and he reported decreased appetite. In anticipation of possibly starting him on substrate reduction therapy with eliglustat, we obtained CYP2D6 genotyping and baseline GD biomarkers. He had reduced leukocyte GCase activity (within the "inconclusive range") in leukocytes, elevated plasma lyso-GL1 levels, and normal chitotriosidase activity, consistent with reports of other cases of AMRF.
Given the similar biochemical pathway underlying AMRF and GD, we explored utilizing established GD therapy for treatment of AMRF. Substrate reduction therapy (SRT), aims to reduce the rate of glycosphingolipid biosynthesis and theoretically does not require functional LIMP-2 to be effective. There has been one case report in which a patient was treated with miglustat, an SRT for Gaucher disease, which resulted in significant reduction in myoclonic jerks, regaining of the ability to sit and eat orally, and improvement in speech. Venglustat, an SRT with blood-brain-barrier penetration, may be able to more effectively treat or stabilize the patient's progressive neurological decline, however this medication is still in clinical trials.
Conclusion: AMRF is a very rare disorder with only about 40 individuals with the condition described in medical literature. The prognosis is poor, and, at this time, there is no treatment beyond symptom management. Our patient presented in his mid-20's with classic AMRF symptoms, including seizures, resting tremor, dysarthria, action myoclonus worsened by stress or fatigue, muscle weakness, and chronic kidney disease. His symptoms are progressing, and despite management with antiepileptics, he is becoming more limited in his activities of daily living. Clinical trials are needed to further explore if SRT is beneficial in ameliorating the neurological and/or renal manifestations of AMRF.

https://doi.org/10.1016/j.gim.2022.01.060

eP024

Metabolomic mapping of rhizomelic chondrodysplasia punctata

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Introduction: Rhizomelic Chondrodysplasia Punctata (RCDP) is an autosomal recessive peroxisome biogenesis disorder, most commonly due to pathogenic variants in the *PEX7* gene causing defects in phytanoyl CoA hydroxylase (*PHYH*), resulting in accumulation of phytanic acid over time. RCDP is characterized by skeletal abnormalities, distinctive facial dysmorphisms, intellectual disability, and respiratory complications. RCDP has both a mild, or non-classic form, and a severe, or classic, form. Individuals with classic RCDP have rhizomelia with proximal shortening of the humerus more pronounced than that of the femur, punctate calcifications in the cartilage with epiphyseal and metaphyseal abnormalities, known as chondrodysplasia punctata, coronal clefts of the vertebral bodies, congenital cataracts, congenital heart disease, profound growth deficiency, severe intellectual disability, and seizures. Unfortunately, this is a severe phenotype where many patients die within the neonatal period and the majority do not survive past the first decade of life because of pulmonary hypoplasia or primary cardiac anomalies. In the non-classic form of RCDP, patients also have congenital or childhood cataracts, rhizomelia, and chondrodysplasia punctata, but the rhizomelia is variable and the chondrodysplasia is typically only described as mild epiphyseal changes. Additionally, they have more mild intellectual disability and growth deficiency compared to their classic form counterparts. Clinically, the major difference is that those with the mild form of RCDP are able to walk, with or without support and able to communicate, verbally or non-verbally whereas those with the classic form cannot. Biochemically, there is a deficiency of plasmalogens in red blood cells that differs based on classic versus non-classic forms and elevated concentration of phytanic acid in plasma. Specifically, plasmalogen deficiency causes the RCDP phenotype and the residual level determines the severity of the phenotype.
Methods: To characterize the metabolome of patients with RCDP as well as potentially identify novel biochemical markers, we will utilize both plasma and urine samples from 21 patients with molecularly confirmed *PEX7* or *GNPAT* pathogenic variants and murine models that have undergone metabolomic analysis via standardized published methods. Global metabolic profiling is accomplished using untargeted mass spectrometry technology based metabolomic platforms to identify about 900 unique compounds and about 500 known human analytes in plasma and over 1,200 biochemicals in urine. Untargeted metabolomics can not only screen for numerous inborn errors of metabolism that previously would have required multiple different biochemical tests, but it can also identify novel biomarkers for metabolic diseases. Because of the unique challenge of analyzing individual samples, the data for each sample is analyzed as z scores. A z-score threshold was set where a particular analyte was consistently altered across all samples to aid in identification of biomarkers of interest. Additionally, integrated pathway analyses that are clinically validated and in use for biomarker validation was utilized to further characterize the metabolic pathways of interest.
Results: Analyzing the RCDP patient samples' untargeted metabolomic profiles, we found that there were 58 compounds with z scores of >2 or <-2, with 42 compounds with an average z score of -2 or less and 16 compounds with an average z score of 2 or greater. The three most relevant subcellular pathways included plasmalogen, lysoplasmalogen, and medium chain fatty acid pathways. The two most common Kegg Pathways included metabolic pathways and glycerophospholipid metabolism, and the two most common HMDB pathways included lipid metabolism and glycerophospholipid metabolism. The most relevant super pathway was the lipid pathway. As expected, plasmalogens where the most significantly altered metabolite in the RCDP patients' plasma samples. There were no plasmalogens identified in the urine. Of note, there were five patients of interest who appeared to have a unique biochemical profile as compared to the rest of the RCDP group. These patients were a mix of both classic and non-classic RCDP, yet had more mild z score compound concentrations.
Conclusion: While the five patients with more mild z score compound concentrations as compared to the rest of the group did not seem to fit into a single phenotype in regards to classic versus mild RCDP, untargeted metabolomics is a powerful tool and can distinguish different groups of RCDP patients. Further research is needed to correlate these groups with clinical severity, as it is possible that the unique metabolic aberrations can be correlated with specific phenotypic features such as growth velocity, cardiac anomalies, brain abnormalities, etc.

https://doi.org/10.1016/j.gim.2022.01.062