with improved nutritional markers. Furthermore, improvement of IBD symptoms allowed spacing of meals and cornstarch doses and improved fasting intolerance. Reduction of maximum empagliflozin dose was needed due to arthralgia. No other significant side effects of empagliflozin were observed, including hypoglycemia. This report also highlights novel use of global metabolomics for monitoring plasma levels of 1,5-anhydroglucitol to assess empagliflozin dose responsiveness and guide dietary management as well as G-CSF therapy. Clinical improvement correlated to rapid normalization of 1,5-AG levels in plasma that was sustained after dose reduction.

Conclusion: SGLT2 inhibitors are a new and safe treatment option for GSD-Ib-associated neutropenia and neutrophil dysfunction leading to overall improvement in other manifestations of the disease. Global untargeted metabolomics is an efficient method to assess biochemical responsiveness to treatment.

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Genotype-phenotype correlation of glycogen storage disease type IV

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Introduction: Glycogen storage disease type IV (GSD IV) is a rare autosomal recessive disease caused by glycogen branching enzyme deficiency, encoded by GBE1. The deficiency results in variable clinical features, age of onset, and disease severity. GSD IV is arbitrarily divided into several subtypes based on the continuum of symptoms. The most common Classic Hepatic subtype presents in the first few months of life with hepatomegaly, followed by rapid deterioration into cirrhosis and lethal liver failure requiring liver transplant. The Non-progressive Hepatic subtype is thought to be rare and can present with hepatomegaly in childhood with or without myopathy and cardiomyopathy, with those affected surviving into adulthood. The most severe Fetal/Neonatal Neuromuscular subtype can present with fetal akinesia, hypotonia, dilated cardiomyopathy, and death in early infancy. The Congenital Neuromuscular subtype presents in the newborn period with profound hypotonia, respiratory distress, and typically with dilated cardiomyopathy, that can lead to death in childhood. A milder Childhood Neuromuscular subtype can lead to myopathy or cardiomyopathy in late childhood. Certain genotypes in GBE1 are associated with Adult Polyglucosan Body Disease (ABPD), characterized by adult-onset neuropathy, spasticity, autonomic dysfunction, and mild cognitive decline. Recently, Isolated Cardiomyopathy subtype was described in a patient with biallelic GBE1 missense variant. The diagnosis of GSD IV is challenged by the variable presentation and confounding histology, even within the same family. At initial early presentation, the classic hepatic subtype can be indistinguishable from the non-progressive hepatic phenotype, yet liver transplantation arrangement should be initiated rapidly after the diagnosis. Early and accurate diagnosis of hepatic phenotypes is critical in enlisting the patient for liver transplant candidacy. However, previous reviews of GSDIV genotype-subtype associations have not addressed the prediction of Hepatic phenotypes based on GBE1 genotype. We performed a comprehensive review of case reports and case series of the spectrum of glycogen branching enzyme deficiency of all subtypes to analyze genotype-phenotype correlation.

Methods: An independent English literature search of the PubMed and Google Scholar databases was performed, using the keywords "glycogen storage disease", "adult polyglucosan body disease" "GBE", and "GBE1". The search was performed with no time restrictions for publication year. Manual inspection of the manuscripts was conducted to include published case reports and case series describing clinical features and outcomes of patients with GSD IV. Studies were excluded if they did not describe clinical patient data, if the diagnosis was not confirmed by enzyme activity/GBE1 sequencing or if the patient was previously described in the published literature. After studies were reviewed for inclusion, data extraction was performed. Author name, bibliographic details, number of patients, patient sex, age of disease onset, the clinical presentation of disease with specific organ involvement, and clinical outcomes were recorded. Each reported case was classified into one of the six GSD IV subtypes described above, based on patients' presenting symptoms described in the respective case report. GBE1 genotypes were recorded, if available.

The GBE1 variant descriptions were standardized according to the HGVS nomenclature. Variant Validator https://variantvalidator.org/ was used to verify the DNA nomenclature. GBE1 genotypes for cases in each subtype were analyzed.

Results: One hundred sixty-eight cases from 99 publications were selected, which reported 132 variants in the GBE1 gene. The cases consisted of 33 cases of Classic Hepatic subtype, 20 cases of Non-progressive Hepatic subtype, 54 cases of Fetal/Neonatal Neuromuscular subtype, 7 cases of Congenital Neuromuscular, 16 cases of Childhood Neuromuscular subtype, 26 cases of APBD subtype and 1 case of Isolated Cardiomyopathy. Ten cases did not include sufficient clinical information to enable classification into one of the seven subtypes.

All Classic Hepatic subtypes with known genotype had one severe variant (splice-site, non-sense, frameshift) in compound heterozygosity with a missense variant. The mild variant p.Tyr329Ser commonly seen in APBD was also commonly seen in Non-Progressive Hepatic subtype in compound heterozygosity with a sever variant (missense variant leading to complete loss of the GBE activity or splice site variant).

We were not able to find genotypes characteristic to either Hepatic subtype. Prediction of the Hepatic subtypes based on the GBE1 genotype alone remain difficult. Non-sense variants and splice-variants were seen in both subtype in compound heterozygosity with a missense variant. Large exonic variants were not found in either Hepatic subtype. Variants found in both subtypes are similarly distributed across the gene with no specific common hot spots.

Having at least one truncation variants due to a large deletion, non-sense, frameshift or splice-site variants have been implicated in the severe Fetal/Neonatal Neuromuscular subtype and we confirmed this finding.

We found that Fetal/Neonatal Neuromuscular subtype was most frequently reported, contrary to the previous report that the Classic Hepatic subtype is the most common subtype. Publication biases likely play a role in reporting the more severe phenotype.

Our work adds to the previous reviews on GSD IV genotypes, along with a recent review on APGD, especially for the updated genotype description according to the HGVS nomenclature.

Conclusion: The current literature regarding glycogen storage disease type IV is limited; however, multiple studies suggest a potential link between genetic variation within the GBE1 gene and disease severity as well as timing of symptoms. Our current study shows that the most severe and frequently reported subtype, Fetal/Neonatal Neuromuscular, is associated with multiple truncation variants. Although these findings are limited by the rarity of the disease, this work provides an in-depth review of genotype-phenotype correlation in glycogen storage disease type IV. Further studies are warranted to better understand the impact that genetic variations play in disease presentation and outcomes.

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