# HEPATIC GLYCOGEN STORAGE DISEASES (A RETROSPECTIVE STUDY)

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*ABSTRACT*

***Background:*** *Liver glycogen storage diseases (GSD) are metabolic disorders that result in abnormal storage amounts or forms of glycogen, and often have hepatomegaly and hypoglycaemia as presenting features.* ***Methods and Results:*** *A retrospective study was done to evaluate 13 patients (aged between 3-96 months; median 15 months) who were followed-up for liver glycogen storage disease in Gazi University School of Medicine Department of Pediatric Metabolism and Nutrition. Four patients were enzymatically diagnosed to have GSD Type I, one patient GSD Type III and 1 patient X-linked liver glycogenosis. Liver biopsy specimens of 5 patients were compatible with glycogenosis. The most frequent complaints were abdominal distension (85 %) and seizures (39 %). Physical examination revealed mostly hepatomegaly (92 %). Elevation of transaminases was found in 92% of the patients, whereas hypercholesterolaemia was found in 62%, hypertriglyceridemia in 92%, hyperuricemia in 30% and lactic academia was detected in 46%. Metabolic acidosis and hypoglycaemia was observed in 30% and 61% of the patients respectively. Nutritional therapy was begun in all patients and they have developed well except one patient who died due to sepsis.* ***Conclusion:*** *New treatment modalities such as liver transplantation and gene therapy would probably increase survival for glycogen storage diseases in the future.*

***Key Words:*** *Glycogen Storage Diseases.*

## INTRODUCTION

The hepatic glycogen storage diseases are a group of inherited disorders of enzymes regulating the breakdown of glycogen. They include defects of the glycogen synthase (GSD 0), microsomal glucose-6-phosphatase complex (GSD I), the debranching enzyme (GSD III), hepatic phosphorylase (GSD VI) and phosphorylase b kinase (GSD IX) (1).

Thirteen patients who are followed-up with the diagnosis of glycogen storage disease in Gazi University Medical Faculty Department of Pediatrics Division of Pediatric Metabolism and Nutrition will be presented.

## MATERIALS AND METHODS

The study involves 13 patients (six female, seven male) who are followed-up with the diagnosis of hepatic glycogen storage disease. The patients were aged between 3-96 months (median 15 months). The parents of 10 patients were relatives (eight parents 1st degree, one 2nd and one 3rd degree).

Retrospectively, the occurrence of abdominal distension, convulsion, hepatomegaly and characteristic facial appearance were investigated clinically as well as haemoglobin, white blood cells, blood alanine and aspartate aminotransferase, triglyceride, cholesterol, uric and lactic acid, glucose levels and the development of metabolic acidosis in all patients.

The diagnosis of glycogen storage disease was made enzymatically in six of the patients. The deficient enzyme was glucose-6-phosphate hydrolase in two (GSD Ia), glucose-6-phosphatase translocase in two (GSD Ib), glycogen-debranching enzyme in one (GSD III) and phosphorylase kinase in one (X Linked Liver Glycogenosis) and also by liver histology (enlarged hepatocytes, diffuse vacuolation of hepatocytes with large amounts of glycogen) and clinical features in 5 (4 GSD Ia and 1 X Linked Liver glycogenosis). Two patients were thought to have GSD Ia clinically. One of the patients with GSD Ia died due to severe gastroenteritis and sepsis.

## RESULTS

Regarding the clinical findings, abdominal distension was present in 11 patients hepatomegaly in 12 and characteristic face in four. Five patients had hypoglycaemic convulsions (Table 1).

Table 1 : The clinical findings of 13 patients with liver glycogenosis.

| CLINICAL FEATURE | NUMBER | % |
|---|---|---|
| Hepatomegaly | 12 | 92 |
| Abdominal distension | 11 | 84 |
| Hypoglycemic convulsions | 5 | 38 |
| Characteristic face | 4 | 30 |

In the laboratory investigations, AST and ALT were elevated in 12 of the patients, 12 patients had hypertriglyceridemia, and eight had hypercholesterolaemia. Four patients had elevated uric acid levels and six had elevated lactic acid levels. Eight patients had attacks of hypoglycaemia and four had acidotic attacks. Nine patients had iron deficiency anemia (Table 2).

Body weights of three patients were below the 3rd percentile, four were below the 10th percentile, two below the 25th, three below the 50th and one below the 75th percentile.

Table 2: The biochemistrical features of 13 patients with liver glycogenosis.

| BIOCHEMICAL FEATURE | NUMBER | % |
|---|---|---|
| Elevated AST and ALT | 12 | 92 |
| Hypertriglyceridemia | 12 | 92 |
| Anemia | 9 | 69 |
| Hypercholesterolemia | 8 | 61 |
| Hypoglycemia | 8 | 61 |
| Elevated lactic acid | 6 | 46 |
| Elevated uric acid | 4 | 30 |

Table 3: Body weight and height percentiles of the 13 patients with liver glycogenosis.

| PERCENTILES | WEIGHT | | HEIGHT | |
|---|---|---|---|---|
| | NUMBER | % | NUMBER | % |
| Below 3rd | 3 | 23,2 | 6 | 46,3 |
| Below 10th | 4 | 30,7 | 1 | 7,6 |
| Below 25th | 2 | 15,3 | 4 | 30,8 |
| Below 50th | 3 | 23,2 | 2 | 15,3 |
| Below 75th | 1 | 7,6 | | |

Heights of six patients were below the 3rd percentile, one was below the 10th percentile, four were below the 25th percentile and two were below the 50th percentile (Table 3).

One patient with GSD Ib has been given GC-SF treatment for leucopenia.

All the patients are beling followed-up and clinical and biochemistrical tests as well as ultrasonographic examinations are performed at regular intervals.

None of the patients have had signs of cirrhosis or portal hypertension until this date.

## DISCUSSION

Inborn errors of metabolism are not rare in Turkey due to the high frequency of consanguineous marriages (2). There are difficulties in performing enzymatic or genetic analysis and in practice the classification of the patients is primarily made on clinical features.

Eight of our patients were followed-up by GSD I glycogenosis. Cushingoid appearance, fasting hypoglycaemia (<1.5 g/L) with lactic acidosis (>5 mmol/L), hyperlipidemia and hyperuricemia make up the clinical picture. Hepatic aminotransferases are usually normal or mildly elevated. Liver histology reveals steatosis and glycogen storage with no fibrosis. Histochemical stains for (G-6-P) are negative and the enzyme is undetectable in the liver. In our series of 10 patients with GSD I, all had

hyperlipidemia, nine had elevations of liver enzymes and four had lactic acidemia. Eight patients had hypoglycaemia and all the attacks were symptomatic. The initial aim of dietary treatment in GSD I is to provide a continuous supply of exogenous glucose to maintain normal blood sugar and suppression of counter regulatory responses (1). This is best achieved in infants by frequent daytime feeding, use of oral uncooked cornstarch, which is hydrolysed in the gut to release glucose slowly over hours, and continuous nocturnal enteral glucose feeds. If dietary control is strict in infancy, normal growth and development will be attained (3). However in our patients the main difficulty is in adapting the child to this strict diet.

In GSD Ib neutropenia could develop due to bone marrow deposition and subcutaneous GC-SF is used successfully in the treatment (4).

In GSD III the metabolic defect is milder, as other routes of gluconeogenesis are intact and there is no renal involvement. The defect is expressed in muscle in 85% of cases (Type IIIa). As the abnormally structured residual glycogen is fibrogenic, hepatic fibrosis and cirrhosis are common complicating features. Diagnosis is confirmed by identifying the deficient enzyme in leucocytes or liver tissue. Moreover, antenatal diagnosis is possible by enzyme measurement or mutation analysis on chorionic villi samples. Dietary treatment is similar to GSD type I, but a higher protein intake is recommended because of the demand for gluconeogenic amino acids (1).

The most important diagnostic tools in glycogen storage diseases seem to be enzymatic and molecular analysis (5,6). However histopathologic and clinical evaluations are still valuable in countries where the former two techniques are not available. Also the prenatal diagnosis of the disease is very important so as to prevent all these difficulties in the follow-up of the patients.

Growth retardation is one of the expected complications of GSD as was observed in our patients (7) and dietary therapy is important for normal or nearly normal physical growth and development (1).

It remains unclear whether all the long-term complications of glycogen storage disease can be prevented by dietary therapy and this fact stimulates a demand for further investigations (8,9). New treatment modalities such as liver transplantation and gene therapy would probably increase survival in glycogen storage diseases in the future.

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**REFERENCES**

1. Wolfsdorf JI, Holm IA, Weinstein DA. Glycogen storage diseases. Endocrinol Metab Clin North Am 1999; 28: 801-823.
2. Tunçbilek E, Ulusoy M. Consanguinity in Turkey in 1988. Turk J Population Stud 1988, 11: 35-46.
3. Chen YT, Bazzarre CH, Lee MM, Sidbury JB, Coleman RA. Type I glycogen storage disease: Nine years management with cornstarch. Eur J Pediatr 1993; 152 (suppl 1): 56-59.
4. Wendel U, Schroten H, Burdach S, Wahn V. Glycogen storage disease type Ib: Infectious complications and measures for prevention. Eur J Pediatr. 1993; 152 (suppl 1): 49-51.
5. Zak B, Epstein E, Baginski ES. Determination of liver microsomal glucose-6-phosphatase. Ann Clin Lab Sci 1977; 7: 169-177.
6. Akanuma J, Nishigaki T, Fujii K, Matsubara Y, Inui K, Takahashi K, Kure S, Suzuki Y, Ohura T, Miyabayashi S, Ogawa E, Iinuma K, Okada S, Narisawa K. Glycogen storage disease type Ia: Molecular diagnosis of 51 Japanese patients and characterization of splicing mutations by analysis of ectopically transcribed mRNA from lymphoblastoid cells. Am J Med Genet 2000 13; 91: 107-112.
7. Willems PJ, Gerver WJ, Berger R, Fernandes J. The natural history of liver glycogenosis due to phosphorylase kinase deficiency: A longitudinal study of 41 patients.Eur J Pediatr 1990; 149: 268-271.
8. Smit GPA. The long term outcome of patients with glycogen storage disease type Ia. Eur J Pediatr. 1993; 152 (suppl 1): 52-56.
9. Lee PJ, Leonard JV. Hepatic glycogen storage disease-problems beyond childhood. J Inherit Metab Dis 1995; 18: 462-472.