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Hepatocellular adenoma and metabolic balance in patients with type Ia glycogen storage disease

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Abstract

Glycogen storage disease type I (GSD I) is a metabolic disorder resulting from defects in the glucose-6-phosphatase system. Approximately 75% of adolescent and adult patients develop hepatocellular adenomas, which can lead to considerable morbidity and mortality. The pathogenesis of adenomas is unclear and the risk of developing adenomas in treated patients is uncertain. The objective of this study was to determine whether metabolic imbalance was related to the occurrence of adenomas in patients with GSD I, and to determine what specific biochemical pathways were involved. We performed a 1:1 case–control retrospective study; cases were GSD I patients with adenomas and controls were GSD I patients without adenomas. Controls and cases were matched according to age at diagnosis, age at adenoma detection, and gender. We investigated biochemical abnormalities indicative of metabolic balance and exogenous factors potentially related to the onset of adenomas in the two groups. We detected no significant differences in dietetic treatment, compliance to treatment, or biochemical parameters related to metabolic balance between the two groups. In conclusion, we were unable to identify any significant differences in metabolic balance between GSD I patients who developed adenomas and those who did not.

Keywords: Glycogen storage disease type I; Hepatocellular adenoma; Metabolic balance

Glycogen storage disease type I (GSD I) is an inborn metabolic disorder resulting from defects in the glucose-6-phosphatase system [1]. Glucose-6-phosphatase plays a central role in glycogenolysis and gluconeogenesis, hydrolyzing glucose-6-phosphate to glucose. Because of inadequate glucose production, patients with GSD I have severe fasting hypoglycemia and secondary biochemical abnormalities, including hyperlactacidemia, hyperlipidemia, and hyperuricemia. Marked hepatomegaly is caused by glycogen and lipid storage. However, except for glucose homeostasis, liver function is normal and cirrhosis does not develop. Hepatocellular adenomas and chronic renal insufficiency are the most severe complications in adolescent and adult GSD I patients. In a European GSD I study cohort, adenomas were present in 75% of adolescent or adult patients [2]. A similar prevalence was observed in a GSD I population in the United States [3].

Adenomas have significant morbidity due to severe iron refractory anemia and hemorrhage into the tumor; the risk of malignant transformation is estimated at 10% [4]. The pathophysiology of adenoma is unclear and the risk of adenoma developing in patients treated for GSD I is uncertain. Metabolic imbalances are believed to be the cause of adenomas, but the exact pathophysiological mechanism is not known [4]. We wanted to determine whether metabolic imbalance was related to the occurrence of adenomas in patients with GSD I, and what specific biochemical pathway was involved.

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Study design and methods

Patients

Our study included 54 patients with GSD I (44 GSD Ia and 10 GSD Ib; 28 males, 26 females; 0.9–43.7 years of age) from two Italian metabolic disease units. GSD I was diagnosed by evaluating glucose-6-phosphatase activity in intact and disrupted microsomes and/or mutation analysis of the glucose-6-phosphatase gene or glucose-6-phosphate transporter gene. The two metabolic disease units have maintained similar treatment and follow-up protocols for GSD I patients for more than 20 years: during the day, all patients received frequent meals and uncooked cornstarch administration. At night, infants and younger children were treated with a glucose-polymer solution via continuous nocturnal gastric drip, while older children, adolescents, and adult patients were administered uncooked cornstarch [5]. In all patients, dietary treatment was initiated immediately after diagnosis. All patients were screened for hepatocellular adenoma by liver ultrasonography every six months. In patients with adenomas, their size and number were monitored by liver ultrasonography or MRI. Twenty-five of 54 patients had one or more liver adenomas; two of those patients underwent tumor resection and were diagnosed with adenoma based on established histological criteria. Two patients received liver transplants due to multiple adenomatosis; in one of these patients, carcinoma was diagnosed histologically.

We performed a retrospective, 1:1 case–control study. Cases were GSD I patients with adenomas (GSDIA), and controls were GSD I patients without adenomas (GSDIWA). Controls and cases were matched according to: (1) age at GSD I diagnosis; (2) age at adenoma detection (the matched control was a patient who had reached that age without developing an adenoma); (3) gender; (4) follow-up in the same unit. These criteria restricted enrollment to only 20 GSD Ia patients, 10 cases, and 10 controls. Patients with GSD Ib were not matched with patients with GSD Ia because patients with GSD Ib have intermittent severe neutropenia, neutrophil dysfunction, inflammatory bowel disease, and they are more prone to metabolic derangement.

We collected information about age, gender, previous use of steroids or oral contraceptives, alcohol intake, and associated diseases. Furthermore, we obtained information about nutritional and therapeutic regimens, body mass index (BMI), laboratory abnormalities indicative of GSD metabolic balance (hemoglobin, clotting factors, triglyceridemia, cholesterolemia, uricemia, lactacidemia, creatininemia, 24-h microalbuminuria, 24-h proteinuria), and laboratory abnormalities associated with hepatocellular adenoma in the general population (γ-glutamyltransferase and C-reactive protein) during the five years before adenoma occurrence for cases and during the preceding five years for controls.

Study procedures conformed to our institution's guidelines for human studies. All patients (or their guardians) provided informed, written consent. All information was recorded on a paper form and then entered into a database. Each case was identified by a four-digit code and only the person responsible for enrolling the patient had access to all of the patient's personal data.

Statistical analysis

Descriptive data for continuous variables were reported as mean ± standard deviation (SD) or median and range, as appropriate. Descriptive data for categorical variables were reported as absolute and relative frequencies. Mann–Whitney U test was used to compare biochemical data from the two groups. Categorical variables were compared using χ^2 test. Fisher's exact test was preferred whenever expected number in any cell was <5. A P-values $\leqslant 0.05$ were considered statistically significant, and all P-values were based on two failed tests. Statistical analysis was performed using SPSS for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

Ten cases and 10 controls (six males and four females in each group) screened from a population of 54 GSD I patients were included in this study. The median age at GSD I diagnosis was 8 months (range, 2–24 months) for the cases and 9 months (range, 4–204 months) for the controls. All patients were followed at the same metabolic disease unit from diagnosis through the time of this study. The groups did not differ in genotype; R83C and Q347X were the most frequent mutations in both groups. The median age at adenoma occurrence for cases was 18.5 years (range, 11–26 years; Table 1). None of the cases or controls had hepatitis B or C. None had been treated with hormones and none had other risk factors for adenoma. Cases and controls did not differ in dietetic treatment. Acute metabolic derangement (severe hypoglycemia/hypoglycemic convulsions, hypoglycemic coma) or other acute complications were not reported for any patient in either group (Table 2).

The only statistically significant difference between the two groups was BMI (Fig. 1). The results of our analysis of biochemical parameters indicative of metabolic balance are reported in Fig. 2. Despite some differences concerning triglyceridemia and lactic acidemia at various times, overall metabolic balance over the five years preceding the onset of adenoma was not significantly different in the patient group as compared to the control group (Fig. 2). No patient experienced adenoma regression during follow-up.

Discussion

Our retrospective case–control study failed to demonstrate significant differences in metabolic balance between GSD I patients with and without adenomas. We began our study based on the clinical observation that some

Table 1
General and genetic characteristics

	Patients $n = 10$	Controls $n = 10$
Gender		
Male, n (%)	6 (60)	6 (60)
Female, n (%)	4 (40)	4 (40)
Median age at GSD diagnosis in months (range)	8 (2–24)	9 (4–204)
Median age at adenoma diagnosis in years (range)	18.5 (11–26)	—
Genotype		
R83C/R83C	1	4
R83C/Q347X	3	1
R83C/E110K	1	—
Q347X/Q347X	1	2
Q347X/R295C	—	1
Q347X/G188R	1	—
Q347X/203X	1	—
G22R/G22R	1	1
S298P/S298P	1	—
	—	1

Patients, patients with glycogen storage disease type I who developed adenoma; controls, patients with glycogen storage disease type I who did not develop adenoma.