Adult polyglucosan body disease: a postmortem correlation study. Neurology 61:263–265.
10. Burrow TA, Hopkin RJ, Bove KE et al. (2006): Non-lethal congenital hypotonia due to glycogen storage disease type IV. Am J Med Genet 140:878–882.
11. Raju GP, Li HC, Bali DS et al. (2008): A case of congenital glycogen storage disease type IV with a novel GBE1 mutation. J Child Neurol 23:349–352.
12. Li, S., Chen, C., Goldstein, L., Wu, J., Lemyre, E., Burrow, A., Kang, B., Chen, Y. and Bali, D. (2009): Glycogen storage disease type IV: novel mutations and molecular characterization of a heterogeneous disorder. J Inherit Metab Dis. DOI 10.1007/s10545-009-9026-5.
13. Lee K., Seo K., Lee H. and Kim J. (1998): Glycogen storage disease type-IV: A case report. J Korean Med Sci; 13: 211-214.
14. Hendriksz, J. Christian and Gissen Paul (2010): Glycogen storage disease. Symposium: inborn errors of metabolism. Pediatrics and child health. Elsevier Ltd; 21(2):84-89.