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Crohn-like disease long remission in a pediatric patient with glycogen storage disease type Ib treated with empagliflozin: a case report

Margherita Calia*, Andrea Mario Luciano Arosio*, Viola Crescitelli, Anna Fornari, Roberta Pretese, Serena Gasperini and Giovanna Zuin

***Abstract*:** Glycogen storage disease type Ib (GSD Ib) is a rare hereditary glycogen disorder that results in inadequate maintenance of glucose homeostasis, accumulation of glycogen in different organs, loss and dysfunction of neutrophils. Crohn's-like disease is observed in up to 24–77% of GDS Ib cases. Recently, empagliflozin has been recommended as a treatment for neutrophil dysfunction in GDS Ib patients with or without Crohn's-like disease. There are no guidelines for the treatment of inflammatory bowel disease (IBD) manifestation in GSD Ib patients, although some cases have been treated with granulocyte colony-stimulating factor and others with IBD conventional therapy, resulting in partial IBD remission. Herein, we describe a child with GDS Ib and Crohn's-like disease who was treated with empagliflozin and achieved complete remission after 2 years of treatment. This case is the first one with such a long follow-up evaluation including endoscopic and magnetic resonance enterography assessment. Our clinical evidence of remission of IBD manifestation in our GSD Ib patient and the role of neutrophils in GDS Ib described in the literature suggest a strong association with IBD pathophysiology and neutrophil function. The use of empagliflozin resulted in significant improvements in gastrointestinal symptoms, reduced drug usage, and enhanced quality of life in the patient, with a favorable safety profile, offering a promising new therapeutic option for this population.

Keywords: case report, empagliflozin, glycogen storage disease type Ib, inflammatory bowel disease, pediatric

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Correspondence to:
Giovanna Zuin
Pediatrics, Fondazione IRCCS San Gerardo dei Tintori, Via G. B. Pergolesi, 33, 20900 Monza (MB), Italy
giovanna.zuin11@gmail.com

Margherita Calia
Andrea Mario Luciano Arosio
Viola Crescitelli
Anna Fornari
Roberta Pretese
Serena Gasperini
Pediatrics, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italia

*These authors contributed equally

Introduction

Glycogen storage disease type Ib (GSD Ib) is a rare inborn error of glycogen metabolism. The annual incidence at birth is 1:100.000 and type b represents 20% of GSD I.[1] It is inherited as an autosomal recessive trait caused by a mutation in the SLC37A4 gene, which is located on the long arm of chromosome 11 and results in glucose-6-phosphate translocase (G6PT) deficiency. This deficiency leads to inadequate maintenance of glucose homeostasis, accumulation of glycogen in the liver and kidney cells, and loss and dysfunction of neutrophils.[2]

In GDS Ib, the metabolic derailment leads to failure to thrive with muscle hypotrophy, central obesity, and a typical doll-like facial appearance. The evidence of hepatomegaly is constant. The immune defect results in frequent infections, oral aphthosis, and perianal abscesses. In addition, GDS Ib patients show an increased risk of inflammatory bowel disease (IBD), indeed Crohn's-like disease is observed in up to 24–77% of all cases.[3,4] The median age of onset of gastrointestinal symptoms ranges from 5 to 12 years, and the clinical manifestations are mostly Crohn's-like, most often located in the small intestine.[3] The

pathophysiology is still unclear, but it seems to be related to neutropenia and neutrophil dysfunction.

Due to the impaired neutrophil survival and neutrophil dysfunction resulting from reduced phagocytic activity associated with an impaired metabolic burst, the treatment approach involved chronic administration of granulocyte colony-stimulating factor (G-CSF). This treatment has demonstrated effectiveness in increasing neutrophil count with relatively low doses (median 3 mcg/kg/day) and significantly elevating the median absolute neutrophil count by fivefold. These effects are sufficient to reduce the occurrence of infections and mitigate the severity of IBD, such as oral aphthosis, abdominal pain, and changes in stool consistency.[2]

The increased apoptosis and neutrophil dysfunction in GSD Ib patients seem related to the intracellular accumulation of 1-5-anhydroglucitol (1,5AG). The renal sodium–glucose cotransporter 2 (SGLT2) is responsible for the reabsorption of glucose and 1,5AG.[5] The selective inhibition of SGLT2 reduces the concentration of the 1,5AG in blood and in neutrophil cytoplasm, improving neutrophil life span and function. Empagliflozin is an SGLT2 inhibitor approved to treat type 2 diabetes in adults. Recently, Wortmann *et al.* recommended the use of empagliflozin as an alternative treatment for neutropenia and neutrophil dysfunction in patients with GDS Ib.[6]

Clinically, the use of empagliflozin improved the symptoms related to neutrophil dysfunction, such as frequent infections, mucosal and urogenital lesions, as well as IBD manifestations.[6]

In the literature, there are few reported pediatric cases that investigate the impact of empagliflozin in IBD manifestations in GSD Ib patients.[6–10]

Herein, we describe a child with GSD Ib and Crohn's-like ileitis treated with empagliflozin who achieved complete clinical, endoscopic, and histological remission after more than 1 year of treatment.

The present case report is designed following the CAse REport (CARE) guidelines.[11] The signed consent to publish this case report was obtained from the patient's parents; however, to ensure privacy and confidentiality, all patient-specific information has been de-identified.

A case report

We present a case of a 10-year-old boy with GSD Ib. Due to the recurrent severe hypoglycemia and neutropenia at 1 month of life, GSD Ib was suspected and confirmed through genetic testing (the variants c.1042_1043del in homozygosity was found on the SLC37A4 gene). Since then, dietary management with small and frequent feedings was started. At 1 year of age, cornstarch was introduced, reaching a maximum dosage of 6.8 g/kg with a fasting period of up to 4 h. Due to the presence of neutropenia since the diagnosis, at 1 month of life, G-CSF (starting dose 2 γ/kg/die) and antibiotic prophylaxis were initiated (evening single dose).

Since the age of 7 years, the patient developed recurrent severe oral aphtosis and frequent infections, which were treated with increasing doses of G-CSF (up to a maximum dose of 9 γ/kg/die during infections without interruptions). As a side effect, he developed severe splenomegaly and hypersplenism. The growth pattern was regular on the sixth percentile for weight and height on the WHO growth chart[12] with a body mass index (BMI) of 15 kg/m^2. No diarrhea nor abdominal pain was reported. At the age of 8 years, a gastroenterological consultation was performed: laboratory test showed a persistent mild increase in erythrocyte sedimentation rate (ERS) and negative C-reactive protein (CRP), fecal calprotectin was high (500 µg/g; normal value 50), ASCA IgA was found. Based on the clinical and laboratory assessment, a diagnosis of Crohn's-like disease was hypothesized.

Magnetic resonance enterography (MRE) showed segmental thickening of the ascending colon wall at the ileocecal valve levels. The known splenomegaly was described with a bipolar diameter of 20 cm. The endoscopic evaluation displayed mucosal hyperemia of the cecum with edema, ulcerative lesion, and substenosis of the ileocecal valve. No other findings on the colon, sigma, and rectum were found. Chronic inflammation was reported at the histologic evaluation. Thalidomide was started in combination with G-CSF based on our previous experience in treating Crohn's disease children, its efficacy in treating oral aphtosis, and its immunomodulatory effect.[13] Quick

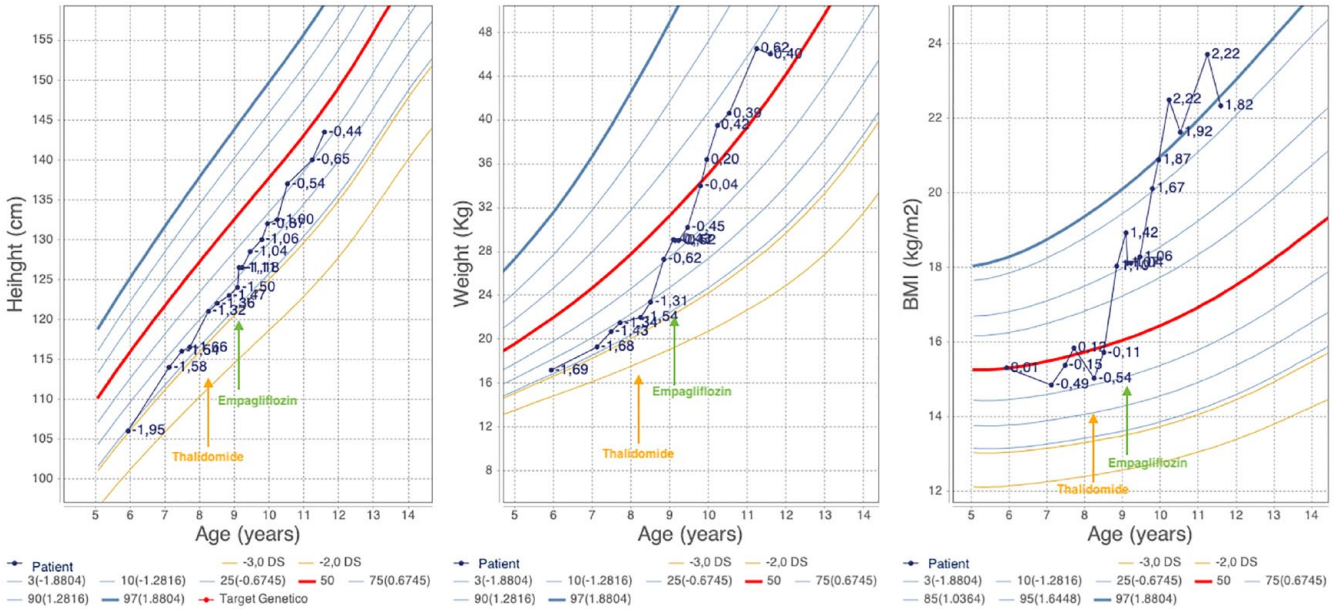

Figure 1. WHO growth curves for height, weight, and BMI during treatment with thalidomide and empagliflozin, the measurements are expressed in standard deviations (SD).
BMI, body mass index.

resolution of oral aphtosis was obtained with concomitant weight gain. However, after 9 months of treatment, no improvement at MRE and endoscopy evaluation was observed.

At the age of 9 years, we decided to add a new treatment with empagliflozin to the ongoing therapy, based on the recently reported efficacy of this drug in a few cases with GSD Ib and Crohn's-like disease in the literature.[6–10]

Informed written consent was obtained from the patient's parents, according to the International and Italian Metabolic Board (MetabERN), after discussing the potential benefits and adverse effects of the treatment.

The patient was admitted to the pediatric ward for clinical monitoring during the introduction of the new therapy. The starting dose was 0.1 mg/kg per day for the first 2 days, then increased to 0.2 mg/kg in two doses from day + 3 of treatment as planned by the Board of Italian and European experts coordinated by MetabERN. During admission, the patient's vital parameters, glycemia, and urine dipstick were monitored. Mild glycosuria was expectedly observed due to the drug's mechanism of action. Only one asymptomatic episode of hypoglycemia (58 mg/mL) was detected in the first days. No other adverse effects were observed. The patient continued the treatment at home, with weekly increases in dosage. Considering the good tolerance to the treatment, the dosage was increased to the target dose of 0.5 mg/kg per day indicated by previous studies after 30 days.[6] Despite the glycosuria, no major urogenital tract infections occurred.

Clinically we observed that, despite the suspension of thalidomide after 45 days of empagliflozin treatment, no episodes of oral aphtosis were reported, and stools were solid. IBD remained clinically silent with a Pediatric Crohn's Disease Activity Index score equal to 0 at 3, 12, 18, and 24 months.

After the beginning of the new treatment, the patient's weight and height significantly improved, with a gain of 17 kg in the following 2 years (going from the 33rd centile to the 70th percentile on the WHO growth chart).[12] The height gain on the WHO growth chart[12] went from the 7th to the 26th percentiles and the BMI improved from 19 to 24 kg/m^2 (see Figure 1).

After 4 months of empagliflozin therapy, laboratory results showed a normalization of erythrocyte sedimentation rate (ESR) with CRP always

Table 1. Inflammation index values under empagliflozin treatment.

Months	ESR (mm/h)	CRP (mg/dL)	Fecal calprotectin (µg/g)
0	51	2.96	150
+4	19	0.07	77
+8	10	0.30	51
+14	8	0.12	41
+18	9	0.37	115
+24	19	0.81	10

ESR n.v. < 15 mm/h; CRP n.v. < 0.5 mg/dL; fecal calprotectin n.v. <50 µg/g.
CRP, C-reactive protein.

negative (Table 1). Calprotectin was used as an indicator of bowel inflammation and was persistently below 300 µg/g, a cutoff that identifies children with mucosal healing (see Table 1).[14] The blood and bowel inflammatory index remained persistently negative during the 2 years of therapy (see Table 1). White blood cells and neutrophils improve over time (see Figure 2). The improvement in the number of neutrophils allowed for a progressive decrease in the G-CSF dosage with an absolute neutrophil count always above 1000/mmc even during the tapering phase of G-CSF (minimal dose 1 γ/kg/die), until suspension after 18 months of empagliflozin treatment. Then white cell count remains above 4000/mmc and the absolute neutrophils count above 1500/mmc (see Figure 2). The tapering and the suspension of G-CSF led to a consequent gradual reduction of hypersplenism and splenomegaly observed at physical examination and the MRE imaging. Furthermore, while on empagliflozin, as expected from the drug action, we observed an increase in specific neutrophil subtypes (mature neutrophils) and a reduction in the immature subsets, no neutrophil function assay was performed.[15] In addition, contrary to the mechanism of action of empagliflozin, based on our clinical experience, initiating this new treatment allowed our dietician to extend the fasting period up to 5 h without any changes in cornstarch dosage.

A complete restaging of IBD was performed at 3 and 12 months after achieving the target dose of empagliflozin.

After 3 months of empagliflozin therapy, MRE confirmed the thickening of the last ileal loop (maximum thickness 7 mm, longitudinal extension 4 cm), but found less edematous imbibition of the adjacent mesenteric adipose tissue and less thickening of the walls of the cecum next to the ileocecal valve. The G-CSF-induced splenomegaly with glycogen nodules was reduced with a bipolar diameter of 17 *versus* 20 cm. The ileocolonoscopy demonstrated the macroscopic resolution of ileal and cecal inflammation, with persistent ileocecal substenosis. The histological evaluation revealed minimal and nonspecific chronic inflammation with initial fibrotic aspects on the ileocecal mucosa.

At 12 months of therapy, MRE demonstrated complete resolution of the concentric thickening of the cecal walls, a reduction in the concentric thickening of the terminal ileal loop (maximum thickness 5 *versus* 7 mm and longitudinal extension of 2 *versus* 4 cm). The G-CSF-induced splenomegaly with glycogen nodules was unchanged with a bipolar diameter of 16.5 cm (normal median spleen long axis at 8–10 years is reported to be 9.2 cm).[16] Colonoscopy showed an open ileocecal valve passed with only a light pressure, the stenosis previously described was no longer appreciable, and normal appearance of the terminal ileum and colon. Histology confirmed a complete inflammatory quiescence with reparative aspects in the right colon.

Literature review and discussion

The treatment of chronic bowel manifestations in patients affected by GSD Ib is complex because the exact pathomechanism of intestinal involvement in GSD Ib is still unclear.[2] Currently, no validated guidelines are available for the treatment management of IBD-like manifestations in GDS Ib patients. Historically, the treatment of the Crohn's-like manifestations in these patients was based on G-CSF chronic supplementation.[17,18] However, only a few cases showed clinical remission of gastrointestinal symptoms on chronic G-CSF therapy alone.[17] Indeed, many cases have not shown major improvement from conventional IBD therapies such as corticosteroids, immunomodulators, and biological drugs, and some have required surgical therapy.[19–21]

Gastrointestinal symptoms appear to be related to neutropenia and neutrophil dysfunction, which are caused by the accumulation of 1,5AG6P. This excess storage inhibits the activity of

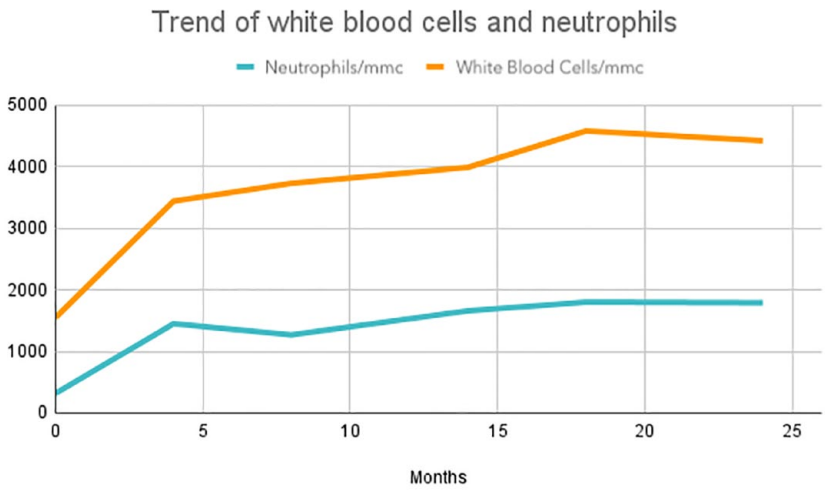

Figure 2. White blood cells and neutrophils values under empagliflozin treatment, G-CSF was suspended at 18 months of treatment.
G-CSF, granulocyte colony-stimulating factor.

hexokinases, leading to a reduction in glucose phosphorylation and disruption of the glycolytic pathway. These metabolic alterations are essential for the immunometabolic activation and patrolling activity function of these cells.[5] Wortmann and Grünert in 2020[6,22] described significant benefits of empagliflozin treatment on gastrointestinal symptoms, neutrophils count, and function in three GSD Ib patients with IBD-like disorders, two of whom were children and showed clinical improvement and a reduction in calprotectin.[6]

In the literature, five pediatric cases of GDS Ib patients with IBD-like manifestations treated with empagliflozin are described. All of them have shown improvements in gastrointestinal manifestations such as stool frequency and consistency, abdominal pain, and oral aphtosis, with a decrease in IBD clinical scores.[6–10] Only Rossi *et al.*[7] described imaging and endoscopic features of a child of 14 years old with Crohn's-like ileitis treated with empagliflozin. A dramatic improvement in the disease extension and activity was found at the MRE after 3 months, but no major endoscopic changes were noted after 5.5 months of treatment: the ileocolonoscopy still showed persistent ileocecal valve ulcer and stricture with the impossibility to pass through with the scope.[7]

Our results confirm what was previously reported in the literature. Yet, our experience is the first one with such a long follow-up including clinical, endoscopic, and imaging evaluation. After 14 months of treatment, our patient had a clinical, endoscopic, and histologic Crohn's-like IBD remission. Moreover, we can observe the complete disappearance of the stenotic bowel lesion at 14 months of treatment. After 24 months of treatment, the IBD disease remains clinically silent, with a progressive improvement of the BMI and a persistent negativization of blood and bowel inflammatory index.

Thanks to the clinical, endoscopic, and histological evidence of remission in our patient, combined with the literature evidence highlighting the critical role of neutrophils and their function in GDS Ib patients,[15,22] we can hypothesize that IBD-like manifestations in this population strongly associated with the functionality and abundance of these cells. Therefore, we can conclude that defective metabolism and related antimicrobial activity are pivotal factors in CD-like intestinal inflammation[23] and have been suggested to contribute to Crohn's disease pathogenesis.

The improvements in gastrointestinal symptoms, the reduction in the number of drugs administered, and especially the suspension of the injection of G-CSF, along with the extended fasting period following the initiation of empagliflozin, have resulted in a remarkable improvement in the quality of life of our patient. As mentioned by Grünert *et al.*, the SGLT2 inhibitor is a 'life

changer' for both GSD Ib patients and their caregivers.[24] The drug safety profile appears to be favorable, as no major complications were observed in our case, consistent with findings reported in the literature.[24]

Conclusion

The data we report suggest good efficacy and safety of empagliflozin therapy in maintaining long-lasting IBD clinical, endoscopic, and histologic remission, in improving anthropometric data, and enhanced quality of life in patients with GSD Ib and Crohn's-like symptoms. Furthermore, this case supports the hypothesis of a strategic role of neutrophil dysfunction in IBD disorders and could help better understand the pathogenesis of IBD. Future studies in larger series should evaluate the efficacy and safety of long-term treatment on maintaining clinical, endoscopic, and histologic remission in Crohn's-like disease in children affected by GSD Ib.

Author's note

Summary of our work: IBD manifestations are observed in cases of GSD Ib. We describe a child treated with empagliflozin who achieved mucosal healing after 1 year.

Declarations

Ethics approval and consent to participate

Full informed written consent and signed was obtained from the parents of the patient included in this study.

Consent for publication

The signed consent to publish this case report was obtained from the patient's parents.

Author contributions

Margherita Calia: Conceptualization; Data curation; Formal analysis; Resources; Writing – original draft; Writing – review & editing.

Andrea Mario Luciano Arosio: Data curation; Writing – original draft.

Viola Crescitelli: Supervision; Visualization.

Anna Fornari: Supervision; Visualization.

Roberta Pretese: Investigation; Writing – review & editing.

Serena Gasperini: Conceptualization; Data curation; Investigation; Methodology; Writing – review & editing.

Giovanna Zuin: Conceptualization; Investigation; Project administration; Writing – original draft; Writing – review & editing.

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Margherita Calia e Andrea Mario Luciano Arosio wrote the manuscript. Viola Crescitelli, Anna Fornari, Serena Gasperini, Roberta Pretese, and Giovanna Zuin played important roles in patient care and critically revised the manuscript for important intellectual content. All authors have accepted responsibility for the entire content of this manuscript and have approved its submission.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Research data supporting this publication are available in our hospital archives.

ORCID iD

Margherita Calia https://orcid.org/0009-0002-4851-9795

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