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Letter to the Editor: New Observation

Myotonic Discharges in Infantile Sandhoff Disease

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Sandhoff disease, also known as type 2 GM2 gangliosidosis, is an autosomal recessive lysosomal storage disorder associated with severe neurological disease and premature death.[1,2] The underlying cause is biallelic pathogenic variants in *HEXB* (OMIM 606873), the gene encoding the β-subunit of hexosaminidase. Infantile Sandhoff disease, the classic and most severe form, presents between 2 and 9 months of age and usually results in death before age 3 years.[1] Clinical manifestations include developmental delay or regression, visual and hearing impairments, increased myotatic reflexes, axial hypotonia with limb spasticity, cherry-red spots on fundoscopy, and seizures.[1] While there have been descriptions of nerve conduction and electromyography (EMG) abnormalities in juvenile- and adult-onset Sandhoff disease, the peripheral neurophysiological abnormalities in infantile-onset Sandhoff disease have not been described in detail.

A female infant was referred for hypotonia. She was born late preterm (35 weeks, 5 days) via emergency cesarean section to non-consanguineous Filipino parents. There was no known family history of developmental delay, autism, epilepsy, migraines, or other neurological disorders. The father had two children from a previous partner, one of whom was a 4-year-old with glucose-6-phosphate dehydrogenase deficiency.

For the first 4–5 months of life, the proband appeared developmentally normal, with age-appropriate head control, fixing and following, and symmetrical limb movements. She then had motor regression and eventual global developmental impairment. At age 6 months, she had more difficulty supporting the head, had a weak grip and lost axial tone and strength. Moreover, she could not roll over, sit, or reach for objects. At age 9 months, she began to roll over but could not support her head. Fine motor skills were also delayed; she could not reach for objects but held light objects in her hand and brought her thumb to her mouth. The patient also cooed and hummed. At age 14 months, the patient presented with multiple episodes of unprovoked focal status epilepticus. The seizures typically involved unilateral clonic jerking, stiffness, drooling and lateral gaze deviation. Multiple episodes occurred in this manner, separated by a few minutes of possible altered consciousness (not crying or babbling) for up to 1 hour.

On physical examination, the patient was awake and alert, with no exaggerated startle, but had limited interaction. Head circumference was approximately the 50th percentile (44.5 cm at age 9 months). Neurological examination showed intact rooting reflex, marked appendicular and axial hypotonia, and intermittent nystagmus. Fundoscopic examination by an ophthalmologist showed a cherry red spot with surrounding retinal ischemia. Power was reduced in both the upper and lower extremities. Deep tendon reflexes were 2+ bilaterally in the upper and lower extremities. Plantar responses were upgoing, and palmar grasp reflex was still present bilaterally at age 9 months.

Electroencephalography showed diffuse background slowing and multifocal spikes. Brain MRI at age 14 months showed T2 hyperintensities (with corresponding T1 hypointensity) in the frontal and temporal white matter as well as the caudate and putamen. Based on marked hypotonia, EMG was performed. Concentric needle exam of the left deltoid muscle showed increased insertional activity with myotonic discharges (clearly sustained, 2 s or longer), while the left tibialis anterior and vastus lateralis muscles were within normal limits; no clinical myotonia was apparent. The compound muscle (motor) action potentials (CMAP) of the left median, ulnar and posterior tibial nerves showed normal amplitudes, distal latencies and conduction velocities. The sensory nerve action potentials of the left median, ulnar and sural nerves showed normal amplitudes, latencies and conduction velocities. The F-waves for the left median and posterior tibial nerves were normal. The H-waves were also normal bilaterally.

Serum creatine kinase was normal at 61 U/L (reference range 31–449 U/L). A panel of metabolic tests including ammonia, lactate, plasma amino acids, acylcarnitine profile, long chain and very long chain fatty acids, urine oligosaccharides, urine organic acids, carbohydrate-deficient transferrin, serum pyruvate kinase, CSF amino acids and CSF pyruvic acid was also normal/reassuring. Methylation testing for Prader–Willi syndrome was normal. Chromosomal microarray identified two apparently incidental copy number variants: a 900 kb deletion at Xp22.31 (classified as pathogenic, associated with X-linked ichthyosis) and a 1.79 Mb duplication at 2q12.3–13 (classified as of uncertain significance).

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A 116-gene neuromuscular disorders gene panel (GeneDx) did not identify any pathogenic variants. A follow-up developmental disorders gene panel (Blueprint) including more than 4780 genes identified compound heterozygous *HEXB* missense pathogenic variants: c.1645G>A, p.(Gly549Arg) (paternally inherited) and c.1513C>T, p.(Arg505Trp) (maternally inherited) (NM_000521.4). Sadly, the patient had continued progressive degeneration in function and died at age 15 months.

Although this is the first description of electrical myotonia in infantile Sandhoff disease, Jain et al. previously reported a 14-month-old male patient with clinical signs of neuropathy and nerve conduction testing indicating a patchy sensorimotor neuropathy affecting both upper and lower limbs; EMG findings were not reported.[3] There are also published data from patients with later-onset *HEXB* phenotypes. Patients with adult Sandhoff disease most commonly have a lower motoneuron disorder pattern with progressive deterioration in CMAPs in all nerves, but a minority also have sensory axonal neuropathy[4] or motor neuronopathy.[5] There are fewer data for juvenile Sandhoff disease; some patients have been reported with axonal motor neuropathy,[6] while others have had normal EMG and nerve conduction testing.[7]

In summary, this patient with infantile Sandhoff disease had electrical myotonic discharges identified during EMG, a finding that has not previously been reported. Electromyographic myotonia in infancy is uncommon and has a relatively short differential diagnosis, including Pompe disease, myotonic dystrophy type 1, myotonia congenita, the SCN4A-related conditions (paramyotonia congenita, potassium-aggravated myotonia and hyperkalemic periodic paralysis), Schwartz–Jampel syndrome and certain congenital myopathies (e.g., centronuclear myopathy).[8] Sandhoff disease can now be added to this list.

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