

Case Report

Forbes Disease: A Case Report

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Abstract

Glycogen storage disease (GSD) type 3 (Forbes disease) is an autosomal recessive inborn error of metabolism caused by loss of function mutations of the glycogen debranching enzyme (Amylo- 1, 6-glucosidase [AGL]) and (oligo-1,4-1,4-glucanotransferase) gene, which is located at chromosome band 1p21.2. GSD 3 is characterized by the storage of structurally abnormal glycogen, termed limit dextrin, in both skeletal and cardiac muscle and/or liver; with great variability in resultant organ dysfunction. Here we describe a 16 year-old boy diagnosed as a case of epilepsy at the age of 8. He presented to us with inadequately controlled seizure, profound proximal weakness, hepatosplenomegaly and right-sided ballotable kidney. The final diagnosis of glycogen storage disease was made by clinical features, lab reports and liver histopathology that revealed PAS positive diastase labile glycogen accumulation within swollen hepatocytes. The particular interest of this paper is to present a case of glycogen storage disease and demonstrate the difference between that entity and other storage diseases.

Key words: Forbes disease, glycogen storage disease, type 3 GSD

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Introduction

A glycogen storage disease results from the absence of enzymes that ultimately convert glycogen compounds to glucose. Enzyme deficiency results in glycogen accumulation in tissues. In many cases, the defect has systemic consequences, but in some cases, the defect is limited to specific tissues. Most patients experience muscle symptoms, such as weakness and cramps, although certain GSDs manifest as specific syndromes, such as hypoglycemic seizures or cardiomegaly¹. There are a number of sub-divisions of GSD. In this report our main focus is GSD 3 because it is compatible with our case. In 1928, Snappes and van Creveld provided the first description of 2 patients with GSD type 3. Both patients had hepatomegaly and reduced ability to

mobilize hepatic glycogen stores. In 1953, Forbes provided an extensive clinical description of a third patient with GSD type 3 and suggested that the glycogen in both liver and muscle tissues had an abnormal structure². Illingworth and Cori isolated the glycogen from the tissues of this patient and showed that it had extremely short outer chains³. This structure had previously been termed a limit dextrin by Cori and Cori. They predicted that the patient's condition was caused by a debranching enzyme deficiency. In 1956, Cori and Cori specifically demonstrated the enzyme deficiency in GSD type 3⁴.

Although Snappes and van Creveld's patients with GSD type 3 were the first individuals in whom a defect in glycogen metabolism was reported, Cori and Cori demonstrated in 1952 that the absence of glucose-6-phosphatase activity was the enzyme defect in GSD I (von Gierke disease). Indeed, GSD I was the first inborn error of metabolism in which the precise enzyme defect was identified³.

Case Report

A 16 year-old boy was diagnosed as a case of epilepsy at the age of 8 and was on regular use of anti epileptic drugs. The boy got himself admitted with the complaints

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of inadequately controlled seizure and gradual deterioration of intellect for last one year along with profound proximal weakness for preceding eight months.

On examination he had coarsefacies, hepatosplenomegaly, right sided ballotable kidney and scoliosis. He was hemodynamically stable. On investigation, complete blood count revealed– Hb-14.2 gm/dl, ESR-5mm in 1st hour, WBC- $9 \times 10^9/L$ with Polymorph-60%, Lymphocyte-33%, Eosinophil-3%, Monocyte- 9%, Platelet count- $2,20 \times 10^9/L$, Urine Microscopy revealed Proteinuria (+). His fasting blood sugar was 4.2 mmol/l, S. SGPT – 265 unit/L, alkaline phosphatase- 903 unit/L, S Calcium – 8.7 mg/dl, S phosphate – 5.6 mg/dl, S Lactate- 18 mg/dl, S CPK-1327 unit/L, EMG – primary muscle disease, X-ray Lumbosacral spine revealed dysostosis multiplex involving thoracolumbar vertebrae with kyphoscoliosis (fig-1), USG of whole abdomen showed hepatosplenomegaly (Liver was 20 cm with mildly increased ecogenicity and spleen was mildly enlarged) and size of both kidneys were at the upper normal limit. Echocardiography revealed basal and mid-septum was hypokinetic with EF – 55%, MRI of brain, CT scan of head and EEG were normal. Liver histology with hematoxylineosine and PAS stained reaction demonstrated – PAS positive diastase labile glycogen



Figure-1: Appearance of the patient: Coarsefacies.

particles accumulated within the swollen hepatocytes, liver architecture was distorted suggestive of chronic hepatitis progressing to cirrhosis (fig 2 & 3).



Figure-2: X-ray Lumbosacral spine revealed Dysostosis multiplex involving thoracolumbar vertebrae with kyphoscoliosis.

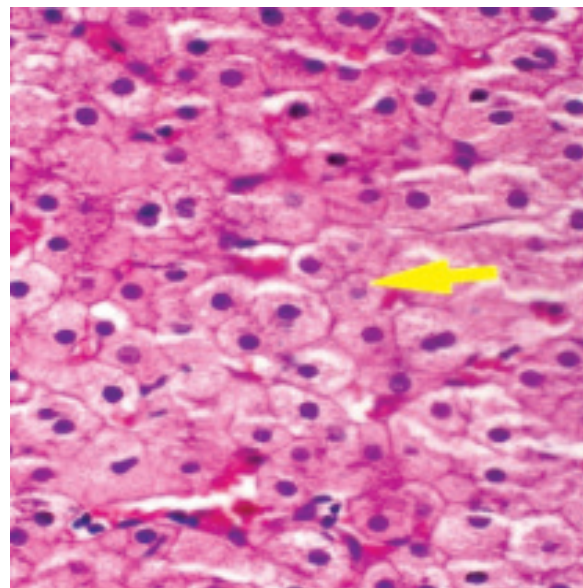


Figure-3: H&E X 400 showing swollen hepatocytes with cytoplasmic rarefaction and glycogenated nuclei

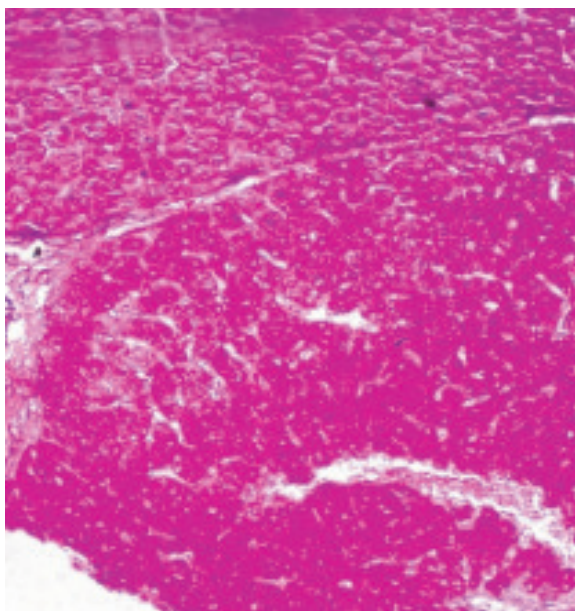


Figure 4: PAS X 100 showing glycogen stained hepatocyte with PAS stain

Discussion

Approximately 80% of patients are glycogen debranching enzyme (GDE) deficient in both liver and muscle (type IIIa) and 15% of patients have GDE absent in liver but retained in muscle (type IIIb). It presents in early childhood and has an incidence of 1:50,000 to 1:70,000². Our case also presented in early childhood. Liver, skeletal muscle and heart are the main organs involved in various levels of severity. In our case all the three organs were involved along with renal involvement. Gross hepatomegaly, hypoglycemia, seizures and growth retardation are the main presentations in type 3 GSD. Our case also had similar presentation except growth retardation. Majority of the cases with hepatic involvement present with protruded abdomen because of gross hepatomegaly and also have raised serum aminases and serum cholesterol. During childhood and early adulthood the symptoms seem to regress and normal adulthood appears in most patients except few cases who may develop cirrhosis with or without sequelae of portal hypertension⁵. Therefore hepatological follow up is required during adulthood. This was very much applicable for our case as his liver histopathology showed distorted architecture with features of early cirrhosis. The serum concentration of uric acid, lactate and ketones were normal. Deficiency

of amylo-1-6 glucosidase can be demonstrated in one of the following tissue, leukocytes, erythrocytes, liver, muscle, fibroblast or chorionic villi^{6,7}. In our patient we could not perform erythrocyte glycogen content as well as amylo-1-6 glucosidase activity in leukocyte as these assays are not available in Bangladesh.

The considered differential diagnoses for the case was firstly tuberous sclerosis, as he presented with seizure, mild mental retardation with coarse facies. It was easily excluded by the absence of any structural abnormality in brain as well as in skin. Our second differential was Mucopolysaccharidoses (Hunter) because of his coarse facies, mild mental retardation, hepatosplenomegaly and skeletal abnormality. But it was also excluded by liver biopsy report.

His skeletal abnormality can be explained by drug induced osteomalacia (prolong use of multiple anti epileptic drugs). Anticonvulsants induced osteomalacia is not commonly recognized complication following long term antiepileptic medication. The frequency of problem is related to the non ambulatory patients receiving high dose of anticonvulsant (phenobarbitone, phenytoin, and carbamazepine) medications for several years with suboptimal intake of vitamin D as well as limited exposure to sunlight⁸. Biochemical evidences of osteomalacia were alteration of serum Calcium, Phosphate, Alkaline phosphatase and radiological changes. Diagnosis was established by exclusion of other causes particularly malabsorption, renal and hepatic diseases. Though our patient had no evidence of malabsorption but he had significant abnormality in hepatic and renal function tests. So the cause of osteomalacia in our patient was not confirmed whether it was solely anticonvulsant induced or a feature of combined abnormality.

The third differential was GSD type I (von Gierke disease) as both type I and type 3 share overlapping features⁹. But it was excluded by the absence of severe hypoglycemia and normal S lactate, uric acid and urinary ketone level.

The recommended treatment for GSD type 3 comprises frequent high protein feedings during the day and a high protein snack at night; energy is distributed as 45% carbohydrates, 25% protein and 30% fat². Carbohydrates should be given frequently round the clock when the patient is young. Gastric drip feeding at

night may be introduced in the infant if hypoglycemia is a problem¹⁰. Uncooked corn starch therapy can be started in the older child and is very useful¹¹. Our patient was explained to take feeds of corn starch every two hours with rice and lentils in between the meals.

The prognosis for a relatively normal life is good. But when there is evidence of chronic hepatitis, the risk of hepatic failure and hepatocellular carcinoma worsen the prognosis directly⁵. To date, over 50 AGL mutations have been discovered in GSD3^{12,13}. Recently four rare missense mutations (L620P, R1147G, Y1445ins and G1448R) were also identified and found that they alter diverse cellular functions¹⁴. Prenatal diagnosis and carrier detection is possible with the help of identification of the highly informative DNA polymorphic marker in the AGL gene¹⁵.

Conflict of interest: None

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