Hypercalcemia in glycogen storage disease type I patients of Turkish origin

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Glycogen storage disease type I (GSD I) is an autosomal recessive disorder caused by defects in the glucose-6-phosphatase complex. Deficient activity in the glucose-6-phosphatase-α (G6Pase) catalytic unit characterizes GSD IA and defects in the glucose-6-phosphate transporter protein (G6PC) characterize GSD IB. The main clinical characteristics involve fasting hypoglycemia, hyperuricemia, hyperlactatemia, and hyperlipidemia. Hypercalcemia arose as an unknown problem in GSD I patients, especially in those with insufficient metabolic control. The aim of the present study was to obtain the prevalence of hypercalcemia and to draw attention to the metabolic complications of GSD I patients, including hypercalcemia in poor metabolic control. Hypercalcemia frequency and the affecting factors were studied cross-sectionally in 23 GSD I pediatric subjects. Clinical diagnosis of GSD I was confirmed in all patients either through documentation of deficient G6Pase enzyme activity levels on liver biopsy samples or through G6PC gene sequencing of DNA. Hypercalcemia was detected in 78.3% of patients with GSD I. Different from the previous report about hypercalcemia in a GSD IA patient who had R83H and 341delG mutations, we could not identify any genotype–phenotype correlation in our GSD I patients. Hyperlactatemia and hypertriglyceridemia correlated significantly with hypercalcemia. Furthermore, no differences in serum calcium concentrations could be demonstrated between patients with optimal metabolic control. We observed hypercalcemia in our series of GSD I patients during acute metabolic decompensation. Therefore, we speculate that hypercalcemia should be considered as one of the problems of GSD I patients during acute attacks. It may be related with prolonged lactic acidosis or may be a pseudohypercalcemia due to hyperlipidemia that can be seen in GSD I patients with poor metabolic control.

Key words: glycogen storage disease, hypercalcemia, metabolic decompensation.

Glycogen storage diseases (GSDs) are a group of inherited metabolic disorders of glycogen metabolism. There are over 12 types, and the overall incidence is 1 case per 20,000 to 43,000 live births. GSD type IA (GSD IA, McKusick 232200) is an autosomal recessive disorder caused by a deficiency in glucose-6-phosphatase (G6Pase, EC 3.1.3.9), the key enzyme in the regulation of blood glucose levels[1,2]. GSD I has four main subsets based on clinical and biochemical findings combined with molecular analysis. The largest subtype (type IA) is caused by a deficiency of G6Pase activity in the liver, kidney and intestine, and a second type is GSD IB (glucose-6-phosphate translocase deficiency) or a deficiency in the microsomal transport protein for glucose-6-phosphate (GSD IC and GSD ID). The clinical manifestations of GSD I include hepatomegaly, nephromegaly, failure to thrive, doll-like facial appearance, protuberant abdomen, thin extremities, fasting hypoglycemia, hyperuricemia, hyperlactatemia, elevated levels of lipids, bleeding tendency, and gout related to hyperuricemia[3]. GSD IB has additional distinctive features such as recurrent infections, neutropenia, impaired neutrophil function that predisposes to enterocolitis, increased prevalence of autoimmune thyroid

disease, and amyloidosis[4]. After the introduction of intensified dietary treatment consisting of either nocturnal gastric drip feedings and/or complex carbohydrates, both morbidity and mortality have improved dramatically. Hypercalcemia arose as an unknown problem in GSD I patients, especially in those with insufficient metabolic control. The aims of the present study were to obtain the prevalence of hypercalcemia, establish endocrine and metabolic abnormalities in 23 GSD I (22 GSD IA, 1 GSD IB) patients that may influence serum calcium concentration, and understand the genotype-phenotype correlation between different G6Pase gene mutations and hypercalcemia.

Material and Methods

A normal serum calcium level is 8-10 mg/dl (2-2.5 mmol/L) with some interlaboratory variation in the reference range, and hypercalcemia is defined as a serum calcium level greater than 10.5 mg/dl (>2.5 mmol/L). Hypercalcemia detected in our patients was asymptomatic and diagnosed incidentally from routine blood tests. Hypercalcemia frequency and the affecting factors were studied cross-sectionally in 23 pediatric subjects with a clinical diagnosis of GSD I (14 males, 9 females, age: 7.13 ± 5.3 years) who were followed in Gazi University Hospital Pediatric Metabolic Clinic between 1990 and 2010. Twenty-two patients had GSD IA and 1 patient had GSD IB. Their ages at diagnosis ranged from 3 months to 120 months, and the major symptoms in metabolic decompensation state were hepatomegaly, hypoglycemia, hyperlactatemia, metabolic acidosis, and interestingly, hypercalcemia. Treatment efficacy is evaluated by monitoring clinical parameters (extent of hepatomegaly, growth curve, etc.) and biological parameters (hypoglycemia, lactic acidosis, hyperuricemia, hyperlipidemia). Poor metabolic control defines fasting blood glucose concentration <60 mg/dl, blood lactate >2.5 mmol/L, blood uric acid >5 mg/dl, triglycerides >250 mg/dl, and cholesterol >200 mg/dl[5]. Clinical diagnosis of GSD I was confirmed in all patients either through documentation of deficient G6Pase enzyme activity levels on liver biopsy samples or through *G6PC* gene sequencing of DNA extracted from peripheral blood mononuclear cells.

Statistical Analysis

Descriptive data are presented as medians and ranges (between brackets) in view of the small number of patients. Comparisons of continuous variables were performed with the Mann–Whitney U test, and significance in changes in a patient's data was assessed by the two-factor analysis of variance (ANOVA) test. A value of $p<0.05$ was considered significant.

Results

Hypercalcemia was detected in 78.3% of patients with GSD I. Calcium levels of the study group were 10.76±0.99 (9.2-13.3) mg/dl and the triglyceride levels were found to be 755.04±411.38 (252-1850) mg/dl in acute metabolic decompensation state. Germline mutation analysis of the *G6PC* gene revealed that R83C, a common mutation seen in GSD Ia, accounted for 13 out of 23 mutant alleles in our patients. In the present study, other than homozygous for R83C, sequence analysis detected R83C heterozygous, G270V homozygous and G339C heterozygous mutations in patients with GSD I. We could not find a significant correlation between different G6Pase gene mutations and hypercalcemia. The correlation between hypercalcemia and hypertriglyceridemia was statistically significant ($p=0.15$: $p<0.05$). We observed that in our series of hypercalcemic GSD I patients, plasma lactate concentration correlated significantly with hypercalcemia ($p=0.13$: $p<0.05$). Lactate levels of the study population were found to be 4.9±2.92 (1.17-13.74) mmol/L. Furthermore, no differences in serum calcium concentrations could be demonstrated between patients in optimal metabolic control. Therefore, whether the results obtained from our patients could be applied to other patients with different mutations must be explored.

Discussion

If untreated, GSD I patients manifest with several complications such as hypoglycemic seizures, hepatomegaly, growth retardation, life-threatening lactic acidosis, hyperlipidemia, gout related to hyperuricemia, proteinuria, and nephrolithiasis with progressive renal failure. Treatment aims at preventing hypoglycemia in order to avoid neurological involvement and long-term complications and to assure

normal growth. Treatment is essentially dietary and consists of frequent meals, continuous nocturnal nasogastric drip feeding, ingestion of slow- releasing carbohydrates (uncooked starch), and restricted intake of both fructose and galactose, which are both metabolized via glucose-6-phosphate and thus aggravate hyperlactacidemia and thereby metabolic control. Other complications include a prolonged bleeding time, iron refractory anemia, pulmonary hypertension, osteoporosis with risk for fractures, hepatocellular carcinoma, and an increased prevalence of thyroid autoimmunity[6,7]. We observed hypercalcemia in our series of GSD I patients during acute metabolic decompensation. Our study group with hypercalcemia in metabolic decompensation had normal calcium levels and lower triglyceride levels in optimal metabolic control. Therefore, we speculate that hypercalcemia should be considered as one of the problems of GSD I patients during acute attacks. It may be related with prolonged lactic acidosis or may be a pseudohypercalcemia due to hyperlipidemia (sometimes laboratory tests show misleading acute hypercalcemia in hyperlipidemic serum samples) that can be seen in GSD I patients with poor metabolic control[8]. The most commonly seen G6PC mutation in our study population was pR83C, which correlated with the observation that only three mutations

(pR83C, p.W77R, p.R170Q) have been reported in the other 23 Turkish patients analyzed[9]. Different from the previous report about hypercalcemia in a GSD IA patient who had R83H and 341delG mutations, we could not identify a genotype–phenotype correlation in our GSD I patients[10]. Further research is needed to identify metabolic abnormalities that may influence the serum calcium concentration in GSD I patients.

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