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Endocrine complications of patients with hepatic type of glycogen storage disease

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Introduction

- Glycogen storage disease (GSD) is an inherited metabolic defect of glycogenolysis and gluconeogenesis.
- Fifteen types of GSD have been identified. They are categorized into hepatic and muscle/cardiac types according to the involving organ.
- Patients with hepatic type of GSDs are associated with endocrine abnormalities such as short stature, delayed puberty, fasting hypoglycemia, and dyslipidemia. In addition, patients with GSD 1b are also at risk of autoimmune hypothyroidism.

Objectives

- This study was performed to investigate endocrine complications in patients with hepatic type of GSD.

Subjects and Methods

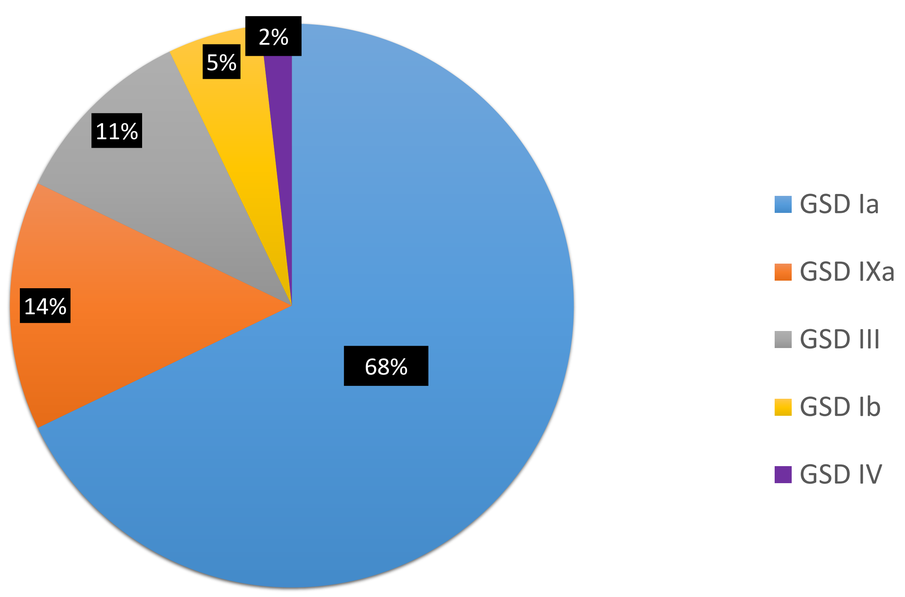
- This study included 56 patients with hepatic type GSD who were diagnosed between January 1995 and December 2018; GSD type Ia, Ib, III, IV, and IXa.
- All patients were genetically confirmed by Sanger sequencing of the causative genes. Patients with muscle glycogenosis were excluded in the study.
- Clinical and endocrine characteristics were retrospectively analyzed such as height, weight, hypoglycemia, lipid profiles, and bone mineral density.

Results

Etiologic spectrum of patients

- A total of 56 patients from 46 families with hepatic type GSD were included: GSD type Ia (38 patients from 34 families), Ib (N = 3), III (6 patients from 4 families), IV (N = 1), and IXa (8 patients from 4 families)

Figure 1. Proportion of patients with hepatic GSD according to type



Growth

- Mean height- and weight-SDS at diagnosis were -1.84 ± 1.9 and -1.45 ± 1.6 respectively.
- Of these, short stature (height-SDS <-2) was apparent in 23 patients (41%).
- Twenty out of 38 (52.6%) GSD type Ia, two of 6 (33.3%) GSD type III, and one of 8 (12.5%) GSD type IXa patients were diagnosed with short stature.
- Serum IGF-1 and IGFBP-3 levels were measured in five patients with GSD-type Ia. Three of them (60%) had significantly lower levels of lGF-1 levels. The mean serum IGF-1 of these three patients was 5.1 ± 4.4 ng/mL. They showed profound short stature with the mean current height-SDS of -5.84 ± 1.4.
- A total of 24 patients (M = 14, F = 10) reached adulthood (age > 18 yrs) at the last visit. Their mean age was 27.3 for male patients and 27.0 for female patients, respectively. The average of final adult heights were 158.8 cm (SDS -2.98) in males and 158.4 cm (-0.54 SDS) in females.

Table 1. Clinical characteristics and growth profile

GSD type	Ia	Ib	III	IV	IXa	Total
Number of patients	38	3	6	1	8	56
Female	13	1	2	1	0	17
Male	25	2	4	0	8	39
Mean age at diagnosis (yr)	9.1	4.3	1.4	1.8	2.9	7.0
Short stature (n / Total) (%)	20 / 38 (52.6%)	0	2 / 6 (33.3%)	0	1 / 8 (12.5%)	23 / 56 (41%)
Mean height SDS at diagnosis	-2.31 ± 2.1	-1.14 ± 0.7	-1.24 ± 1.2	-0.29	-0.8 ± 1.03	-1.84 ± 1.9
Mean weight SDS at diagnosis	-1.26 ± 1.8	0.09 ± 1.2	-0.17 ± 0.7	-0.04	0.18 ± 1.1	-0.81 ± 1.7
Mean current age (yr)	19.8	16.8	11.8	13.2	6.7	16.8
Mean current height SDS	-1.76 ± 1.7	-1.78 ± 1.8	-1.06 ± 1.0	0.71	-0.46 ± 0.6	-1.45 ± 1.6
Mean current weight SDS	-0.88 ± 1.5	-0.1 ± 3.7	0.19 ± 0.8	0.21	-0.17 ± 0.6	-0.6 ± 1.5

Hypertriglyceridemia

- Hypertriglyceridemia was found in all patients with hepatic GSD at the initial presentation.
- The mean serum triglyceride (TG) level in patients with GSD type Ia was the highest (659.7 ± 490 mg/dL), and GSD type IXa patients showed the mildest abnormalities (186 ± 99.9 mg/dL).
- Fenofibrate was administrated to the adolescent and adult patients with persistent hypertriglyceridemia.
- The mean serum TG level was 520±448.3 mg/dL at diagnosis and decreased to 346.3±390.5 mg/dL at last follow-up (*P* = 0.04).

Table 2. Lipid profiles of hepatic GSD patients

GSD type	Ia	Ib	III	IV	IXa	Total
Mean TG at Diagnosis (mg/dL)	659.7 ± 490	275 ± 103.8	259.5 ± 71.9	112	186 ± 99.9	520±448.3
Mean TG at last follow-up (mg/dL)	441.8± 429.4	302.5 ± 228.4	141.8 ± 79.8	No data	93.7 ± 47.6	346.3±390.5

Thyroid function

- Thyroid functions including thyroid stimulating hormone (TSH) and free T4 level were analyzed in 24 patients. As a result, all patients showed normal thyroid function in our cohort.

Vitamin D deficiency and osteoporosis

- Serum vitamin D concentration was analyzed in 37 patients. Vitamin D deficiency (25-hydroxyvitamin D3 <20 ng/mL) was found in 19 of 37 patients (51.3%). The mean 25-hydroxyvitamin D3 of these patients were 11.8 ± 4.3 ng/mL.
- Dual-energy X-ray absorptiometry analysis was performed in 16 patients. As a result, osteoporosis (bone mineral density Z score <-2 SDS) was documented in 11 patients. The mean Z-score of L-spine was –3.24 ± 0.7 (range – 4.0 to – 2.1)

Conclusions

- This study described that patients with GSD type 1a developed significant growth retardation.
- In addition, other endocrine abnormalities such as dyslipidemia, osteoporosis, vitamin D deficiency can be associated with hepatic GSD.
- Dietary treatment with uncooked cornstarch improves growth and partially corrects the biochemical findings.
- Future longitudinal studies with a large number of patients may allow a better understanding of factors that impact endocrine complications.

Disclosure statement

The authors have nothing to disclose.