Genetics Corner: HACD1-Associated Congenital Myopathy in an Infant of Chaldean Ethnicity.

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Case Summary:

A genetics consultation was requested for a 41 week 5 day gestation female with congenital hypotonia and poor feeding. She had been admitted to the NICU on the second day of life from a community hospital. She was born after a routine pregnancy by induced vaginal delivery, with vacuum assist, for post-dates and through clear amniotic fluid to a healthy 35-year old G3P3 mother. A nuchal cord was present. All growth parameters were appropriate for her gestational age: birth weight 3320 g, birth length 53.3 cm and head circumference 33.5 cm. CPAP was administered for six minutes for weak cry, low tone and grunting. She did well in room air. Apgar scores were 6 and 8 at 1 and 5 minutes respectively. She had significant head lag, generalized hypotonia and excessive oral secretions. She had little interest in feeding and took only 4 ml. An upper GI study was normal. She achieved full enteral feedings by gavage on day 2 of life. There were no signs of sepsis.

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A limited needle EMG showed no electrophysiologic evidence of anterior horn cell disease, neuropathy, myopathy, neuromuscular junction transmission defect or demyelination. A brain MRI showed a small collection of extra-axial fluid along the left cerebral hemisphere, measuring up to 7 mm, most consistent with a subdural hygroma with a nonspecific prominence of the left occipital horn.

Speech and occupational therapists noted significant pharyngeal dysphagia. She had frank aspiration of all consistencies (thin, nectar, honey) on a swallow study on day 6 of life and no improvement on video swallow study at 3 weeks of age. She was not considered safe to feed orally due to high risk of aspiration. A gastrostomy tube was placed on day 23 of life.

The parents denied consanguinity. They are both of Chaldean descent. Chaldeans are a Catholic religious minority, ethnically Assyrian rather than Arab, who trace their roots to Babylon in Northern Iraq. The father is 39 years old. The parents have two other healthy children: a 3-year old girl and an 18-month old male. The family history was negative for congenital anomalies, early or unexplained deaths or chronic diseases.

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On physical exam she was awake and alert but flaccid in a "frog leg" position with an NG tube in place. She was nondysmorphic and moved all extremities spontaneously. A head ultrasound was normal.

The initial genetics evaluation focused on Prader-Willi syndrome which was essentially ruled out with normal chromosome microarray and a DMA methylation test for chromosome 15. She was discharged home at 4 weeks of age. She returned as an outpatient for an evaluation in genetics clinic. A clinical exome performed on an outpatient basis revealed homozygous likely pathogenic variants in HACD1: 373_375+2del, diagnostic for a congenital myopathy.

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Assessment:

This child has HACD1-associated congenital myopathy (OMIM 619967), an autosomal recessive nonprogressive disorder. It causes hypotonia at birth, early feeding problems and delayed motor skills. Walking, sometimes with a waddling gait, is usually achieved by 2 ½ years. A Gower's sign can persist into adulthood but there is usually gradual improvement in muscle weakness with age. Muscle biopsy can show fiber size disproportion. There is no respiratory involvement and cognitive development is normal.

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There are a few reports of this variant in other affected individuals from Iraq, making it likely that this is a founder mutation (1). Abbasi-Moheb, et al. reported 3 patients with the same or similar pathogenic variant, all of whom had generalized muscle weakness and motor delay. The main clinical features were generalized muscle weakness, poor head control, feeding problems with poor suck, failure to thrive and Gower sign for one at 4 years, no longer present at age 7.

This small intronic deletion alters the highly conserved splice donor site for exon 2 of the HACD1 transcript. It is predicted to abolish canonical splice donor activity causing skipping of exon 2 and a shift in the reading frame. A stop codon is introduced at the very beginning of exon 3.

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HACD1 encodes an endoplasmic reticulum associated protein, 3-hydroxyacyl-CoA dehydratase, that catalyzes the third step in elongation of long chain fatty acids to very-long-chain fatty acids (VLCFA). Very long chain fatty acids are incorporated into membrane lipids such as phospholipids and sphingolipids. Depending on their chain length and degree of (un)saturation, their functions differ. VLCFA have a role in promoting strong membrane curvature and vesicle fusion. Myoblast fusion, a necessary step for optimal myofiber growth, is the result of a complex relationship between lipids and proteins, which has not been fully elucidated. However, HACD1 has been shown to be a key regulator of a lipid-dependent muscle fiber growth mechanism (2).

Low levels of VLCFA are expected in this condition. Laboratory studies, including VLCFA, free and total carnitine and acylcarnitine profile, are pending. An echocardiogram and ECG are recommended because cardiac sequelae have been reported rarely (3). Management may include supplementation with Coenzyme Q10 and low-dose carnitine. Adding peanut oil and peanut butter to the diet is recommended as a dietary source of cerotic acid, a 26 carbon long chain saturated fatty acid (26:0), also found in beeswax, from which it derives its name. Parental testing for the variant in HACD1 is in progress.

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One intriguing consideration for future therapy is an antisense oligonucleotide (ASO) designed to silence this intronic splicing variant and enable normal splicing of exon 2. ASO technology is the basis for nusinursen (Spinraza), the FDA approved therapy for spinal muscular atrophy (4) that acts by correcting an SMN2 exon 7 splicing error.

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Practical applications:

1. Pay attention to the family history. Members of small reproductive isolates have an increased risk for homozygous autosomal recessive disorders. Recognize the importance of this aspect of the family history, even in the absence of consanguinity.
2. Measure VLCFA as part of the evaluation of the hypotonic infant. Both high and low levels are significant.
3. Recognize that unexplained poor feeding and hypotonia are indications for exome testing.

References:

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Disclosures: The author has no disclosures

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