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Case of late-onset Sandhoff disease due to a novel mutation in the *HEXB* gene

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Sandhoff disease is one of a group of autosomal recessive conditions known as the GM2 gangliosidoses. Normal breakdown of GM2 gangliosides is performed by the enzyme β-hexosaminidase A. This enzyme consists of 2 subunits (α and β), which are encoded by the *HEXA* and *HEXB* genes, respectively. Mutations in either of these genes result in buildup of the GM2 gangliosides, with *HEXA* mutations producing a phenotype of Tay-Sachs disease and *HEXB* mutations causing Sandhoff disease.

The classic form of Sandhoff disease presents in infancy with symptom onset between ages 2 and 9 months. Symptoms include progressive weakness, intellectual disability, vision and hearing impairment, exaggerated startle response, seizures, and death usually before age 3. Late-onset forms of Sandhoff disease have been described but are much rarer. Adult-onset cases can present with a wide spectrum of symptoms, including spinocerebellar ataxia, motor neuron disease, sensorimotor neuropathy, tremor, dystonia, and psychosis.[1] Specifically, in reviewing cases with the motor neuron disease phenotype, most reports describe predominant lower motor neuron features, with few cases showing both upper and lower motor neuron findings similar to amyotrophic lateral sclerosis.[2,3] More recent reports have identified an increasing number of novel sequence variants (often compound heterozygous point mutations) that are associated with the motor neuron disease phenotype,[4,5] although the mechanism by which these variants produce this specific phenotype is not well understood.

Case presentation

A 40-year-old woman was referred for evaluation of slowly progressive weakness of the lower extremities over the course of 3 years. She reported weakness affecting both legs, difficulty standing from a chair, poor balance, and twitching in her thigh muscles. Additional symptoms included anxiety, mood fluctuations, decreased concentration, generalized fatigue, and poor sleep. She denied numbness, pain, arm weakness, difficulty with breathing, speaking, or swallowing.

On physical examination, she had mild weakness in the hip flexors, knee flexors, and knee extensors, with full strength in all other muscle groups. There was mild atrophy of the knee extensors with rare fasciculations. Deep tendon reflexes were reduced at the knees, but intact elsewhere. Tandem gait was slightly impaired. The rest of the neurologic examination was within normal limits.

Brain MRI revealed mild cerebral and cerebellar atrophy with preferential involvement of the superior vermis. Lumbar spine MRI was significant for mild degenerative changes at the L3-L4 levels and bilateral neural foraminal stenosis at the L5-S1 levels. EMG and nerve conduction

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Figure G473S conservation across species

Hs	P	L	D	F	G	G	T	Q	K	Q	K	478
Mm	P	L	N	F	E	G	S	E	K	Q	K	457
Dr	P	Q	N	F	N	G	T	D	A	Q	K	464
Dm	L	K	S	I	A	G	D	Y	E	H	H	520
Ce	P	T	N	F	N	G	T	V	A	Q	K	466

Multiple protein alignment highlighting the evolutionary conservation of glycine 473 in the human hexosaminidase subunit beta (HEXB) amino acid sequence. Labels: Hs = *Homo sapiens*; Mm = *Mus musculus*; Dr = *Danio rerio*; Dm = *Drosophila melanogaster*; Ce = *Caenorhabditis elegans*. The numbers on the right side of each sequence correspond to the last amino acid depicted.

studies was normal except for neurogenic units in the knee extensors and hip flexors. The creatine kinase level was normal.

The pure motor nature of the findings and the EMG results suggested a chronic form of lower motor neuron disease, and the MRI findings did not adequately explain her symptoms. The picture was not typical of any of the common lower motor neuron diseases. Because there is no inclusive panel for genetic motor neuron diseases and the affected gene could not be pinpointed clinically, whole-exome sequencing (WES) was performed for further evaluation. WES revealed a compound heterozygous mutation in the *HEXB* gene on chromosome 5 (c.298delC pathogenic variant and G473S likely pathogenic variant). Subsequent hexosaminidase enzymatic testing revealed reduced total hexosaminidase activity in leukocytes (14% that of normal controls), consistent with a GM2 gangliosidosis. In addition, there was a high ratio of hexosaminidase A to B activity (79%), supporting a diagnosis of Sandhoff disease.

Discussion

This case describes 2 new sequence variants found in a patient with clinical symptoms of Sandhoff disease. The population frequency of these 2 sequence variants was investigated using the Genome Aggregation Database (gnomAD), which aggregates data on 123,136 exomes and 15,495 genomes from unrelated individuals.[6] The c.298delC variant in *HEXB* is predicted to result in loss of protein function and is absent from the gnomAD, indicating a very rare, likely pathogenic variant. The G473S variant in *HEXB* has been observed only once in the heterozygous state in the gnomAD. The amino acid position 473 is highly conserved across evolution, with an invariant glycine residue present from *Caenorhabditis elegans* and *Drosophila melanogaster* to various species of vertebrates (figure).[7] The presence of these 2 sequence variants in the compound heterozygous state, combined with the enzymatic assay showing decreased hexosaminidase activity, implies that these sequence variants are pathogenic and are responsible for the loss of enzymatic activity.

Late-onset Sandhoff disease is rare but should remain a diagnostic consideration in adults presenting with slowly progressive lower motor neuron disease, and discovery of new pathogenic sequence variants such as the ones discussed in this case will help further understanding of this disease and facilitate diagnosis in future patients.

Author contributions

A.R. Sung reviewed the literature, drafted the initial manuscript, and made multiple subsequent revisions. P. Moretti investigated the 2 sequence variants discussed in this manuscript in genetic databases and interpreted the data. A. Shaibani collected clinical data during clinical consultation with the patient and performed testing that led to the discovery of the discussed sequence variants; he also made multiple revisions to the manuscript.

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Disclosure

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