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Novel phenotype of aortic root dilatation and late onset of metabolic decompensation in patient with TMEM70 deficiency

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Background: TMEM70 deficiency causing mitochondrial complex V deficiency, nuclear type 2 [MIM: 614052] is the most common nuclear encoded defect affecting ATP synthase and has been well described in the literature as being characterized by neonatal/ infantile onset of poor feeding, hypotonia, lethargy, respiratory compromise, heart failure, lactic acidosis, hyperammonemia, and 3-methylglutaconic aciduria progressing to a phenotype of developmental delay, failure to thrive, short stature, non-progressive cardiomyopathy, microcephaly, facial dysmorphisms, hypospadias, persistent pulmonary hypertension of the newborn, and Wolff Parkinson White syndrome as well as metabolic crises followed by developmental regression. Our school-aged patient with TMEM70 deficiency has the unique presentation of aortic root dilatation and no history of metabolic decompensation, as well as unique biochemical markers ascertained on untargeted metabolomics, including elevated Z scores for 3-methylglutaconate, 3-methylglutarylcarnitine, alanine, and lactate in addition to the commonly described increased 3-methylglutaconic acid on urine organic acids.

Case presentation: Our patient is a 7 year old male first evaluated in our Metabolic Clinic at the age of eleven months due to medical history significant for hypertrophic cardiomyopathy and intrauterine growth restriction, originally noted on the anatomy ultrasound at about 20 weeks gestation. He was born at 38 weeks gestation to a 33 year old G3P3 with no complications during pregnancy or delivery. His birth weight was 2.3 kg (2nd percentile) and his birth length was 48 cm (29th percentile). At birth, his hypertrophic cardiomyopathy diagnosis was confirmed by echocardiogram, and he was also noted to have severe asymmetric septal hypertrophy with a Z score of 16 and mid-cavity left ventricular obstruction as an infant. At 6 months of age, he was started on a beta blocker for sudden death risk reduction due to the obstructive hypertrophic cardiomyopathy. There is no family history of other birth defects, cardiac problems, intellectual disability, unexpected deaths, or consanguinity. Both maternal and paternal ethnicity is Honduran. The proband was diagnosed as failure to thrive and is currently <1st percentile for both weight and height at the age of 7. He has appropriately met his developmental milestones and is in regular education without special education support or therapies. The patient's dysmorphic features include mild frontal bossing, arched eyebrows, upslanting palpebral fissures, mild hypertelorism, deep set eyes, and midface hypoplasia. Mild hypotonia as well as grade III/VI systolic ejection murmur best heard at the upper sternal border has been also noted on physical examination. Genetic testing included Blueprint Panel through Baylor Genetics that revealed homozygous c.563T>C, p.L188P variants in *TMEM70* associated with mitochondrial complex V deficiency, nuclear type 2 [MIM: 614052]. These variants were classified as variants of unknown clinical significance in disease genes related to the clinical phenotype and predicted to be pathogenic through SIFT and Polyphen-2. Additionally, both parents were found to be heterozygous for this variant. Biochemical testing showed 3-methylglutaconic acid significantly elevated to 122 (Reference range less than or equal to 10 mmol/mol creatinine) on urine organic acid analysis, consistent with the diagnosis of TMEM70 deficiency. Additionally, 3-methylglutaric acid was increased at 45 (Reference range less than or equal to 3 mmol/mol creatinine). Untargeted metabolomics analysis revealed elevated Z scores for 3-methylglutaconate at 7.8, 3-methylglutarylcarnitine at 4.9, alanine at 2.7, and lactate at 2.5. Our patient's echocardiograms have consistently shown severe mixed hypertrophic/ left ventricular non-compaction phenotype, moderately dilated aortic root, severely dilated sinotubular junction, and severely dilated ascending aorta.

Conclusion: Adding to the previously published phenotypic characterization of TMEM70 deficiency, our patient has the unique cardiac phenotype of left ventricular noncompaction, dilated aortic root, sinotubular junction, and ascending aorta, as well as late onset metabolic decompensation as opposed to the classically described non-progressive cardiomyopathy and infantile onset of heart failure, lactic acidosis, and hyperammonemia. Furthermore, untargeted metabolomics in this patient has identified unique biochemical markers including 3-methylglutaconate, 3-methylglutarylcarnitine, alanine, and lactate, adding to biochemical diagnostic testing modalities beyond the known 3-methylglutaconic acid elevation on urine organic acids.

https://doi.org/10.1016/j.gim.2022.01.063

ePO26

Newborn screening for Pompe disease: The Indiana experience

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Introduction: Pompe disease (OMIM# 232300) was added to the newborn screen in 2020. During our initial 18 months of screening, 2 newborns with infantile-onset Pompe disease (IOPD) and 6 newborns at risk for late-onset Pompe disease (LOPD) were identified. One of the newborns with IOPD was CRIM-positive, the other was CRIM-negative; both were started on treatment with alglucosidase alfa (Lumizyme) before 4 weeks of age. One newborn with variants consistent with LOPD presented with borderline left ventricular hypertrophy (LVH), prompting us to start treatment. Of the 5 other infants at risk for LOPD, 2 have persistent elevations of CK levels with normal muscle strength and echocardiograms; they are being closely monitored. Two have normal development and CK levels and 1 moved out of state. A literature review of surveillance recommendations for infants at risk of LOPD revealed a lack of consensus on optimal timing for treatment initiation in infants showing early signs of disease, such as elevated CK levels without overt weakness. We feel it is important to share our data in order to assist other states who are also new to newborn screening for Pompe disease.

Methods: The pilot program for newborn screening of lysosomal storage diseases began 6/1/2020 with an official start date of 7/1/2020. Pompe disease, Krabbe disease, and Hurler syndrome were added. To screen for Pompe disease, Indiana chose a three-tiered approach to testing. Initial screen consists of qualitative acid alpha-glucosidase (GAA) enzyme activity on dried blood spot. If abnormal, the dried blood spot card is sent to Mayo Clinic for quantitative GAA activity and (Cr/Crn)/GAA ratio. Second-tier test results are reported to the newborn screen lab, who notifies our coordinator if positive. These patients are scheduled in clinic for initial evaluation and counseling by a physician and genetic counselor. Following positive second-tier testing, reflex *GAA* sequencing through Mayo Clinic is ordered. Sequencing results are typically received at roughly two weeks of age. The purpose of this three-tiered approach is to definitively diagnose all patients with IOPD and clarify CRIM status in time to start treatment before 4 weeks of age.

Results: Since screening began, 2 infants with infantile-onset Pompe disease (IOPD) and 6 infants with late-onset Pompe disease (LOPD), as determined by their variants on *GAA* sequencing, have been identified. One infant identified with IOPD was CRIM-positive started on Lumizyme 40 mg/kg weekly at 3.5 weeks of age. His echocardiograms, urine Hex4, and CK levels have remained within the normal range, and he is meeting gross motor milestones ahead of