

Case Report

Glycogen storage disease type Ib without immunodeficiency: 60 years from the first symptoms to the final diagnosis

Agata Rawiak^{1*}, Małgorzata Średzińska², Ewa Ehmke vel Emczyńska-Seliga¹, Barbara Piątosa³, Emilia Samborowska⁴, Magdalena Kaczor¹, Dariusz Rokicki¹, Dorota Wesół-Kucharska¹, Milena Greczan¹

¹ Department of Pediatrics, Nutrition and Metabolic Diseases, Children's Memorial Health Institute, Warsaw, Poland

² Outpatient Clinic for Metabolic Diseases, Children's Memorial Health Institute, Warsaw Poland

³ Histocompatibility Laboratory, Children's Memorial Health Institute, Warsaw, Poland

⁴ Laboratory of Metabolic Disorders, Children's Memorial Health Institute, Warsaw, Poland

* Correspondence to: Agata Rawiak, Department of Pediatrics, Nutrition and Metabolic Diseases, Children's Memorial Health Institute, Aleja Dzieci Polskich 20, 04-730 Warsaw, Poland. Phone: +48 730657707; E-mail: a.rawiak@ipczd.pl

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Abstract

Glycogen storage disease type Ib (GSD Ib) is a rare, genetically determined disorder belonging to the group of inherited metabolic diseases that disrupt glycogen metabolism. It usually manifests in early childhood with recurrent episodes of severe hypoglycemia, hyperlipidemia, hyperuricemia, hepatomegaly, and profound immunodeficiency due to neutropenia. The presented case concerns a 61-year-old patient diagnosed with GSD Ib in adulthood, based on genetic testing that revealed two pathogenic variants in the *SLC37A4* gene. The disease followed an atypical course—without neutropenia or increased susceptibility to infections, while the predominant manifestations were dyslipidemia and hepatomegaly. After the implementation of dietary therapy, including regular administration of uncooked cornstarch, good metabolic control was achieved with normalization of liver size. This case illustrates the considerable clinical heterogeneity of GSD Ib and highlights the importance of considering inborn metabolic disorders in adult patients with chronic, unexplained biochemical abnormalities.

Keywords: glycogen storage disease type Ib, hypoglycemia, hepatomegaly, neutropenia, hyperlipidemia

Introduction

Glycogen storage disease type Ib (GSD Ib) is a genetically determined metabolic disorder caused by a defect of the microsomal glucose-6-phosphate (G6P) transporter (G6PT) located in the endoplasmic reticulum [1, 2]. The accumulation of excessive amounts of G6P in the cytoplasm disturbs both gluconeogenesis and glycogenolysis, leading to increased lipolysis and overproduction of triglycerides and cholesterol. Accumulated G6P also stimulates the pentose phosphate pathway, resulting in overproduction of uric acid [2].

In the typical course of GSD Ib, patients present with severe immunodeficiency caused by profound neutropenia. In 2019, studies by Veiga-da-Cunha et al. and Wortmann et al. identified the accumulation of

1,5-anhydroglucitol-6-phosphate (1,5-AG6P) as a key factor disrupting energy metabolism in neutrophils. During maturation, neutrophils lose most mitochondria, relying primarily on anaerobic glycolysis for energy. The presence of 1,5-AG6P inhibits this process, leading to impaired antimicrobial function and premature apoptosis. Previously, patients with neutropenia in GSD Ib were treated with granulocyte colony-stimulating factor (G-CSF) with limited efficacy and multiple adverse effects. The identification of 1,5-AG6P's role enabled the use of sodium-glucose cotransporter type 2 (SGLT2) inhibitors, which enhance urinary excretion of 1,5-AG, thereby reducing its plasma concentration and improving neutrophil survival and function [1, 3].

In GSD Ib, the classic clinical picture consists of severe hypoglycemic episodes, typically beginning in



early childhood, with characteristic laboratory abnormalities including hypertriglyceridemia, hyperuricemia and hyperlactatemia [2]. Due to the activation of alternative metabolic pathways, low plasma glucose concentrations may remain asymptomatic.

Frequent, sometimes life-threatening infections resulting from defective neutrophil function are often the first clinical manifestation. Later in life, recurrent oral aphthous lesions and chronic diarrhea (nonspecific inflammatory bowel disease, Crohn-like) are also observed [4]. Liver abnormalities, such as glycogen and lipid accumulation, are frequently associated with elevated transaminase activity. Despite ongoing therapy, many patients develop hepatic adenomas (most commonly between the second and third decades of life), which increase the risk of hepatocellular carcinoma (HCC) [4].

Over the course of the disease, glycogen accumulation may also involve renal tubules and glomeruli, leading to arterial hypertension, proteinuria, renal tubular acidosis and renal insufficiency, most commonly observed in adult patients [4].

Pulmonary hypertension may occur as a rare complication of GSD Ib, although it typically develops in individuals with an additional predisposing condition [2, 5]. Several reports suggest a possible association between hyperlipidemia observed in GSD Ib and an earlier onset of atherosclerotic changes compared with the general population, predisposing patients to cardiovascular events [4, 6].

Furthermore, abnormalities of coagulation (impaired platelet adhesion and aggregation) have been described, as well as osteoporosis (reduced bone mineral density may appear as early as in childhood), short stature, and delayed puberty [2, 7].

An increased prevalence of autoimmune thyroiditis and hypothyroidism has also been reported among GSD Ib patients. The predisposition to autoimmune disorders (including inflammatory bowel disease, myasthenia gravis, thyroiditis, and rheumatoid arthritis) appears to be associated with impaired T-lymphocyte function [8].

Case report

The patient, currently 61 years old, was first evaluated in early childhood (at approximately 3 years of age) for episodes of hypoglycemia (lowest documented glucose level: 43 mg/dL) that did not improve after glucagon administration and were accompanied by

progressive abdominal enlargement. Physical examination revealed hepatomegaly and splenomegaly. Liver biopsies performed three times showed steatosis and mild fibrosis. Laboratory tests demonstrated persistent hypertriglyceridemia (225–1057 mg/dL, normal <200 mg/dL) and elevated total cholesterol (104–260 mg/dL, normal <200 mg/dL), along with recurrent elevation of transaminases (AST up to 230 U/l, ALT up to 220 U/l), with intact hepatic function (normal albumin, INR). No neutropenia was ever detected during nearly 60 years of follow-up. Clinically, apart from recurrent sinus infections, there was no increased frequency of bacterial infections or gastrointestinal symptoms. No significant elevation of uric acid levels was observed (maximum 6.4 mg/dL, normal <7 mg/dL), nor of lactate concentrations (maximum 3.1 mmol/L, normal <2.2 mmol/L). Ultrasound examinations performed on multiple occasions consistently revealed significant hepatomegaly with increased hepatic echogenicity.

At the age of 3, the patient was diagnosed with fatty liver disease and nonspecific glycogen metabolism disorder (suspected von Gierke disease). Dietary management included frequent high-carbohydrate meals and reduced fat intake due to hypercholesterolemia. Lipid-lowering drugs (fibrates) were added without significant improvement. At age 11, dietary recommendations were modified to limit carbohydrate intake (exclusion of sugar and sweets, allowing thermally processed fruits such as boiled apples), leading to partial improvement—temporary normalization of triglycerides—but persistent hepatomegaly and hepatic steatosis. Occasional episodes of hypoglycemia were still observed.

In adolescence, the patient was under endocrinological follow-up for delayed puberty, however growth remained within the 10th–25th percentile and no major retardation was observed.

Throughout adulthood, lipid-lowering therapy (atorvastatin, gemfibrozil, fenofibrate) achieved only partial reductions in cholesterol and triglycerides. Moreover at the age of 57 hypertension was diagnosed, without evidence of chronic kidney disease.

In 2025, the patient was referred to the Metabolic Diseases Outpatient Clinic at the Children's Memorial Health Institute, where GSD types IX, VI or III were initially suspected (due to mild course and slightly elevated creatine kinase, CK: 230–460 U/L, normal <190 U/L).

Only at the age of 61, genetic testing confirmed two pathogenic variants in the SLC37A4 gene (c.1042_1043del and c.733G>T), establishing the diagnosis of GSD Ib.

Dietary management was adjusted to include regular meals every 3 hours, restriction of complex carbohydrates to 25–30 g per meal, and elimination of sugar, sweets, fruits (fructose), and dairy products (galactose). Uncooked cornstarch was added as a suspension in water—30 g after each meal and 60 g before bedtime.

Following these modifications, laboratory parameters improved: fasting glucose normalized, triglyceride and cholesterol levels stabilized, and uric acid levels were within normal range. Over time, hepatomegaly resolved and ultrasound examinations demonstrated normalization of hepatic echogenicity. Normal 1.5-anhydroglucitol (13.9 µg/mL, N:10–30 µg/mL, Nowatzke et al. 2004) levels and preserved oxidative burst confirmed normal neutrophil function.

Discussion

GSD Ib typically begins in early childhood, with most patients becoming symptomatic before 1 year of age, presenting with hypoglycemia, hepatomegaly, hyperlipidemia, and neutropenia. Reduced absolute neutrophil count (ANC) and neutrophil dysfunction are hallmark features distinguishing GSD Ib from GSD Ia. In the large European cohort of 57 patients, neutropenia was diagnosed before 12 months in 64%, and between 6 and 9 years in an additional 18% of cases. In the majority of patients gastrointestinal manifestations co-occur – approximately 77% of individuals with neutropenia have been reported with a Crohn-like phe-

notype [3, 9]. Available publications confirm the possibility of an atypical course of GSD Ib—without neutropenia and without neutrophil dysfunction. However, this phenomenon is exceptionally rare: a literature review summarized in Table 1 includes only seven such cases [9–12]. It has been suggested that the absence of neutropenia in the clinical presentation of GSD Ib may result from residual activity of the G6PT transporter associated with certain pathogenic variants in the SLC37A4 gene [10]. Nevertheless, the available studies have not demonstrated a correlation between the specific mutation type and this rarely observed GSD Ib phenotype [13, 14].

Although historically survival into adulthood was limited, advances in dietary therapy and infection control have substantially improved outcomes, and adult survival into the 3rd–5th decade is now common. Several adult case reports describe diagnosis at ages 25, 30, and even above 50 years, often in individuals with attenuated or atypical phenotypes. For example, Kure et al. described two patients aged 25 and 6 years, both with preserved neutrophil function and mild disease [10]; Angaroni et al. reported a 15-year follow-up of a woman without neutropenia [11]; and Boru et al. documented diagnosis at age 43 due to hepatocellular adenomas [15]. Although most complications such as hepatic adenomas typically emerge in the 2nd–3rd decade, long-term follow-up indicates that patients may survive into late adulthood, with hypertension and renal disease increasingly contributing to morbidity. These data highlight both the marked phenotypic variability of GSD Ib

Table 1: Literature review – clinical course of GSD Ib without neutropenia.

Author, year	Comments
Kure et al., 2000	Two patients (1. a 25-year-old adult, 2. a 6-year-old child) with genetically confirmed GSD Ib (patient 1 – compound heterozygous mutation G339D/R415X in the SLC37A4 gene; patient 2 – homozygous mutation c.794G>A in the SLC37A4 gene). Both exhibited a mild disease course, with hyperuricemia and hepatomegaly, but without neutropenia, with preserved neutrophil function, and no recurrent infections or hypoglycemia. Residual G6PT transporter activity was maintained [10].
Angaroni et al., 2006	A female patient with GSD Ib (splicing mutation c.985-1G>C in the SLC37A4 gene) presenting with typical features of the disease (hepatomegaly, hypoglycemia, nephromegaly, hyperuricemia, lactic acidosis, hyperlipidemia). During 15 years of follow-up, no neutropenia or severe infections were observed [11].
Martens et al., 2006	A 16-year-old patient with genetically confirmed GSD Ib (homozygous deletion 1211-1212delCT in the SLC37A4 gene – one of the most common mutations in GSD Ib). Neither neutropenia nor impaired neutrophil function was observed [12].
Visser et al., 2000	A multicenter European study including 57 patients with GSD Ib reported neutropenia in 54 cases (94.7%). Among these, neutropenia was first diagnosed before the age of 1 year in 64% of patients, and between 6 and 9 years of age in an additional 18%. In three patients, no neutropenia was observed [9].

and the fact that survival into the 5th and even 6th decade is achievable, especially in individuals without severe neutropenia or inflammatory bowel disease.

The standard treatment of GSD Ib includes dietary management—characterized by restriction of simple sugars (among others fructose and galactose), frequent meals with nocturnal feeding, and supplementation with uncooked cornstarch—which collectively help prevent hypoglycaemia and lactic acidosis.

Furthermore, optimized metabolic management leads to stabilization of serum triglyceride concentrations, uric acid levels, and liver function. Achieving these parameters within physiological ranges is intended to reduce the progression of hepatomegaly, diminish the likelihood of hepatic adenoma development, preserve renal function, and prevent other secondary organ complications.

Because GSD Ib is characterized by chronic neutropenia and defective neutrophil activity, therapy focuses on restoring adequate neutrophil counts and enhancing immune function. To date granulocyte colony-stimulating factor (G-CSF) has been used, however in recent years, the introduction of SGLT2 inhibitors has emerged as a therapeutic option. These agents have proven effective in reducing complications, improving metabolic control and decreasing the frequency of infections in patients with GSD Ib. In the present case, neither neutropenia nor reduced NADPH oxidase activity was observed – therefore SGLT2 inhibitor therapy has not been initiated to date.

The reported case represents an example of an atypical, mild clinical course of GSD Ib. The absence of neutropenia and recurrent infections highlights the considerable phenotypic heterogeneity of the disorder and suggests that its clinical spectrum may be very broad. Furthermore, the presented case indicates that, despite its restrictive nature, dietary management is achievable and plays an important role in preventing severe complications. Moreover, it emphasizes the importance of considering inherited metabolic disorders in adults with chronic biochemical abnormalities of unexplained origin.

Despite the patient's currently good clinical condition and stable metabolic parameters, ongoing follow-up remains necessary. Particular attention should be paid to the risk of hepatic adenomas and hepatocellular carcinoma, as well as the potential development of renal complications later in the disease course. The prognosis in GSD Ib depends not only on the effectiveness of dietary management but also on the early detection of organ-specific complications.

Conclusion

GSD Ib can present with atypical, oligosymptomatic forms, making diagnosis challenging. Absence of neutropenia and neutrophil dysfunction does not exclude the disease and underscores the need for genetic testing even in adults with chronic unexplained biochemical abnormalities. Dietary therapy and cornstarch supplementation remain the cornerstone of treatment and metabolic stabilization.

Conflict of interest

The authors declare no conflicts of interest.

Consent to participate

Written informed consent was obtained from all the participants.

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