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Abstract

Glycogen storage disease type 1b (GSD 1b) is a rare autosomal recessively inherited disease (SLC37A4). GSD 1b is a deficiency of a transporter for glucose-6-phosphate (G6PT) in the endoplasmic reticulum (ER) membrane. Reduced transport of G6P into the ER interferes with gluconeogenesis and glycogenolysis, leading to episodes of postprandial hypoglycaemia, hyperlactatemia, hyperuricaemia, hypertriglyceridaemia and hypercholesterolaemia. Typically, the first noticeable symptoms are short stature, massive hepatomegaly and a characteristic face with prominent cheeks (referred to as a 'doll face'). Patients with GSD 1b also exhibit frequent, life-threatening infections and inflammatory bowel disease (Crohn-like), which are caused by abnormal neutrophil function. So far, granulocyte colony-stimulating factor (G-CSF) used to prevent infections has not been fully effective and numerous side effects have been observed.

As a result of G6PT deficiency, 1,5-anhydroglucitol phosphate (1,5 AG6P) is stored in the cytoplasm of neutrophils, which inhibits anaerobic glycolysis. This energy deficiency leads to excessive apoptosis of neutrophils and impairs their bactericidal and fungicidal activity (e.g. abnormal chemotaxis, phagocytosis, impaired 'oxygen burst'). Empagliflozin (EMPA), an inhibitor of the sodium-glucose cotransporter type 2 (SGLT2), decreases the reabsorption of 1.5 AG from urine, which reduces the concentration of 1.5 AG6P in neutrophils.

This study aimed to assess the effect of treatment with the SGLT2 inhibitor, specifically on neutropenia and its complications in patients with GSD1b.

The following conclusions were drawn from the analysis of the study results:

1) In the Polish pediatric population, the most common first manifestation of GSD 1b is severe infection during the neonatal-infant period. As in many congenital neutropenias, during an infection, in patients with GSD 1b, the bone marrow can "shed" more neutrophils, potentially masking a chronic deficiency of these cells. Therefore, especially in the presence of recurrent, severe infections or suspected GSD 1b, it is necessary to monitor blood counts with manual smears after the symptoms of infection have resolved or CRP has normalized.

2) Despite its significant severity, hypoglycaemia in the course of GSD 1b is relatively rarely symptomatic, which demonstrates the need to actively look for it (e.g. fasting blood glucose determination, prolonged starvation test) in patients diagnosed with this condition.

3) G-CSF treatment of neutropenia in patients with GSD 1b does not restore neutrophils' normal number or antimicrobial activity.

4) EMPA's inclusion in the treatment has a beneficial effect on the frequency of infections and symptoms of inflammatory bowel disease, mainly due to an improvement in neutrophil antimicrobial function.

5) EMPA's use, despite its hypoglycaemic effect, is safe in patients with GSD 1b.

6) EMPA positively affected all parameters of neutrophils' antimicrobial activity except the synthesis of intracellular and plasma antimicrobial peptides (AMPs), including defensins. AMP production was higher during G-CSF treatment.