ePO04

Screening for metabolic abnormalities in a cohort of patients with hypermobility

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Introduction: We created a special focus clinic for patients presenting with the constellation of findings centered on hypermobility. There has been much speculation over the role of metabolism and mitochondrial function in this patient population but few studies examining biochemical intermediates in this group. We decided to systematically test for metabolic disruption in this group to evaluate the mostly anecdotal evidence around biochemical disruption.
Methods: Children's National Medical Center created a multi-disciplinary hypermobility clinic to better serve these patients. The clinic includes several specialists such as geneticists, pain medicine physician, and physical therapist. Patients with Beighton score of 5 or greater with significant fatigue and/or pain are referred from genetics clinic or pain clinic to the Hypermobility Clinic. These patients have had the following labwork: lactic acid and pyruvate to evaluate for mitochondrial dysfunction, growth differentiation factor (GDF) 15 in plasma to look at mitochondrial function, mature tryptase and UniCAP total tryptase to evaluate for mast cell activation syndrome, creatine kinase to look at muscle breakdown, and total and free carnitine to evaluate fat metabolism and mitochondria.
Results: Forty-two patients participated in the clinic who met the inclusion criteria (see methods above). These patients were comprised of 38 females, 4 males (2 cis-gendered, 2 assigned female at birth). Of that cohort, 31 participants (28 females, 3 males: 1 cis-gendered and 2 assigned female at birth) completed all or some metabolic lab evaluation. The average lactate level was 1.06 mmol/L (reference range 1.0-2.5 mmol/L) with range from 0.6-3.7 mmol/L. Average pyruvate was 0.78 mg/dL (reference range 0.3-1.5 mg/dL) with range of 0.51-2.95 mg/dL. GDF15 averaged 435 pg/mL (reference range <750 pg/mL) with range 268-991 pg/mL. Mature tryptase was below the detectable range in all participants. UniCAP total tryptase average was 4.41 ng/mL (reference range 1.0-11.4 ng/mL and above 20 ng/mL indicative of mastocytosis), and range was 0-16 ng/mL. Creatinine kinase average was 89 units/L (reference range 28-142 units/L) with range of 37-313 units/L. Average total carnitine was 36 mcmol/L (reference range 34-78 mcmol/L) and range 19.8-91 mcmol/L. Free carnitine averaged 28 mcmol/L (reference 25-54 mcmol/L) with sample range of 14-75 mcmol/L. Thirty-four percent of patients had low total carnitine and 31% had low free carnitine.
Conclusion: We did not find consistent biochemical evidence of mitochondrial dysfunction, for example abnormal lactate, pyruvate, or GDF15, in the cohort of patients with joint hypermobility. The only laboratory values that were frequently out of reference range were free and total carnitine. Although carnitine deficiency is seen in metabolic patients, these values can commonly be low due to inadequate intake from diet. If it were due to mitochondrial dysfunction, one would expect derailments in some of the other biochemical markers. Many of the patients with low carnitine were or had been referred to a nutritionist for optimization of their diet. Some of the patients were offered a trial of carnitine supplementation to see if it improved their energy. Overall, in our cohort of patients with hypermobility in the multi-disciplinary clinic, there were no data diagnostic for metabolic disorder.

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Complex glycerol kinase deficiency and X-linked intellectual disability

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Background: Glycerol kinase deficiency (GKD) is caused by pathogenic variants of the *GK* gene on chromosome Xp21. Three forms of GKD are recognized, characterized as infantile, juvenile, and adult forms. While the juvenile and adult forms are recognized as isolated GKD, the infantile form manifests itself as part of the Xp21.3 contiguous gene deletion syndrome, also known as complex GKD. This syndrome is composed of genes associated with Duchenne muscular dystrophy (*DMD*), X-linked congenital adrenal hypoplasia (*NR0B1*), and intellectual disability (*IL1RAPL1*).
Case presentation: A 2-year-old male born to a primigravida mother, uncomplicated pregnancy and birth, birth weight of 7lbs 7oz, and uneventful postnatal period, presented to the genetics clinic with a history of global developmental delay. There was also a family history of developmental delay and intellectual disability in the patient's mother and sister. Significant findings on examination included a startling appearance, absent eyebrows and temporal thinning, high forehead, frontal bossing, and axial hypotonia. Laboratory findings included elevated creatine kinase (CK) of 14809 units/L (reference range 27-160 units/L), aspartate aminotransferase (AST) of 307 (reference range 20-60 units/L) and alanine aminotransferase (ALT) 265 units/L (reference range 15-45 units/L) , and elevated triglycerides at 683 mg/dL (reference range 44-157 mg/dL). Organic acid analysis by gas chromatography-mass spectrometry (GC-MS) and chromosomal microarray was performed for further evaluation. Organic acid analysis showed abnormal accumulation of glycerol. Chromosomal microarray detected a 4.2 Mb deletion of Xp21.3p21.1(29296579_33551038), including complete copies of *GK, DMD*, and *NR0B1* genes as well as multiple exons of *IL1RAPL1*. This confirmed his glycerol kinase deficiency (GKD) as part of the Xp21.3 contiguous gene deletion syndrome.
Conclusion: Our patient's presenting and ongoing symptoms were related to his chromosomal abnormality, however, may have been identified earlier through a urine organic acid screen. Testing of affected family members was also recommended. In addition, he will require continuous follow-up with a multidisciplinary team including genetics, metabolic dietician, developmental pediatrics, speech, and physical therapies, endocrinology, and neuromuscular specialties. This case demonstrates the importance of educating providers who care for those with developmental delays, that metabolic screening is still an integral part of the initial workup. In addition, these screens may help prevent delays in diagnosing and managing treatable genetic conditions.

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