Conclusion: The results of this study confirmed that NAD+ measurements from DBS are comparable to a previously validated whole blood method. The chemically treated DBS cards provide acceptable stability to allow for at home sampling, reasonable shipping conditions, and potential for sample batching within the laboratory. Optimization of the chemical coating further stabilizes NAD+ within the DBS card and thereby improves the robustness and quality of the assay.

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ePO33

COASY-associated pontocerebellar hypoplasia – A possible additional secondary target detectable by expanded newborn screening?

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Background: Carnitine palmitoyl transferase I (CPT I; OMIM: 255120) deficiency is an autosomal recessive disorder that impairs long-chain fatty acid transport into the mitochondria, subsequently leading to isolated elevations in free carnitine and a reduction in long chain fatty acids. CPT I deficient patients typically present with heart failure, hypotonia, hepatic abnormalities, and hypoketotic hypoglycemia during fasting periods. Although clinically similar to other long chain fatty acid oxidation disorders, CPT I deficiency was initially thought to have a unique metabolic derangement. The latter has recently been challenged by individuals presenting with apparently identical biochemical abnormalities, yet without pathogenic variants in the expected gene. Contrarily, these patients harbor variants in the *COASY* gene which encodes for a dual functioning enzyme responsible for the final steps (4-phosphopantethine adenyl transferase and dephospho-CoA kinase) of coenzyme A synthesis. Biallelic pathogenic variants in *COASY* may result in severe hypotonia, episodes of dystonia, pontocerebellar hypoplasia, and/or neurodegeneration via iron accumulation in the brain, among other. Considering the heterogenous clinical presentation of previously reported cases, as well as the indistinguishable biochemical presentation of CPT I and *COASY*-related disorders, these diseases clearly provide a diagnostic challenge.
Case presentation: Two female siblings presenting with hyperglycemia, severe hypotonia, and respiratory insufficiency were admitted to the University of Rochester Medical Center neonatal intensive care unit, on two separate occasions. Upon examination, evidence of poor Moro and deep tendon reflexes, along with a resting 'frog-legged' appearance, were observed. Initial brain magnetic resonance imaging (MRI) of the siblings revealed symmetric areas of diffusion restriction in the bilateral hippocampi, globus pallida, thalami, and posterior limbs of the internal capsule suggestive of hypoxic injury or metabolic disease. Subsequent MRI in the older sibling revealed progressive atrophy of the cortical and brainstem structures consistent with pontocerebellar hypoplasia. Although the newborn screening and confirmatory plasma acylcarnitines/carnitine results of these patients were suggestive of CPT I deficiency, molecular testing excluded this inborn error of metabolism. Nonetheless, exome sequencing revealed homozygous variants of uncertain significance in the *COASY* genes of both siblings, suggesting a possible COASY-related disease, even though clinical abnormalities did not correlate with previously reported cases. When comparing the biochemical data of these patients to previously confirmed CPT I patients using Collaborative Laboratory Integrated Reports web application (CLIR; https://clir.mayo.edu), the ratios of markers not currently considered by standard newborn screening appeared to vary notably between these diseases.
Conclusion: *COASY*-related disorders may be indistinguishable from CPT I by newborn screening and conventional post-analytical interpretation. However, utilizing CLIR, we identified metabolite marker ratios that may differentiate between these diseases.

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ePO34

Novel use of global untargeted metabolomics in a patient with glycogen storage disease Ib receiving off label empagliflozin treatment

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Background: Glycogen storage disease type Ib (GSD-Ib) is a rare inborn error of glycogen metabolism. Affected individuals present with fasting intolerance, severe hypoglycemia, hepatomegaly, and lactic acidosis. The disorder is uniquely associated with neutropenia and neutrophil dysfunction causing serious infections, inflammatory bowel disease (IBD), mucosal lesions, and impaired wound healing. Recently, kidney sodium-glucose co-transporter-2 (SGLT2) inhibitors such as empagliflozin, known to reduce plasma levels of 1,5-anhydroglucitol (1,5-AG) and its toxic derivatives in neutrophils, have been described as a new treatment option in case reports of patients with GSD-Ib from Europe and Asia.
Case presentation: We hereby report our experience with an 11-year-old girl with GSD-Ib presenting with short fasting hypoglycemia, neutropenia with neutrophil dysfunction, recurrent infections, suboptimal growth, iron-deficiency anemia, recurrent abdominal pain, and loose stools. Treatment with daily empagliflozin resulted in improvement in neutrophil counts and function, leading to resolution of recurrent infections and mouth sores with significant reduction in G-CSF needs. Significant improvement in IBD symptoms with normalization of inflammatory markers and bowel imaging has led to weight gain