Case presentation: Patient 1
The proband is an 11-year-old girl, second child of healthy non-consanguineous parents of Mexican-Mestizo origin (Northern Mexico). She has a family history of a younger brother similarly affected. She was born at 39 weeks of gestation following a normal pregnancy; birth weight was 3,710 g (>90th centile), and height of 57 cm (>90th centile). She began crawling at 12 months, walking at 24 months and said her first word at 5 years. Bilateral moderate hearing loss was diagnosed at 9 years old following a history of recurrent otitis in infancy. The physical examination showed height of 138 cm (5th centile), weight of 3,680 g (25th centile), and head circumference of 50.5 cm (<3th centile), language delay, coarse flat facies, broad forehead with prominent metopic suture, thick eyebrows, oblique upward palpebral fissures, telecanthus, and blue nevus on sclerae, anteverted nostrils, dental anomalies, hypertrichosis, lubar blue spots, prominent abdomen, hepatomegaly and skeletal anomalies.
Patient 2
This is a 6-year-old boy, brother of patient 1, who was born at 35 weeks of gestation following an uncomplicated pregnancy. At birth he presented respiratory distress, the weight was 2,800 g (50th centile) and length was 52 cm (>90th centile). He began walking at 25 months and at present days he is not able to talk. He has history of bilateral inguinal hernia, recurrent otitis, hypoacusia and tonsillectomy. The physical examination showed somatometry in normal percentiles, language delay, coarse facies, dolichocephaly, broad forehead with frontal protuberances, blue nevus on sclerae, flat nasal tip, telecanthus, mid-facial retrution, hypertrichosis, blue dorso-lumbar spots, prominent abdomen, hepatomegaly and skeletal anomalies.
According to the clinical features, AM type 2 was suspected; therefore, an enzymatic determination of leukocyte alpha-mannosidase (E.C. 3.2.1.24) was performed in the patient and his sister. The residual enzyme activity was found to be decreased (6%: 3.57 nMol/mg prot/h; ref: 56.53 - 200.42 nMol/mg prot/h). *MAN2B1* gene was analyzed using the massive sequencing technique based on amplicon sequencing. The amplicons cover both the coding region and the highly conserved exon-intron junctions. The minimum coverage for each amplicon is >20x. The reference sequence is: MAN2B1: NM_000528.3.
A homozygous duplication of a cytosine at position 89 (c.89dup, p.Pro31Thrfs*43) was identified in both patients, which causes a change in the reading frame from codon 31 and a termination codon 42 positions forward.
Conclusion: The worldwide prevalence of AM is estimated in 1/500,000–1/1,000,000 live births. Most of the patients have been reported in Germany, United States, United Kingdom, Turkey and Poland. This disease is widely underdiagnosed, particularly in Latin American countries. The prevalence of AM in Mexico is unknown. The present familial case is the first reported in our country.
Alpha-mannosidose deficiency was confirmed in this case by gold standard study and by molecular study. The *MAN2B1*: c.89dupC variant does not have a clinical designation in public databases, however, based on established guidelines it can be classified as a probably pathogenic as it is a loss-of-function variant that has not been reported in any population.
The differential diagnosis includes other lysosomal storage diseases such as mucopolysaccharidoses (MPS) and Gaucher's disease; it is therefore advisable to include a α-mannosidase testing for all patients suspicious to MPS but with a negative MPS test result.
AM although rare, should be considered in the approach to a child with hearing loss, dysmorphism, ID, skeletal deformities, and visceromegaly.
The early detection of the disease, allows, besides accurate genetic counselling, better therapeutic management, since it is currently treatable with enzyme replacement therapy (velmanase alfa). Access to early treatment brings great benefits to patients relieving some severe manifestations, improving the quality of life.

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eP022

Action myoclonus-renal failure syndrome: An atypical storage disorder with a treatment dilemma

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Background: Action myoclonus-renal failure syndrome (AMRF) is a rare, autosomal recessive form of progressive myoclonic epilepsy associated with renal dysfunction, ranging from proteinuria to nephrotic syndrome and end stage renal disease, peripheral demyelinating polyneuropathy, and sensorineural hearing loss. *SCARB2*, the causative gene, encodes lysosomal-membrane type 2 protein (LIMP-2), a transmembrane protein responsible for trafficking of beta-glucocerebrosidase (GCase) to the lysosomes. LIMP-2 is particularly essential to GCase trafficking in neuronal cells, and in brains of LIMP-2 deficient mice, the significant reduction in GCase activity led to lipid storage, disturbed lysosomal function, and alpha-synuclein accumulation leading to neurotoxicity. although its necessity is somewhat tissue-dependent. Thus, *SCARB2* pathogenic variants result in a shortage of GCase in lysosomes, similar to the pathology underlying Gaucher disease (GD), and yet affected patients have a vastly different phenotype to GD.
AMRF typically starts presenting in the late teens to early twenties, and is rapidly progressive, with most patients surviving only 7 to 15 years after symptoms first develop and succumbing to complications of aspiration pneumonia and renal failure. Typically, patients with AMRF are managed symptomatically with antiepileptics for myoclonus and seizure prevention, physical therapy, and dialysis or kidney transplantation for renal insufficiency, however these do not improve neurologic disease.
We report a case of AMRF in a young adult male and discuss the theoretical basis for treatment with substrate reduction therapy classically used in GD.
Case presentation: Our patient, a male of Gambian descent, initially presented at 24 years old with imbalance, falls, and jerking movements in his arms, legs, and jaw. Over time, the intensity and frequency of these symptoms increased. He was admitted to an outside hospital for a seizure-like episode which started during sleep, and video EEG was suggestive of myoclonic epilepsy. Head CT and MRI were normal. EMG showed evidence of conduction blocks, with some motor and sensory axon loss, and he was diagnosed with demyelinating polyneuropathy. An epilepsy gene panel was obtained by his neurologist, which revealed *SCARB2* homozygous pathogenic variants (NM_005506.4(SCARB2):c.956del (p.Leu319fs). The patient denied any family history of AMRF or other hereditary disorders. He was started on valproic acid and levetiracetam and had no further seizures.
The patient was referred to our clinic for evaluation and discussion of possible treatment for a lysosomal storage disorder. On our exam, he had tongue fasciculations, jerking movements of the face and jaw while speaking, and dysarthria. He had a resting tremor of the upper extremities and feet, and he had cerebellar signs with dysmetria and poor coordination with rapid alternating movements. His gait was stable, but he was unable to do heel-to-toe walk without losing balance. He reported difficulty chewing and progressive proximal muscle weakness. He was hypertensive and endorsed foamy-appearing urine.
He was found to have an elevated serum creatinine, microscopic hematuria, and moderate albuminuria, and we referred him to nephrology for further evaluation. A subsequent kidney biopsy showed diffuse podocytopathy without deposits in the glomeruli. A renal ultrasound showed mildly echogenic kidneys, consistent with nonspecific parenchymal disease. An audiology exam was normal. On follow-up several months later, the patient's dysarthria had worsened,

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.

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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.

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