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Clinical properties and disease prognosis in cases of glycogen-storage disease type 1a and type 1b

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Summary

Aim: To describe the characteristics of patients with type I glycogenosis, the presentation types, the main clinical and laboratory signs, and also the disease outcomes on long term follow-up.

Material and Method: 30 patients with glycogen storage disease type I who followed up our clinic were included in these study. The mean age of the patients was 12±24 months (5 month-20 years), and 16 patients were male and 14 were female. Twenty-seven patients were type Ia and three patients were type Ib glycogenosis.

Results: The main complaints were acidotic breathing (93.3%), abdominal protruding (83.3%), and main physical finding was hepatomegaly (100%) on admission. Among laboratory parameters, hypoglycemia, increased transaminase values, hypertriglyceridemia, lactic acidosis, hyperuricemia were the most frequent findings. Short stature, osteoporosis, microalbuminuria, proteinuria and liver adenoma were determined in 50%, 20%, 16.7%, 55.6%, 6.92% of patients after the evaluation of patients in terms of long term complications respectively.

Conclusions: Glycogen storage disease type I is a rare condition, but with possible life-threatening consequences. It has to be kept in mind whenever severe hepatomegaly and/or hypoglycemia are present. Glycogen storage disease type I causes severe complications unless it is not treated appropriately. Early diagnosis and good metabolic control with dietary therapy may prevent these complications and increase life quality of the patients. *(Turk Arch Ped 2013; 48: 117-122)*

Key words: Child, clinical course, glycogen storage disease type I

Introduction

Glycogen storage disease type 1 (GDH 1) is a metabolic disease which occurs as a result of dysfunction in glucose 6 phosphatase (G6Paz) system. Its prevelance is 1/100 000 and it is inherited recessively (AR). While deficiency of glucose 6 phosphate transporter protein (G6PT) which provides transportation of glucose 6 phosphate (G6P) from the cytoplasm to the lumen of the endoplasmic reticulum leads to glucogen storage disease type 1b (GSD 1b), deficiency of G6Pase which provides hydrolysis of G6P to glucose and phosphate leads to glucogen storage disease type 1a (GSD 1a) (1,2). Deficiency of both G6Pase and G6PT lead to disruption in glucose homeostasis and insufficent glucose production in the liver.

In glucogen storage disease 1a, hepatomegaly, lactic acidosis and hypoglycemia are observed as a result of decreased activity of G6Pase in the liver, kidney and intestines. Other findings include doll's face, truncal obestiy, decreased muscle mass, enlarged kidney, delayed puberty, growht retardation, hyperlipidemia and increased uric acid (3). In glucogen storage disease 1 b, neutropenia, neutrophil and monocyte dysfunction, recurrent infections and inflammatory bowel disease (IBD) develop in addition to the findings observed in type 1 a (4,5).

The increase in information about glycogen storage disease 1a and GSD 1b and in the rate of determination of mutation gave the idea of diagnosing GSD 1a and GSD 1b with mutation analysis together with clinical and biochemical abnormalities instead of enyzmatic measurement by liver biopsy which is an invasive method.

With molecular studies early and reliable diagnosis can be made, carriers can be determined and genetic counselling

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can be provided (6). Because of high consanguineous marriage rates in our country (approximately 21.1%) GSD is observed frequently as the other autosomal recessively inherited metabolic diseases (7).

While type I, III and IX constitute 80% of hepatic GSDs, type 1a constitutes approximately 26-34% of this group (8). In this study, we aimed to examine the clicinal properties and short-term and long-term complications in patients with GSD 1a and 1b which are observed frequently in our country.

Material and Method

A total of 30 patients who presented to our clinic with complaints of hypoglycemia and hepatomegaly between 1990 and 2009 and 27 of whom were diagnosed with GSD 1a and 3 of whom were diagnosed with GSD 1b were included in this study. The files of the patients were examined retrospectively and the clinical and laboratory findings at the time of diagnosis and in the follow-up were recorded. A diagnosis of glycogen storage disease type 1a was made with increased amount of glycogen and decreased G6Pase activity in the liver biopsy specimens and/or mutation analysis in the G6Pase gene. A diagnosis of glycogen type 1b was made with clinical and laboratory findings, determination of G6Pase activity in the liver biopsy specimens and/or mutation analysis in the G6Pase gene. The height, body weight and standard deviation values were evaluated using the standarts establisehd by Neyzi et al. (9) for the Turkish children. In assessment of children with a problem of growth, the standard deviation score (SDS) was used (10). Values below -2 SDS were considered as short stature. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), calcium (Ca), phosphorous (P), alkaline phosphatase (ALP) lactic acid, alpha fetoprotein, triglyceride, cholesterol, uric acid, blood glucose, 24-hour urine microalbuminuria and proteinuria, blood pH and blood gas values at the time of diagnosis and in the follow-up were recorded and these values were compared with the normal values for age and gender and screened in terms of increased liver enzymes, hypertriglyceridemia, hypercholesterolemia, increased lactic acid, increased alpha fetoprotein during the follow-up, proteinuria and microalbuminemia which were expected for GSD 1a and 1b (11,12). Abdominal ultrasonography (USG) was performed in terms of liver adenoma and nephrocalcimosis and renal stones. Bone mineral density (BMD) was measured in terms of osteopeny and osteoporosis which are complications of glycogen storage disease type 1. Bone mineral density was evaluated by dual energy X-ray absorptiometry (DEXA) method using “T score” for the adult age group and “Z score” for the peiatric age group. For T and Z scores SD values between -1 and -2 were considered as osteopeny and SD values of -2 and below were considered as osteoporosis. In the patient group, a diet plan in which 60-65% of all the energy was provided from carbonhydrates, 10-15% was provided from protein and the remaining was provided from fats (preferably liquid fats containing high amounts of linoleic acid) was constituted, though this was varied according to the age, body weight, family education and nutrition preference. A nutrition program in which the patient was fed every 2-4 hours with a diet limited in lactose, fructose and sucrose excluding fruit, vegetables and a small amount of dairy products. In addition, raw corn starch for 6 times a day was added to the diet. Care was taken to feed especially the patients below 7 years of age at 24.00 and 03.00.

Statistics

The findings obtained in the study were summarized using descriptive statistics. The data were assessed using “SPSS for Windows version 12” statistical package program. The mean ± standard deviation and percent distributions related with the data were given.

Results

The study was conducted with 30 patients (16 male and 14 female) with a diagnosis of GSD 1 whose mean age was 12±24 months (5 ay-20 years) at the time of diagnosis. Consanguineous marriage was present in 22 of the patients (73.3%)and a familial history of GSD 1 was present in 9 of the patients (30%). The complaints of the patients and their frequencies at the time of diagnosis are shown in Table 1. It was found that increased breathing frequency and abdominal distension were the most common presenting complaints. When the physical examination findings at the time of diagnosis were examined, it was found hepatomegaly was observed in all patients, doll’s face was observed in 63,3% of the patients with GSD 1 (63% of the patients with GSD 1a and 66.7% of the patients with GSD 1b) and blurred consciousness was found in 46.7% of the patients with a diagnosis of GSD 1 (48.1% of the patients with GSD 1a and 33.3% of the patients with GSD 1b). The blood gases were found to be compatible with metabolic acidosis in 93.3% of the patients at the time of diagnosis. The mean follow-up period of the patients was 4.5±3.8 years (5 months- 16,5 years). The mean and standard deviation values for the body weight, height and height SDS are shown in Table 2. The mean and standard deviation values for the laboratory data during the follow-up period are shown in Table 3. When the patients were evaluated in terms of long-term complications, adenoma in the liver was found in two patients with a diagnosis of GSD 1 (in one patient with GDS 1a (3.7%) and in one patient with GSD 1b). Microalbuminuria was found in 6 (20%) of the patients with a diagnosis of GSD 1 (in 5 (18.5%) of the patients aith GSD 1a and in one of the patients with GSD 1b). Proteinuria was found in 5 (16.7%) of the patients

with a diagnosis of GSD 1 (in four of the patients (14.8%) with GSD 1a and in 5 (16.7%) of the patients with GSD 1b) (Table 3). Assessment of bone mineral density of the patients is shown in Table 4.

Discussion

Glycogen storage disease type 1 is a severe autosomal recessive metabolic disease which affects carbonhydrate and purin metabolism. Its prevelance is 1/100 000 live births in the white race and 1/20 000 in Ashkenazi Jews (1,2). The prevalence of hepatic glycogenoses in Turkey is not known. However, the high rates of consanguineous marriages in our country (approximately 21.1%) suggest that the prevalence of GSD 1 is high as the other autosomal recessively inherited metabolic diaseses (7). In the study performed by Saltık et al. (13) in 2000 in 45 Turkish patients with a diagnosis of GSD 1, consanguineous marriage was found with a rate of 77.8%. Similarly, consanguineous marriage was found with a rate of 73.3 and a familial history of GSD 1 was found with a rate of 30% % in our patients with GSD 1 who were included in our study. When the family trees were examined, infant mortality between delivery and 20 months of age with unknown cause was observed with a rate of approximately 16.7%. It is thought that most of these patients were GSD 1 patients whose diagnoses were missed. The gender distribution in glycogen storage disease 1 is almost equal (14,15,16). In our study, 46.7% of 30 GSD patients were female and 53,3% were male. National multi-center studies should be performed to obtain epidemiological data about GSD 1 in our country.

The most prominent clinical findings of the GSD 1a and 1b patients in our study are summarized in Table 1. It was observed that the presenting complaints and findings of the patients were similar to our study in a study (ESGSD I) performed in 288 GSD 1 patients (231 GDS 1a and 57 GSD 1b patients) from 12 European countries to examine the clinical prognosis of glycogen storage disease 1 in the long-term, to establish a protocol for diagnosis and follow-up and to improve treatment methods (14).

Diarrhea episodes which worsen with age may be observed in patients with glycogen storage disease 1 (5). In this study, diarrhea episodes were found in 11.1% of the patients with GSD 1a. In the ESGSD I study (European Study Group for Glycogen Storage Disease Type 1), this rate was found to be 35% (14). However, this high rate in the ESGSD I study may be explained by the fact that the mean age of the patients was higher compared to the mean age of our patients. The cause of diarrhea episodes in glycogen storage disease 1a has not been determined yet (5,15). However, the relation between erythrocyte dysfunction caused by decreased G6Pase activity and diarrhea episodes is being investigated. In this study, diarrhea episodes were found in 66.7% of the patients with GSD 1b. This rate was found to be 55% in the ESGSD I study (14). It is thought that loss of function of mucosal barrier caused by inflammation is the main cause of diarrhea episodes in GSD 1b (5,16).

Table 1. Complaint at the time of diagnosis

Complaint	GSD 1a		GSD 1b		GSD 1	
	n	%	n	%	n	%
Frequent breathing	26	96.3	2	66.7	28	93.3
Abdominal distension	22	81.5	3	100	25	83.3
Seizure	11	40.7	1	33.3	12	40
Diarrhea episodes	3	11.1	2	66.7	5	16.7

GSD: Glycogen storage disease

Table 2. Body weight, height and height SDS values

Variables	GSD 1a	GDH 1b Ortalama ± SS	GDH 1 Ortalama SD
BW (Kg)	21.7±14.9	35.7±18.8	20.2±13.9
Height (cm)	100.0±26.3	125±34.6	97.2±24.5
Height SDS	-1.88±1.17	-1.86±0.45	-1.88±1.1

BW: Body weight

The fact that glycogen storage disease 1 affects lipid and purin metabolism in addition to carbonhydrate metabolism is reflected with hyperlipidemia, hyperuricemia, hyperlactemia and increased liver enzymes in the laboratory tests. In this study, increases in the above-mentioned variables were found in the laboratory tests at the time of diagnosis and during the follow-up period both in patients with GSD 1a and 1b (Table 3). After diet treatment is started in the patients a certain amount of improvement is observed in secondary biochemical disorders. However, hyperlipidemia is frequently observed in GSD 1 patients despite diet treatment. In this study, especially hypertriglyceriedmia is prominent after diet treatment in patients with GSD 1a and 1b. In the ESGSD study, it was shown that the number of patients with hyperlipidemia was higher and hyperlipidemia was more severe in GSD 1a patients compared to GSD 1b patients (14). Hyperlipidemia is thought to be caused by increased lipogenesis arising from the increase in acetyl-CoA and delay in cleaning of serum lipoproteins in GSD 1 (17,18,19,20). In the ESGSD study, the cause of the difference observed in hyperlipidemia between GSD 1a and GSD 1b is not known. In this study, no difference was found between the patients with a diagnosis of GSD 1a and GSD 1b in terms of hyperlipidemia. In our study the number of GSD 1b patients was very low. In GSD 1, increased hemorrhagic diathesis is observed because of

Table 3. Laboratory data during follow-up

Variables	GSD 1a	GDH 1b Ortalama SS	GDH 1 Ortalama SS
Blood glucose (mg/dL) (74-100)	77±22.3	68.3±15	76.1±21.7
AST (U/L) (<41)	132.9±173.3	59.3±70.0	125.6±166.7
ALT (U/L) (<34)	103.4±115.7	57.7±63.5	98.9±111.7
Uric acid (mg/dL) (2,4-5,7)	5.3±2.3	5.8±0.9	5.3±2.2
Triglyceride (mg/dL) (<150)	575.4±373.7	639.3±364.2	581.8±367.1
Cholesterol (mg/dL) (<200)	190.6±51.5	214.0±82	193±53.7
Lactic acid (mmol/L) (0,5-2,2)	4.5±1.6	7,9±5,3	4.8±2.3
Ca (mg/dL) (8,6-10,2)	4.5±1.6	7.9±5.3	4.8±2,3
P (mg/dl) (3.5-5.1)	4.7±0.8	5.2±0.2	4.7±0.8
ALP (U/L) (<462)	245.6±65.9	151.3±30.6	236.2±105.43
AFP ng/ml (0-9)	3.9±3.5	2.9±2.5	3.8±3.3
*Microalbuminuria(mg/gün)	4.4±2.5		4.4±2.5
*Proteinuria (mg/m^2/h)	6.3±10.9	72.6±119.9	14.3±42.3

*Values in 24-hour urine; Normal: < 4 mg/m^2/h. Nephritic level= 4-40 mg/m^2h; Nephrotic = > 40. mg/m^2/h; Microalbuminuria. 30-300 mg albumin in a 24-hour urine sample

Table 4. Assessment with BMD

BMD	GSD 1a		GSD 1b		GSD 1	
	n	%	n	%	n	%
Normal	6	25	-	-	6	22.2
Osteopenia	5	20.8	1	33.3	6	22.2
Osteoporosis	13	54.2	2	66.7	15	55.6

disruption of platalet functions (21,22). In this study, severe and/or frequently recurring epistaxis was found in 30% of the patients.

Moderate growth retardation which is especially noted in the school age in glycogen storage disease 1 is a significant finding which is observed in most of the patients and short stature is common among adult patients (13,23,24). Parscau et al. (25), reported growht retardation in 22 GSD 1 patients who were in the prepubertal age group in the study they performed. Talente et al. (24) found short stature in 90% of the patients in a study in which they evaluated 37 GSD 1a patients and 5 GSD 1b patients who were aged 18 years and older. In another stury, Wolfsdorf et al. (26) reported that the heights of 23 GSD 1 patients were below the values appropriate for the chronological age. In our study, the heights of 50% of the patients were below -2 SDS and the height measurement in 73.3% of the patients was below the value which was appropriate for the chronological age. The cause of growht retardation has not been explained fully yet. There is no definite proof for deficiency of growth hormone. However, the positive relation between metbolic control and growth suggests that chronic metabolic (lactic) acidosis may inhibit the activity of growth hormone (27).

Hepatic adenoma which is one of the long-term complications of glycogen storage disease 1 was found in two male patients in this study (a 17-year-old GSD 1a patient and a 20-year-old GSD 1b patient). In our study, the rate of adenoma was 6.92% and it was predominant in the male gender as shown in previous studies (28). In previous studies, the prevalence of adenoma ranged between 16% and 75% according to the age group of the patients examined and it was reported to be found in 75-80% of the patients aged older than 25 years (14,23,24,25,29). The low rate in this study may be related with the fact that the study was conducted with a substantially young age group with a mean age of 6.2±5.1 years (0.5-20 years).

Osteopeny is another complication which is observed frequently in glycogen storage 1 patients. Many metabolic and endocrin disorders observed in GSD 1 may inhibit normal bone formation and lead to mineralization changes (30). Decreased bone mineralization has been reported in both adult and pediatric GSD 1 patients in different studies (30,31). In this study, osteopeny was found in 22.2% of the patients and osteoporosis was found in 55.6% of the patients. Bone mineral density (BMD) should be assessed in patients who are being followed up with a diagnosis of glycogen storage disease 1 and early treatment should be started in patients in whom BMD is found to be low.

A sever complication which developes with advanced age is renal disease in which glomerular and tubular functions are affected (38,39). The first finding of glomuerular disease is hyperfiltration. Following hyperfiltration microalbuminuria and proteinuria develop (8.34). The freqency of proteinuria was found to be 13% and the frequency of microalbuminuria was found to be 31% in the ESGSD I cohort study which included the highest number of patients (17). In the same study, it was reported that the frequency of proteinuria and microalbuminuria increased with age; proteinuria was found at a mean age of 16 years and microalbuminuria was found at a mean age of 13 years. In this study, microalbuminuria was found in 20% of the patients and proteinuria was found in 16.7% of the patients. ACE inhibitor treatment was started in 2 of our patients who were older than 15 years, since proteinuria continued despite diet treatment.

Conclusively, GSD 1 which occurs more frequently in our country compared to the world because of a high rate of consanguineous marriage leads to severe complications, if not treated appropriately. Providing adequate metabolic control with early diagnosis and treatment can prevent development of complicaitons and increases the quality of life.

Conflict of interest: None declared.

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