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Clinical characteristics and long-term outcomes of patients with glycogen storage disease type 1b: a retrospective multi-center experience in Poland

Charakterystyka kliniczna i długoterminowe wyniki pacjentów z glikogenozą typu 1b: retrospektywne doświadczenie wieloośrodkowe w Polsce

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Abstract
Glycogen storage disease type 1b (GSD 1b) is an inherited metabolic defect caused by a deficiency of microsomal glucose-6-phosphate (G6P) transport protein across the endoplasmic reticulum membrane. Patients with GSD 1b have hypoglycemia episodes, lactate acidosis, hypertriglyceridemia, hypercholesterolemia, hyperuricemia, neutropenia and in imaging studies hepatomegaly and/or nephromegaly.
The primary goals of treatment are to maintain proper blood glucose levels and to increase the number of properly functioning neutrophils.
The aim of the study was a retrospective analysis of the clinical picture and treatment results of pediatric patients with type 1b glycogen storage disease from Poland.
The study included 13 patients from 3 clinical centers, with a median age at diagnosis as 5 months. In 11/13 patients, the diagnosis was confirmed by molecular test, by the presence of pathogenic variants on both alleles of the *SLC37A4* gene. Ten out of 13 patients developed the first symptoms in the form of severe infection (sepsis and/or pneumonia) already in the neonatal-infant period. A hypoglycemia episode was observed before diagnosis in 8/13 patients, of which 4/8 patients presented symptoms in the form of generalized relaxation and/or seizures. Two patients developed hypertension, and 4/13 required long-term treatment of inflammatory bowel disease.
Key words:
glycogen storage disease type 1b, glycogenosis 1b, *SLC37A4*, neutropenia, filgrastim, inflammatory bowel disease.

Introduction

Glycogen storage disease type 1b (GSD 1b) is a rare inherited metabolic defect caused by a deficiency of the microsomal glucose-6-phosphate (G6P) transport protein across the endoplasmic reticulum (RE) membrane. Glucose-6-phosphate is found in the RE, which converts G6P into glucose [1, 2].

A transporting protein deficit results in the excessive accumulation of G6P in the cytoplasm, which hinders the ability to obtain glucose in the process of gluconeogenesis, as well as excessive stimulation of the glycolysis process and the pentose phosphate cycle. Excess substrate in the first process induces pyruvate overproduction, which through the Krebs cycle stimulates lipogenesis and thus triglyceride and cholesterol production. Pyruvate, which is not metabolized during the Krebs cycle, is converted to lactate. The excess G6P also causes increased activity of the pentose phosphate cycle, which triggers excessive uric acid accumulation.

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The above abnormalities in patients with GSD 1b result in hypoglycemia episodes, which due to the ketone bodies generated are often asymptomatic [2]. In laboratory tests, untreated patients show typical abnormalities: lactic acidosis, hypertriglyceridemia, hypercholesterolemia, and hyperuricemia [2]. Furthermore, excessive accumulation of lipids and glycogen in the liver and kidneys causes damage to these organs and organomegaly [2]. The initially observed hyperaminotransferasemia normalizes with appropriate treatment in most patients, while hepatic steatosis progresses. When patients are in their 20s and 30s, hepatic adenomas appear with an increased risk of transformation into hepatocellular carcinoma (HCC) [2]. Damage to the proximal convoluted tubule (loss of bicarbonates, glucosuria, phosphaturia, hypokalemia, aminoaciduria), the distal convoluted tubule (hypocitraturia and hypercalciuria) and glomerulus, along with fibrosis, lead to arterial hypertension and renal failure, usually manifesting in adulthood [2].

Patients with GSD 1b have an insufficient number of properly functioning neutrophils, therefore they often present with life-threatening infections in the neonatal period, and later recurrent mouth aphthae and inflammatory Crohn-like bowel diseases [2, 5]. It has recently been discovered that 1, 5-anhydroglucitol-6- phosphate accumulates in the cytoplasm of neutrophilic granulocytes of patients with GSD 1b, which results in reduced energy production and thus shorter survival and worse bactericidal activity [1, 8, 9].

Coagulation disorders (abnormal adhesion, platelet aggregation and/or "von Willebrand-like" platelet defects), osteoporosis, short stature, and excess body weight have also been reported in patients with GSD 1b [2].

GSD 1b is in an autosomal recessive inherited disease. A biallelic defect of the *SLC37A4* gene is confirmation of the diagnosis. Thus far, a genotype-phenotype correlation has not been proven [3, 4].

Nutritional treatment is the primary form of intervention in GSD 1b. Frequent meals are necessary to avoid hypoglycemic episodes as well as excluding fructose and galactose from the diet. These simple carbohydrates enter the biochemical pathway above the defect, which exacerbates biochemical abnormalities, e.g. lactic acidosis. Extending the intervals between meals is achieved with a high-protein diet (up to 2 g of protein/kg) and the supply of raw corn starch, which is a source of slowly digestible carbohydrates. Additionally, in patients with chronic hyperuricemia, allopurinol is used, and in the case of persistent hypertriglyceridemia fibrate drugs. Most patients require antihypertensive treatment; ACEIs and/or ARBs are recommended in the presence of glomerular hyperfiltration [2].

Due to neutropenia, patients with GSD 1b usually require treatment with granulocyte-colony growth factor (G-CSF, filgrastim), which limits infections but does not eliminate them. Despite the use of G-CSF, severe life-threatening infections, impaired wound healing, recurrent mouth aphthae, and severe diarrhea (Crohn-like disease) are still observed. Moreover, this drug is not without side effects, such as bone and joint pain, epistaxis, gingival hypertrophy, splenomegaly, or a greater risk of hematopoietic cancers [6, 7]. Recently, attention has been paid to SGLT2 inhibitors, which reduce 1,5-anhydroglucitol-6-phosphate concentrations in the neutrophil cytoplasm, which unblocks energy production in the cell, prolongs survival, and improves neutrophil function [8, 9].

Table I. Characteristics of the studied patients – age symptoms appeared

Median age at diagnosis (months)	5
Median age of first severe infection – sepsis and/or pneumonia (days of life)	20
Median age of first hypoglycemia episode (months)	3.5
Median age of hepatomegaly diagnosis (months)	4

Aim of the study

The aim of the study was a retrospective analysis of the clinical picture and treatment results of patients with glycogen storage disease type 1b, remaining under the care of the Department of Pediatrics, Nutrition and Metabolic Disorders at the Children's Memorial Health Institute in Warsaw, as well as the Department of Pediatrics, Rheumatology, Immunology and Metabolic Bone Diseases at the Medical University of Bialystok Children's Clinical Hospital of I. Zamenhof and the Department of Pediatric Gastroenterology and Metabolic Disorders at the Pediatric Institute of the Poznan University of Medical Sciences.

Materials and methods

A retrospective analysis of the clinical course of patients with glycogen storage disease type 1b, who in 2021 were under the care of three medical institutions in Poland, was performed.

A total of 13 patients (5 girls and 8 boys) were enrolled in the study. The median age at which the diagnosis was made was 5 months (range: 1 month – 2 years) (Table I). All patients were diagnosed on the basis of the clinical picture and typical abnormalities in laboratory tests. In 11/13 patients, GSD1b was confirmed by molecular test.

The study took into account the clinical condition and abnormalities in laboratory and imaging tests at the time of diagnosis. The course of the disease was analyzed in all patients, paying particular attention to the age at diagnosis and neutropenia severity, the first symptoms of inflammatory bowel disease, hypertension development, and the treatment used.

Results

The first symptoms in the form of severe infection (sepsis and/or pneumonia) were developed by 10/13 patients, mostly already in the neonatal-infant period (median age was 20 days, range: first 24 h – 21/12) (Table I). The majority (11/13) of pa-

tients had hepatomegaly prior to diagnosis, observed from median age of 4 months (range: 9th day of life – 9 months) (Table I). Only in 4/13 patients hepatomegaly was associated with nephromegaly – and if it was, it was observed later – median age was 7 months (range: 3–9 months).

Before diagnosis, a hypoglycemia episode (serum glucose 9–26 mg/dl, median 11 mg/dl) was observed in 8/13 patients (Table I), of which 4/8 patients presented symptoms in the form of generalized relaxating and/or seizures.

At diagnosis, the most common biochemical abnormalities in 12/13 patients were lactate acidosis (median 55 mg/dl (normal < 19.8 mg/dl), range 26–126 mg/dl) and hypertriglyceridemia (median 531 mg/dl, range 246–3181 mg/dl) (Table II, III). Hypertransaminasemia was found in 8/13 patients and the maximum value was AST/ALT 628/515 IU/l.

Pre-diagnosis laboratory tests showed neutropenia in only three patients. However, at diagnosis it was found in 9/13 patients (median neutrophil count 200 cells/ul, 20-954 cells/μl) (Table II). The number of patients (9/13) who developed severe pneumonia and/or sepsis at 1 years old suggests that neutropenia occurred much earlier. Most likely, this had not been found previously because blood counts were performed at the time of infection symptoms, when increased secretion of these cells from the bone marrow is observed in patients with GSD 1b.

Hyperuricemia at diagnosis in the described patients was mild and was observed only in 5/13 (median: 8 mg/dl, range 7–8.3 mg/dl) (Table II).

Ultrasound examination at diagnosis revealed enlarged liver in 12/13 patients, and in 6/12 cases increased echogenicity of its parenchyma (Tables I, III). Hepatomegaly was accompanied by nephromegaly in 2/12 patients (in one case with increased echogenicity of the renal parenchyma).

In 11/13 patients, the diagnosis was confirmed by molecular test; the most common variant was the homozygous c.1042_1043 del (7/13 patients) (Tables III, IV). Comparing the course of the disease in patients with the same mutation is extremely difficult, among others, due to the small size of the group, the significant age differences (11 years between the oldest and the youngest patients), or the differences in compliance with dietary recommendations. However, it appears that no genotype-phenotype correlation can be found, as there were significant differences between the age of onset and the severity of subsequent clinical and biochemical abnormalities (Table IV).

From the moment of diagnosis, all patients were on a diet restricted in easily digestible carbohydrates (fructose and galactose) under the control of a clinical dietitians. From 2015, all patients were on a high-protein diet (up to 2 g of protein/kg). To extend the intervals between meals, raw corn starch was used (on average 1.2 g/kg of b.w./meal), in 2/13 patients Glycosade® was used with good tolerance.

Difficulties in frequent administration of meals orally, and thus inability to maintain normal blood glucose levels, necessitated a gastrostomy in 5/13 patients (median age at surgery was 17 months, range 5 months – 4 years). In 2/5 of these cases, the postoperative course was complicated by impaired wound healing. Due to recurrent infections in the gastrostomy area, one patient had to have the gastrostomy removed, and after many months of nutrition therapy adequate oral intake was obtained.

Table II. Characteristics of the studied patients – laboratory tests confirmed at diagnosis

Deviation in laboratory test	Number of patients	Median concentration (concentration range)
Increased lactic acid concentration (N: < 19.8 mg/dl	12/13	55 mg/dl, 26–126 mg/dl
Increased triglyceride levels (N: < 150 mg/dl)	12/13	531 mg/dl, 246–3181 mg/dl
Decreased neutrophil count (N: to 4 y.o. < 1000, over 1500 cells/μl)	9/13	200 cells/μl 20–954 cells/μl
Increased uric acid levels (N: < 7 mg/dl)	5/13	8 mg/dl, 7–8.3 mg/dl
N: norm		

Additionally, 12/13 patients required filgrastim (G-CSF) due to severe neutropenia (Tables III, V). At diagnosis, a decreased number of neutrophils was observed in 9/13 patients; the median age of G-CSF initiation was 22 months (range: 4 months – 11 years). Despite G-CSF use and a satisfactory number of neutrophils obtained in this way, patients still developed more frequent and more severe infections than their peers, as well as recurrent mouth aphthae (5/12) and diarrhea (6/12) (Table VI). All patients with an increased number of stools and/or pathological stool content underwent colonoscopy, which revealed rectal ulcers (in one patient reaching up to the cecum). Thus, in these patients, mesalazine was added to the treatment (median age at start was 5.5 years, range: 2.5–9 years) (Table V). In 2/6 of patients, the drug was used for six months, and due to lack of changes in the colonoscopy check-up exam, the drug was discontinued, and the symptoms have not yet returned.

In 3/13 patients, due to persistent neutropenia despite treatment, empagliflozin was started off label (Tables III, V). After an average of one year of use, there was an improvement in the number of infections, inflammatory bowel disease severity, and mouth aphthae frequency, with no significant side effects.

The longest follow-up period was 17 years (median follow-up was 10 years, range: 6 months – 17 years), during which time we observed that adherence to dietary recommendations with regard to the composition and frequency of meals normalized the concentrations of lactates and aminotranspherases (AST/ALT) in the serum in all patients. However, elevated uric acid levels persisted chronically in 7/13 patients. Therefore,

Table III. Characteristics of GSD 1b patients – summary

Patients	Sex	Age at diagnosis (months)	Molecular analysis	Initial symptoms (from the earliest)	Lactate at diagnosis (N < 19.8 mg/dl)	Uric Acid at diagnosis (N < 7.0 mg/dl)	Triglycerides at diagnosis (N < 150 mg/dl)	IBD	Hyper-tension	Duration of follow-up (years)	Drugs currently
GN	K	5	c.1042_1043del	INF, HMG	31	N	1064	–	–	17	G-CSF, ALL
LP	M	4	c.1042_1043del	INF, HMG, HGL	N	N	246	+	–	16.5	EMPA, MES, bisphosphonate
SK	M	2,5	c.1042_1043del	INF, HMG, HGL	28	N	N	–	+	15	G-CSF, AH
KS	M	9	c.1042_1043del c.341A>G	HGL, INF, HMG	42	N	1321	+	+	13	EMPA, ALL fibrate, AH, MES
FM	M	5	–	INF, HGL	45	N	272	+	–/+	12.5	G-CSF, ALL
MJ	M	24	c.1042_1043del	HMG, INF	116	N	3181	+	–	10	G-CSF, MES
DM	M	7	–	INF, HMG, HGL	80	8.3	453	–	–	9.5	G-CSF, ALL
ŁK	K	5	c.1042_1043del	HGL, INF	52	N	346	+	–	8	G-CSF, MES, EMPA
SN	K	1	c.1042_1043del c.1015G>T	INF, HMG	26	8.2	481	–	–	7	G-CSF, ALL
PT	M	9	c.1042_1043del	HMG	58	N	3302	–	–	6	no
PA	K	4	c.1042_1043del	INF, HMG, HGL	87	N	314	–	–	5	G-CSF, ALL
WW	M	4	c.1043_1044del	INF, HMG	72	8.0	581	–	–	1.5	G-CSF, ALL
KA	K	2.5	c.1042_1043del c.1175del	INF	126	N	1809	–	–	0.5	G-CSF

HMG – hepatomegaly; HGL – hypoglycemia; INF – infection; G-CSF – granulocyte – macrophage colony stimulating factor; ALL – allopurinol; MES – mesalazin; EMPA – empagliflozin; AH – antihypertension drug; N – norm

they required the use of allopurinol (median age at start: 5 years, range: 1–13 years), which in a dose from 2 mg/kg/day to 6 mg/kg/day normalizes uric acid levels (Tables III, V).

One patient experienced significant hypertriglyceridemia (1020, 1100 mg/dl), which persisted despite no history of hypoglycemia, normal serum lactic acid and uric acid levels. Therefore, at the age of 13, it was decided to include fenofibrate at a dose of 2.5 mg/kg, which resulted in a reduction in TG levels of < 500 mg/dl (Table V).

An increase of lactic acid, uric acid, AST/ALT, and triglycerides was found in the event of non-compliance with the diet, as well as during infections and perioperative periods.

Table IV. Patients with homozygotic molecular variant c. 1042_1043delCT in the *SLC37A4* gene

Patient No (current age)	Initial symptome	Lactic acid Median of check-ups (without infections)	Uric acid Median of check-ups (without infections)	TG Median of check-ups (without infections)	IBD	Hyper-tension	G-CSF Age inclusion (years)	Drugs currently
1. (17)	INF, HMG	31	ALL from 13 years of age	321	–	–	11	G-CSF, ALL
2. (17)	INF, HMG, HGL	17.7	6.5	136	+	–	2	EMPA, MES
3. (16)	INF, HMG, HGL	29	6.2	154	–	+	2	G-CSF, AH
4. (11)	HMG, INF	53	3.9	778	+	–	8	G-CSF, MES
5. (9.5)	HGL, INF	22	4.7	107.5	+	–	1.5	G-CSF, MES, EMPA
5. (6.5)	HMG	48.5	5.2	498	+/–	–	–	no
6. (6)	INF, HMG, HGL	38	ALL from 5 years of age	325	–	–	0.5	G-CSF, ALL

HMG – hepatomegaly; HGL – hypoglycemia; INF – infection
+ recognized
+/– during the observation
ALL – allopurinol, G-CSF – granulocyte colony- stimulating factor, AH – antihypertensive agents, MES – mesalazin, EMPA – empagliflozin

Table V. Pharmacological treatment used

Drug	Number of patients currently receiving pharmacological treatment	Median age at treatment initiation (years)
Filgrastim	12/13	1.75
Allopurinol	7/13	5
Mesalazine	4/13	7
Empagliflozin	3/13	13
Fenofibrate	1/13	13

Table VI. Organ complications in the studied patients

Clinical abnormalities	Number of patients with identified abnormality
Diarrhea (> 3 stools/24 h and/or presence of pathological content)	6/13
Recurrent mouth aphthae (min 1×/ 1 month)	5/13
Pharmacologically-treated hypertension	2/13
Renal failure	0
Hepatic adenomas	0

Two patients (aged 4 and 4.5 years old) developed hypertension, one of them currently (at the age of 13) requires the use of three drugs for satisfactory blood pressure control (Tables III, VI). All patients had normal renal function parameters (urea, creatinine, cystatin C, eGFR) (Table VI).

The intellectual development of most patients was normal. One patient was diagnosed with autism spectrum disorders. One patient was diagnosed with a mild intellectual disability. Four out of 13 patients were overweight (> 97pc), and 2/13 were short (< 3pc).

Two patients were diagnosed and then treated effectively due to epilepsy.

Conclusions

Despite the fact that postprandial hypoglycemia is observed in all patients with glycogen storage disease type 1b, in the discussed patients the first symptoms were most often generalized infection and/or pneumonia. Only in the following months hypoglycemia and hepatomegaly/nephromegaly were observed. Lowered blood glucose was often found only in a provocation test (prolonged fasting). This is probably due to the fact that the diagnosis was made in infancy, when the natural feeding regimen imposes frequent meals (every 2–3 hours).

At present, it seems that the consequences of neutropenia have the greatest impact on the reduction of the quality of life in the described patients. Despite the use of filgrastrim, patients suffered from much more severe and more frequent infections than their peers, and inflammatory bowel disease is often not properly controlled and requires additional treatment (mesalazine). Moreover, all patients reported side effects of the treatment used, including: bone and joint pain (11/12), epistaxis (3/12), and splenomegaly (9/12). Two patients had to have treatment temporarily ceased due to hypersplenism (severe thrombocytopenia; minimum number: 50 platelets/μl), while no patients had confirmed haematologic malignancies to date.

In recent years, due to increasing knowledge of both nutritional and pharmacological treatment in GSD 1b, glycemic control has significantly improved in patients, and thus their metabolic control (normalization of lactic acid, uric acid, triglycerides, and aminotranspherases). In view of the extremely promising reports on the treatment of neutropenia with empagliflozin in patients with GSD 1b, further studies are required. It would be extremely important to create recommendations regarding the monitoring (including the frequency of bone marrow biopsies) and treatment of neutropenia in GSD 1b with G-CSF and/or empagliflozin.

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