

REPURPOSING EMPAGLIFLOZIN TO TREAT NEUTROPENIA IN A TURKISH GIRL WITH GLYCOGEN STORAGE DISEASE TYPE 1B

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ABSTRACT

Recurrent infections in children are alarming symptoms that require further investigation, particularly for various immunodeficiency syndromes. However, concomitant physical examination and laboratory findings, along with detailed investigations on the nature of these infections, might be useful to identify further pathologies, such as neutropenia, which might be the underlying reason behind recurrent infections. In this case report, we aimed to provide a different perspective on recurrent infections in childhood and to highlight the importance of accompanying physical examination findings and careful history-taking. In addition, by using glycogen storage disease type 1b as a model disease, we aim to raise awareness of inborn errors of metabolism as possible differential diagnoses and to prove that through certain therapeutic measures such as drug repurposing, these diseases can be controlled, possibly leading to decreased morbidity and mortality in this patient group, which was once thought to have a devastating prognosis.

Keywords: Glycogen storage disease, hepatomegaly, immunodeficiency, inborn errors of metabolism

INTRODUCTION

Recurrent infections in children are important, as they might be the sign of various disorders, which include benign and temporary to malignant and life-threatening causes (1). Although both the locations of infections and their causative agents can provide valuable information regarding the underlying cause of these recurrent infections, due to this variety and the many unknown conditions yet to be identified, the differential diagnosis of recurrent infections remains a significant challenge (1).

In this case report, we present glycogen storage disease type 1b (GSD1b) as a cause of neutropenia, presenting with recurrent infections in a 6-year-old Turkish girl born to consanguineous parents, who additionally presented with repeating attacks of hypoglycemia and metabolic acidosis, coupled with massive hepatomegaly.

CASE REPORT

Our patient is a 6-year-old female who was diagnosed with GSD1b at the age of 4 months. She was born to third-degree consanguineous parents at term, breastfed for 2 months, and has been under the care of the division of pediatric inborn metabolic disorders and nutrition at the Ege University Faculty of Medicine Children's Hospital since 2019. Her first clinical investigations leading to her diagnosis were initiated after the onset of fever attacks, which was the first symptom observed at the age of two months. Genetic analysis conducted in 2017 revealed a homozygous c.406T16>A mutation in the *SLC37A4* gene, consistent with GSD1b. The patient remained under follow-up at another tertiary care center until 2019.

During her first examination in our center in 2019, the patient had developmental delays, including late speech acquisition and short stature, with her current body weight and height



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being -1.76 standard deviation score (SDS) and -3.34 SDS, respectively. Dymorphological findings such as frontal bossing, hypertelorism, epicanthus, flat nasal bridge, and thin lips were present. The detailed endocrinological investigations were not significant in the patient whose skeletal age was compatible with her calendar age.

Her detailed medical history revealed recurrent infections and fevers since she was two months old, which led to frequent hospitalizations in the last six years. Subsequently, the patient has had a total of 8 hospitalizations in our center since birth due to infection-related episodes of acidosis and hypoglycemia. The most recent hospitalization in January 2024 at our center was prompted by elevated lactate levels, incidentally discovered during a routine outpatient follow-up period.

The patient's initial presentation in our center in 2019 occurred due to acute respiratory distress and a 2-3-day history of persistent cough, complicated by a metabolic decompensation that could not be controlled by the first care providers. The patient had a blood glucose level of 32 mg/dL, a pH of 7.06, and a serum bicarbonate (HCO_3^-) level of 7.5 mmol/L with a lactate level of 21 mmol/L, suggestive of severe hypoglycemia and severe metabolic acidosis. Following the first physical examination, no pathological findings were observed except for massive hepatomegaly, with the liver being palpable in the right upper quadrant. Her triglyceride levels also exceeded >250 mg/dL in repeated measurements during our follow-up for years. A detailed inquiry into past medical history revealed recurrent skin abscesses, two episodes of gastroenteritis, and persisting painful oral ulcers, raising suspicion of autoimmune, autoinflammatory, or rheumatological conditions and various errors of immunity. Measurement of immunoglobulin (Ig) levels revealed normal levels of IgA, IgG, and IgM. The ratio of the

cluster of differentiation 3 positive T cells was minimally low at 55.2% (normal range: 57-85%), which prompted assessment for Epstein-Barr virus (EBV), which came positive with EBV deoxyribonucleic acid (DNA) at 1370 copies/mL. Other laboratory examinations, including direct Coombs, antinuclear antibodies, and cytomegalovirus DNA, were negative. A burst test was conducted to exclude neutrophil function disorders, which came normal; however, her neutrophil counts were repeatedly under 1.5×10^3 , suggestive of consistent neutropenia.

An initial abdominal X-ray revealed hepatomegaly. A Doppler ultrasound examination of the portal vein, performed to reveal the etiology of her massive hepatomegaly, was reported to be normal. However, a consequent abdomen magnetic resonance imaging (MRI) showed a craniocaudal liver length of 151 mm (normal range: <109 mm, adjusted for age and sex) by physical examination findings. Additionally, a grade 2 hepatosteatosis was detected. Abdominal X-ray and MRI findings can be found in Figure 1.

The patient's general condition improved with the administration of necessary antibiotics and supportive therapy. The patient was discharged with a treatment plan that included the following: oil containing medium-chain triglycerides to manage her hypertriglyceridemia, regular raw starch to be mixed with either water or soy milk before consumption, and a dietary plan to prevent further hypoglycemia attacks, consisting of regular feeding periods with four-hour intervals. Additionally, she was prescribed allopurinol for her accompanying hyperuricemia, along with vitamin D and calcium supplements.

During her follow-up appointments in the following years, similar complaints, including recurrent infections, were present and occasionally led to hospitalizations, which are summarized in Figure 2. Her persistent neutropenia preceding

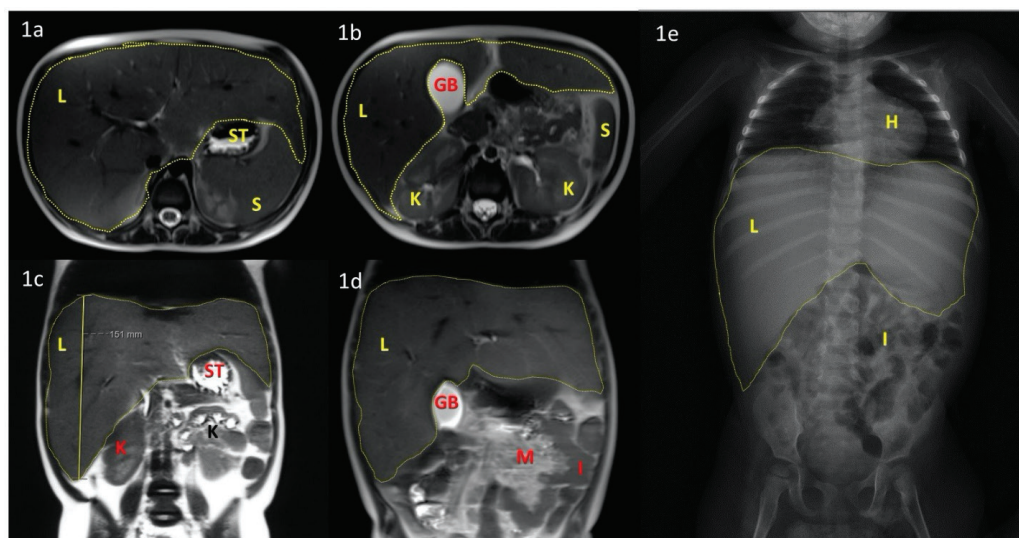


Figure 1: Abdominal MRI and X-ray findings of the patient. a and b) Sagittal upper abdominal T2-weighted MRI slices show massive hepatomegaly, which is occupying both upper quadrants and crossing the midline. c and d) Coronal upper abdominal slices of the same findings, with the liver craniocaudal length reaching 151 mm. e) Abdominal X-ray showed massive hepatomegaly, occupying most of the upper quadrants.

L: Liver, ST: Stomach, S: Spleen, K: Kidney, GB: Gallbladder, I: Intestines, M: Mesentery, H: Heart, MRI: Magnetic resonance imaging

these infections required regular treatment with filgrastim, a recombinant granulocyte-colony stimulating factor (G-CSF), which requires administration of infusions and a subsequent hospital stay or repeated subcutaneous injections. The G-CSF therapy was started as the first decision during her hospital stay between 03.07.2020-01.08.2020. A summary of the evolution of her laboratory results can be seen in Figure 3. After the publication of promising studies on the role of empagliflozin in these patients for the treatment of neutropenia in 2021, a treatment plan with oral empagliflozin has been conceptualized and applied for our patient to wean her off regular G-CSF treatments, as this patient will require lifelong treatment (2). G-CSF therapy was stopped during her hospital stay between 07.07.2021-03.08.2021 and empagliflozin treatment was started at 09.07.2021. Empagliflozin is preferred as it may also alleviate inflammatory bowel disease (IBD) symptoms in this

high-risk patient group (3). The positive effects of empagliflozin on leukocyte and neutrophil counts can be found in Figure 4.

DISCUSSION

Glycogen storage disease type 1 is an autosomal recessive disease, also known as von Gierke's disease. Both forms of GSD type 1, namely 1a and 1b, are characterized by a tendency to develop recurrent hypoglycemia with rapidly and significantly elevated lactate levels, and the presence of hypoketotic hypoglycemia is typical and of utmost diagnostic relevance (4). In GSD1b, the defective enzyme is glucose-6-phosphate translocase within the membrane of the endoplasmic reticulum and is active in the terminal stages of glycogenolysis and gluconeogenesis (4). Glucose-6-phosphate translocase transports substrates across the endoplasmic reticulum,

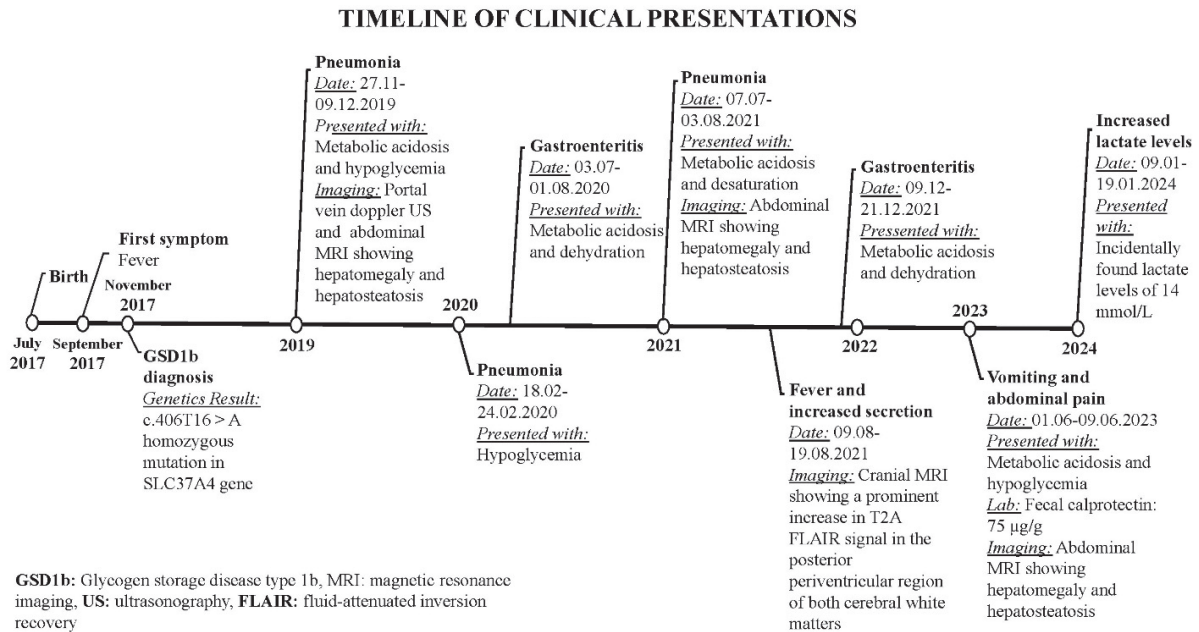


Figure 2: Timeline schema representing the hospital presentations due to underlying infectious diseases.

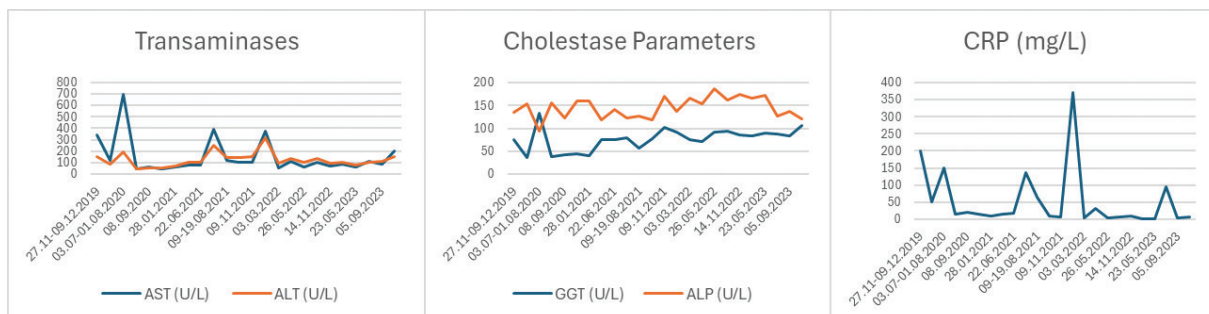


Figure 3: Laboratory parameters throughout the disease, only the highest results from every hospitalization period, and every result from outpatient care are shown. Normal value ranges are AST: <31 U/L, ALT: <34 U/L, GGT: <38 U/L, ALP: 142-335 U/L, and CRP: 0-5 mg/L. The time intervals marked with hyphens represent multi-day inpatient treatments where many measurements took place, and among these, the greatest values have been included in the figure. AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, ALP: Alkaline phosphatase, CRP: C-reactive protein

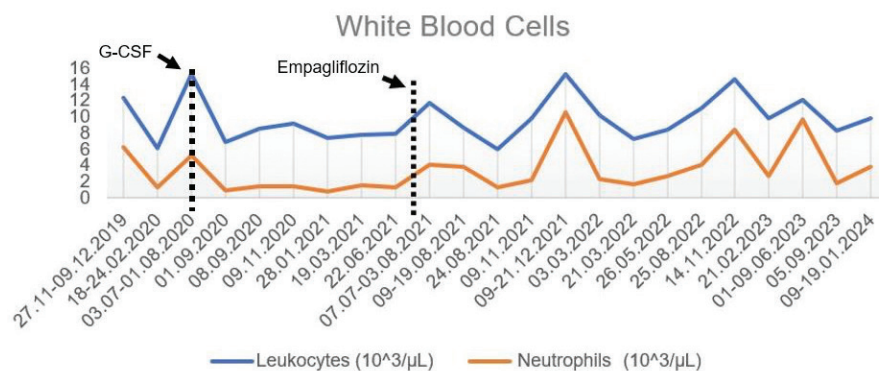


Figure 4: Effect of G-CSF and empagliflozin on leukocyte and neutrophil counts. The peaks are consistent with recurrent infections. The time intervals marked with hyphens represent multi-day inpatient treatments where many measurements took place, and among these, the greatest values have been included in the figure.

G-CSF: Granulocyte-colony stimulating factor

eventually releasing the free glucose into circulation (5). This enzyme can be found in many tissues and organs, such as the kidneys, small intestine, pancreatic islets, and in especially high concentrations in the liver (6). Typical findings, therefore, include hepatomegaly, growth retardation due to a deficiency of growth hormone, hypoglycemia, hyperuricemia, and hyperlipidemia (7, 8). The pathophysiology behind these symptoms is straightforward, while the problem lies in where the glycogen is stored and its toxic accumulation (4). All of which are present in our case as well.

Neutropenia and IBD mimicking autoimmune conditions are, on the other hand, specific for GSD1b (4). There are different hypotheses to explain the reason for increased autoimmunity in GSD1b patients, such as dysfunction of neutrophils and repetitive immunologic activation because of the immunological defect in the exclusion of microbial antigens (9).

Glycogen storage disease 1b patients are more likely to present with autoimmune conditions of the thyroid gland, myasthenia gravis, and IBDs like Crohn's (9). In our patient, a single measurement of fecal calprotectin during an infection-free period was 75 $\mu\text{g}/\text{mg}$ (normal range <50 $\mu\text{g}/\text{mg}$), which might constitute an indication for colonoscopy, but only if the patient becomes symptomatic for IBD.

Although, literature data also highlight impaired activation of some immune pathways, neutropenia and impaired neutrophil function have been long believed to occur in GSD1b patients, mainly due to the accumulation of a toxic metabolite called 1,5-anhydroglucitol-6-phosphate (1,5AG6P) in the neutrophils and presented as 1,5-anhydroglucitol (1,5AG) as a nondegradable glucose analog in plasma, because of the deficiency of transporting protein glucose-6-phosphate transporter in neutrophils leading to a decrease in dephosphorylation of this metabolite (10-12). Inhibition of urinary reabsorption of this toxic metabolite 1,5AG by glucosuria can be achieved with empagliflozin, a sodium-glucose cotransporter-2 (SGLT-2) inhibitor, leading to clinical improvement (13). It is shown, that the levels of plasma 1,5AG and intracellular 1,5AG6P

decrease after the use of SGLT-2 inhibitors (14). However, as seen in our patient, it might not have a significant effect on infection frequency. It is important to note here that treatment with SGLT-2 inhibitors poses an increased risk of urinary tract infections and hyponatremia (15).

Although the prognosis in many of the inborn metabolic disorders has been so far considered devastating, newer therapies such as enzyme replacement therapies, strict dietary measures, or repurposing of the already present medical therapies can benefit these patients significantly in some forms, leading to improved clinical outcomes and near-normal or normal life expectancies (16). The repurposed application of empagliflozin in the presented patient, originally an antidiabetic agent now considered to be beneficial in a great number of conditions ranging from chronic kidney disease to heart failure, presents a good example (17). Besides all the advantages, it shouldn't be forgotten that this is still an experimental therapy and the use of the agent should always be decided by an experienced clinician, after taking into account the risks mentioned above.

Finally, many of the inborn metabolic disorders are underdiagnosed, as some patients can present with an attenuated phenotype, making estimations of their prevalence in the common population challenging (18). Nevertheless, it is important to recognize these patients and refer them to specialists in order not to delay treatment with the existing treatment modalities and prevent further morbidity and mortality.

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