A Case of Subacute Weakness in a 40-year-old Woman

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INTRODUCTION

Sandhoff disease is one of a group of autosomal recessive conditions known as the GM2 gangliosidoses caused by mutations in the *HEXB* gene.

The classic form of Sandhoff disease presents in infancy with symptom onset between ages 2 to 9 months. Symptoms include progressive weakness, intellectual disability, vision and hearing impairment, exaggerated startle response, seizures, and death usually before age 3. Later 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.

We present a case of Sandhoff disease presenting with a motor neuron disease phenotype due to a novel compound heterozygous mutation in the *HEXB gene*.

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, resulting in difficulty standing from a chair and poor balance. She also noticed some 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.

Pertinent Exam Findings:

- Mental status intact
- Cranial nerves intact
- Mild weakness in the hip flexors, knee flexors, and knee extensors. Full strength in all other muscle groups
- Mild atrophy of the knee extensors with rare fasciculations
- No sensory deficits
- Deep tendon reflexes reduced at the knees, but intact elsewhere
- Gait normal except for mild difficulty with tandem gait

WORKUP

- MRI brain: mild cerebral and cerebellar atrophy with preferential involvement of the superior vermis
- MRI lumbar spine: mild degenerative changes at the L3-L4 levels and bilateral neural foraminal stenosis at the L5-S1 levels
- EMG/NCS: normal except for neurogenic units in the knee extensors and hip flexors
- CK: normal

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DIAGNOSIS

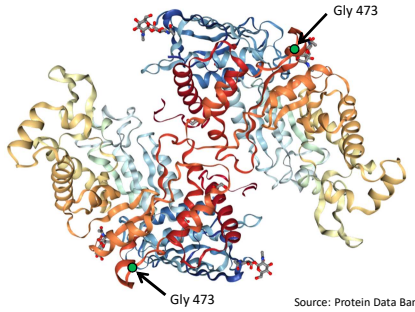
Our patient was diagnosed with adult onset Sandhoff disease based on genetic and enzymatic testing.

- Whole exome sequencing revealed a compound heterozygous mutation in the *HEXB* gene
  - c.298delC (pathogenic variant)
  - G473S (likely pathogenic variant)
- Hexosaminidase enzymatic test results
  - Reduced total hexosaminidase activity in leukocytes (14% that of normal controls – consistent with a GM2 gangliosidosis (Tay Sachs disease or Sandhoff disease)
  - High ratio of hexosaminidase A to B activity (79%) – specific for Sandhoff disease
- Testing of the patient's parents confirmed that the G473S variant and c.298delC variants were present on opposite *HEXB* alleles

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.

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

Figure 1. Multiple protein alignment highlighting the evolutionary conservation of glycine 473 in the human hexosaminidase subunit beta (HEXB) amino acid sequence. Hs: Homo sapiens; Mm: Mus musculus; Dr: Danio rerio; Dm: Drosophila melanogaster; Ce: Caenorhabditis elegans. Numbers on the right side of each sequence correspond to the last amino acid depicted.



Source: Protein Data Bank

Figure 2. 3D hexosaminidase protein structure showing position of glycine 473.

DISCUSSION

Motor neuron disease phenotype is a rarely reported phenotype of Sandhoff disease. Most reports describe predominant lower motor neuron features, with few cases showing both upper and lower motor neuron findings similar to amyotrophic lateral sclerosis. Recently, an increasing number of novel sequence variants (often compound heterozygous point mutations) have been identified that are associated with the motor neuron disease phenotype, although the mechanism by which these variants produce this specific phenotype is not well understood.

We present two new sequence variants found in a patient with adult onset Sandhoff disease with a motor neuron disease phenotype. The two sequence variants were investigated using the Genome Aggregation Database (gnomAD) database, which aggregates data on 123,136 exomes and 15,495 genomes from unrelated individuals.

- c.298delC
  - Causes a frameshift and premature stop codon
  - Predicted to result in loss of protein function through protein truncation or non-sense-mediated mRNA decay
  - Not reported in the gnomAD database, indicating a very rare, likely pathogenic variant
- G473S
  - Predicted to impact secondary protein structure and function
  - Observed only once in the heterozygous state in the gnomAD database

CONCLUSION

- Late onset Sandhoff disease is rare and has a variety of phenotypic presentations, including a motor neuron disease phenotype
- 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

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