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Short Communication

Liver transplantation in glycogen storage disease type Ib: The role of SGLT2 inhibitors

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ABSTRACT

We report on liver transplantation in two patients with GSD Ib on treatment with empagliflozin. The use of this SGLT2 inhibitor resulted in a marked decrease of 1,5-anhydroglucitol which has an important role in the development of neutropenia in this condition. As intended, this caused a significant rise of neutrophil numbers. Liver transplantation alone did not produce the desired effect and our observation argues for continuing SGLT2 inhibitor treatment after transplantation.

1. Introduction

In the past, the indication for liver transplantation (LTx) in patients with glycogen storage disease type Ib (GSD Ib, Online Mendelian Inheritance in Man [OMIM] 232,220) has been decidedly guarded, and thus only rather small series of patients with this procedure have been reported [1]. Overall, recommendations are cautious: while hepatic adenomas and hepatocellular carcinomas, mainly observed in older patients, and poor metabolic control despite optimized medical measures in younger ones are acceptable indications for LTx in GSD Ib [2], a higher complication rate has been reported when compared to other indications for LTx [3]. This is due to neutropenia and granulocyte dysfunction in GSD Ib patients, which result in a higher propensity for infection and risk of wound healing problems or fistula formation. Only in recent years, it could be shown that neutropenia in GSD Ib is the result of a failure to eliminate the glucose-6-phosphate analogue 1,5-anhydroglucitol (1,5-AG)-6-phosphate by the phosphatase G6PC3, present in the endoplasmic reticulum in neutrophils [4]. Shortly thereafter, first GSD 1b patients were successfully treated with SGLT2 inhibitors, that were shown to reduce the renal reabsorption of 1,5-AG [5]. The widespread successful use of these substances in GSD Ib and their impressive effect on polymorphnuclear neutrophil (PMN) number and function have been documented [6]. Here, we report the clinical course of two GSD Ib patients who received LTx, eventually leading to normal glucose homeostasis, and focus on PMN numbers before and after the use of an SGLT2 inhibitor.

2. Patients and methods

2.1. Patient 1

Patient 1 is a now 10-year-old girl with a syndromic neurodevelopmental disorder (recently elucidated as PAN2 deficiency [7]). She concomitantly suffered from GSD Ib (ENST00000645735.2, *SLC37A4* c.1015G>T; p.Gly339Cys, homozygous) and parents requested LTx in 2015 (before SGLT2 inhibitors were considered) to better care for their disabled child and avoid hypoglycemic deterioration in the context of nursing facility care. After LTx with a post-mortem left-sided split and a cautious immunosuppressive regimen with basiliximab, cyclosporine and prednisone, chronic graft failure occurred with massive parenchymal damage (minimal prothrombin time [quick] 32%, maximal INR 2.0), cirrhosis, and severe cholestasis (maximal total bilirubin 35 mg/dl). Because of hypersplenism, the severe neutropenia present since birth (despite G-CSF treatment) turned into pancytopenia.

Abbreviations: 1,5-AG, 1,5-anhydroglucitol; G-CSF, granulocyte colony-stimulating factor; G6PC3, glucose-6-phosphatase C3; GSD Ib, glycogen storage disease Ib; LTx, liver transplantation; OMIM, Online Mendelian Inheritance in Man; PAN2, poly(A)-binding protein-specific nuclease-2; PMN, polymorphnuclear neutrophil; SGLT, sodium-dependent glucose transporter; SLC37A4, solute carrier family 37 (glucose-6-phosphate transporter), member 4; UPLC-MS/MS, ultra performance liquid chromatography - tandem mass spectrometry.

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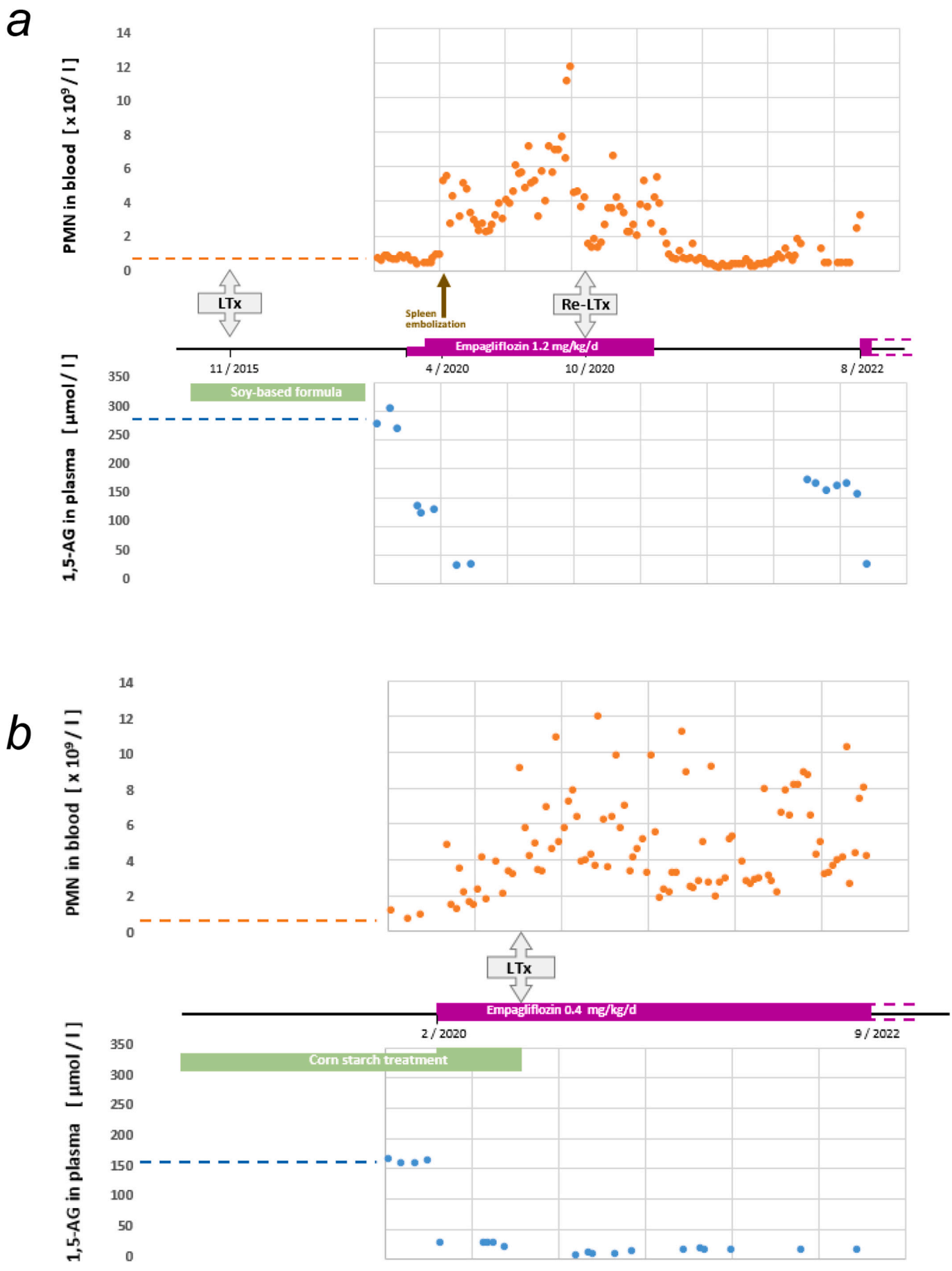

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Fig. 1. PMN counts and plasma 1,5-AG concentration in GSD Ib patients 1 and 2 over time. *a Note* that first LTx in patient 1 had no effect on elevated 1,5-AG and low PMN number. Empagliflozin markedly reduced 1,5-AG concentration with a concomitant increase of PMN number. Discontinuation of empagliflozin after second LTx resulted in a renewed increase in 1,5-AG and a decrease of PMN counts to preoperative values. After restarting empagliflozin treatment, 1,5-AG dropped again and PMN counts normalized. This patient was tube-fed initially with soy-based formula (*shown by green bar*) and later received only oligosaccharides, no starch preparations were given. *b* SGLT2 inhibitor treatment was started preemptively before planned LTx in patient 2. Empagliflozin caused a marked decrease of 1,5-AG concentration and a concomitant normalization of PMN counts. Post-LTx, a slight decrease in 1.5-AG concentration from about 20 μmol/l to about 10 μmol/l was observed, presumably due to concomitant discontinuation of nutritional therapy with corn starch (*shown by green bar*).

At this point, the SGLT2 inhibitor empagliflozin (10 mg/d, 0.6 mg/kg/d) was introduced on an off-label basis, resulting in normal PMN counts for the first time in life after partial splenic embolization. No side-effects were observed.

Soon thereafter, the child required re-LTX (on empagliflozin) which was uncomplicated, but omission of the SGLT2 inhibitor thereafter again resulted in neutropenia, and only after reintroduction of empagliflozin did PMN counts normalize (Fig. 1a). Glucose homeostasis remained stable even after termination of oligosaccharide-based tube feedings.

2.2. Patient 2

Patient 2 is a 3-year-old girl with typical signs of GSD Ib (*SLC37A4* c.1042_1043delCT; p.Leu348Valfs*53, homozygous), including oral aphtosis, frequent infections, and otorrhea at first referral due to severe neutropenia. Parents refused tube feeding, and reasonably satisfactory glucose homeostasis could only be achieved with extreme dietary measures unacceptable to the parents. Therefore, LTx was considered and off-label treatment with empagliflozin (5 mg/d, 0.4 mg/kg/d) was started to improve PMN number and function before this intervention (Fig. 1b). The amount of starch had to be increased by approx. 10% to avoid hypoglycemia. At 2.5 years of age, the child received a left-sided post-mortem split liver with a similar immunosuppressive regimen as patient 1 and with no infectious complications or wound healing problems. However, there was a problem with bile drainage from liver segment 2 requiring temporary internal percutaneous transhepatic biliary drainage. Under ongoing empagliflozin medication, she now has normal glucose homeostasis without any additional dietary measures.

In both children we used ultra performance liquid chromatography - tandem mass spectrometry (UPLC-MS/MS) to measure plasma concentration of the glucose analogue 1,5-anhydroglucitol (1,5-AG), the substrate for production of 1,5-anhydroglucitol-6-phosphate which is responsible for granulocytopenia in GSD Ib, and we correlated results to PMN counts in blood.

3. Results

The evaluation of patient 1 demonstrates that her first LTx had no relevant effect on elevated 1,5-AG concentration and low PMN count. It was not until the start of empagliflozin treatment that PMN numbers increased in parallel to a decrease of 1,5-AG concentration from 200 to 250 μmol/l to about 30 μmol/l, and only recently, when reintroduced after a post-operative discontinuation, did 1,5-AG and PMN counts normalize (Fig. 1a). Our second patient showed a comparable decrease in plasma 1,5-AG from 160 to 20 μmol/l on empagliflozin with a concomitant increase in PMN count. After LTx (and concomitant discontinuation of corn starch treatment) and with continued SGLT2 inhibitor treatment, her 1,5-AG concentration leveled off to about 10 μmol/l (Fig. 1b).

Both patients showed a higher variability of PMN numbers immediately after LTx, but this was probably also stress-related due to this procedure.

4. Discussion

Recent observations in G6PC3-deficient patients (OMIM 612541) with severe congenital neutropenia treated with empagliflozin indicate that SGLT5 (encoded by *SLC5A10*) is the putative renal transporter for 1,5-AG [8]. SGLT2 inhibitors like empagliflozin were shown to inhibit tubular reabsorption of 1,5-AG as a result of glucosuria they induce [5,8], although it is not yet clear whether physiologically they may also have a direct effect on SGLT5. In any case these compounds result in a marked reduction of plasma 1,5-AG concentration that inversely correlates with PMN counts in patients with GSD Ib. The use of these substances significantly increases PMN numbers but also improves PMN function, and therefore, we expect a reduction in the risk of infection-related perioperative complications in this disorder. Particularly in view of the fact that the post-operative course was not without problems in our two patients, it is by no means our intention to advocate an "overly aggressive use of transplantation in this [patient] population" [2] with this report, however, we hypothesize that LTx with early initiation of empagliflozin therapy will have a much more favorable prognosis.

Even before the era of SGLT2 inhibitors, there were some anecdotal cases in which PMN numbers were reported to show a sustained increase after LTx, but the underlying pathophysiology of this phenomenon was not investigated at that time. It is conceivable that the discontinuation of nutritional therapy with starch or soy preparations (both well-known sources of 1,5-AG) had a variable effect on PMN number. This is underlined by our observation that 1,5-AG concentrations on empagliflozin were lower after LTx than usually observed in GSD Ib patients on SGLT2 inhibitors [5]. Thus, logically, these GSD Ib patients after LTx resemble G6PC3-deficient patients who are not on a starch-containing diet, but as previously shown for G6PC3-deficient patients [8], still benefit from a continued therapy with SGLT2 inhibitors to treat their neutropenia that persists after LTx.

Contributors

S. M. conceptualized the study and together with M. P. established the 1,5-AG assay and measured all samples. She analyzed the data and wrote a first draft of the manuscript. K.T., S. S.-J. and R.S. took care of the patients pre- and post-operatively. U.H. was responsible for liver trasplantation. R. S. conceptualized the study, analyzed clinical and laboratory data and finalized the manuscript. All authors were involved in revision of the final version and agree to publication.

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Ethical compliance

The study was performed in accordance with the ethical standards of the local ethics committee. Patients agreed on publication.

Declaration of Competing Interest

The authors declare no conflict of interest.

Data availability

Data will be made available on request.

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