

Adult-Onset Sandhoff Disease in a Filipino Patient: Asymmetric Weakness, Whole *HEXB* Gene Deletion, and Coexisting *MYH7* Pathogenic Variant

Grayson Beecher, MD, Teerin Liewluck, MD, and Margherita Milone, MD, PhD

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Correspondence

Dr. Milone
milone.margherita@mayo.edu

Abstract

Objective

To describe a Filipino patient with adult-onset Sandhoff disease manifesting with an atypical asymmetric lower motor neuron syndrome due to a novel whole *HEXB* deletion in *trans* with a pathogenic missense variant and with a coexisting *MYH7* pathogenic variant.

Methods

We performed clinical, laboratory, myopathologic, and genetic evaluation with next-generation sequencing in the proband and targeted mutational analysis in an asymptomatic sibling.

Results

A 59-year-old Filipino woman presented with 15 years of slowly progressive, asymmetric, proximal-predominant, lower greater than upper extremity weakness, mildly elevated creatine kinase, and generalized cerebellar atrophy. Serum total β -hexosaminidase was significantly reduced, and hexosaminidase A percentage was increased. We identified a novel *HEXB* whole gene deletion in compound heterozygosity with a pathogenic missense variant (c.1513C>T, p.Arg505Trp) previously described in 1 patient with adult-onset Sandhoff disease. The patient, with a family history of cardiomyopathy, has a coexisting *MYH7* pathogenic variant (c.3134G>A, p.Arg1045His), causative of cardiomyopathy but without cardiac involvement, likely due to variable penetrance. Myopathic features were absent from skeletal muscle biopsy.

Discussion

This patient expands the genotypic, phenotypic, and ethnic spectrum of Sandhoff disease and highlights challenges generated by low-penetrant pathogenic variants, especially when considering a potentially polygenic phenotype.

From the Division of Neuromuscular Medicine, Department of Neurology, Mayo Clinic, Rochester, MN.

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Sandhoff disease (SD) is a rare autosomal recessive GM2 gangliosidosis due to pathogenic variants in *HEXB*, encoding the β subunit of β -hexosaminidase.¹ Clinically, GM2 gangliosidoses are indistinguishable and classified based on onset age: infantile (most common, featuring hypotonia, exaggerated startle, spasticity, seizures, blindness, and death before age 4), late infantile/juvenile (onset between 2 and 10 years with psychomotor regression, ataxia, spasticity, and seizures), and adult (least common, presenting with symmetric lower motor neuron (LMN) syndrome, ataxia, tremor, dystonia, and/or psychiatric features). Slow skeletal muscle/ β -cardiac myosin heavy chain (*MYH7*)-related disorders are similarly varied, including autosomal dominant hypertrophic,² dilated,³ and arrhythmogenic cardiomyopathy⁴ and skeletal myopathies with or without cardiomyopathy.⁵ Herein, we describe a Filipino patient with a family history of cardiomyopathy presenting with progressive, asymmetric LMN syndrome due to adult-onset SD with compound heterozygous *HEXB* pathogenic variants, including a novel whole *HEXB* deletion, in addition to a coexisting *MYH7* pathogenic variant.

Case Presentation

The proband is a 59-year-old woman born to nonconsanguineous Filipino parents. At age 44 years, she developed slowly progressive, proximal lower limb weakness and within 10 years proximal upper limb weakness and muscle cramps. Her mother had congestive heart failure (onset in seventies), and a 55-year-old brother had hypertrophic cardiomyopathy (onset age 45 years) without reported muscle weakness. Four additional brothers and 2 sisters were asymptomatic.

Table 1 Neurologic Examination, Laboratory, Electrophysiologic, and Myopathologic Features

| | Descriptive findings |
|---|---|
| Neurologic clinical findings | |
| Mental status | Normal |
| Language | Normal |
| Cranial nerves | Normal |
| Muscle bulk | Atrophy of quadriceps, left > right |
| Tone | Normal |
| Fasciculations | None |
| Power (right/left)^{a,b} | Deltoids: 4/4; iliopsoas: 3/3 Infraspinatus: 4/4; quadriceps: 5/3 Triceps: 3/4; gluteus medius: 4/4 Pectoralis: 4/4; gluteus maximus: 4/4 Flexor digitorum profundus: 4+/4+ |
| Reflexes | Absent left patellar reflex, otherwise normal |
| Cerebellar | Normal |
| Sensory | Normal large and small fiber sensation |

Table 1 Neurologic Examination, Laboratory, Electrophysiologic, and Myopathologic Features (continued)

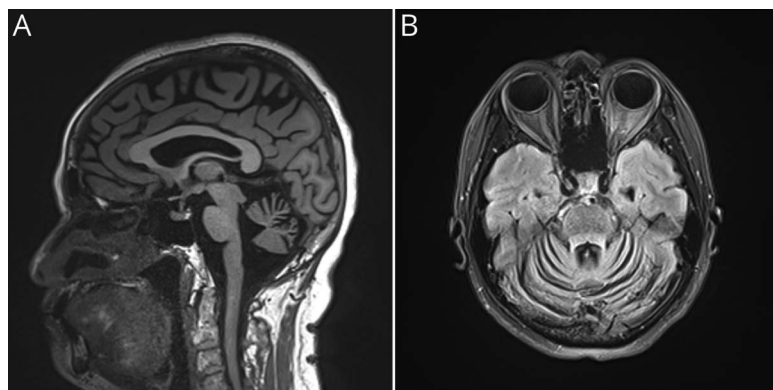
| | Descriptive findings |
|---|--|
| Gait | Waddling gait, preserved heel- and toe-walking |
| Laboratory evaluation | |
| Creatine kinase | 157–224 (normal <192 U/L) |
| Serum total β-hexosaminidase | 0.8 nmol/min/mL (normal: 10.4–23.8 nmol/min/mL) |
| Hexosaminidase A % | 100 (normal: 56%–80%) |
| Pulmonary function testing | Normal |
| Overnight oximetry | Consistent with sleep-disordered breathing |
| ECG, 48-h Holter monitor | Normal |
| Imaging evaluation | |
| MRI of the brain and spine with contrast | Cerebellar atrophy, generalized |
| Fluoroscopic swallowing study | Normal |
| Transthoracic echocardiogram with strain imaging | Normal |
| Electrodiagnostic evaluation | |
| Nerve conduction studies | Normal |
| Repetitive (2 Hz) nerve conduction studies | Normal (ulnar, spinal accessory, and facial nerves) |
| Needle electromyography | Chronic neurogenic changes in cervical, thoracic, and lumbar myotomes with infrequent fibrillation potentials in distal lower limb muscles |
| Muscle histopathology | |
| Right vastus lateralis biopsy (age 49) | Denervation atrophy and minimal nonspecific features (fiber size variability and mildly increased number of internalized nuclei) |
| Right triceps biopsy (age 59 y) | Denervation atrophy and reinnervation without myopathic features |

^a Medical Research Council grading (5 = normal strength).

^b Weak muscles listed only.

Neurologic examination revealed asymmetric, proximal-predominant weakness (Table 1). Laboratory, imaging, electrodiagnostic, and myopathologic findings were as listed (Table 1). Serum hexosaminidase profile suggested SD. Next-generation sequencing panels of genes causative of lysosomal storage disorders, common myopathies, and peripheral neuropathies, including motor axonopathies (eTable 1, links.lww.com/NXG/A521; performed at Invitae, San Francisco, CA, in April 2021), identified a novel deletion of the full coding sequence of *HEXB* and a missense variant (c.1513C>T, p.Arg505Trp). The deletion, as other loss-of-function variants

Figure 1 Cerebellar Atrophy in Adult-Onset Sandhoff Disease



Sagittal (A) and axial (B) T2 fluid-attenuated inversion recovery images demonstrate generalized cerebellar atrophy.

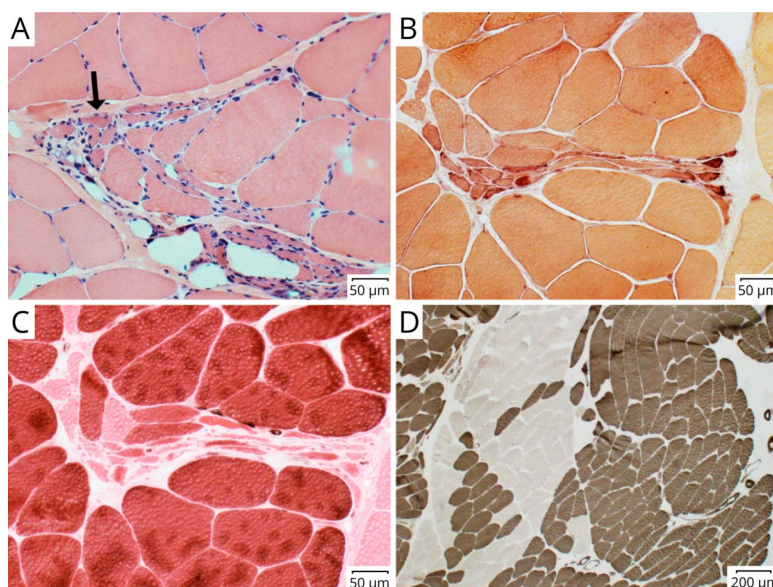
in *HEXB*, is expected to be pathogenic. The missense variant affects a highly conserved amino acid and was reported in compound heterozygosity in 1 patient with adult-onset SD.¹ In silico model predictions for this variant effect on protein structure and function were conflicting (SIFT 0.00, PolyPhen-2 probably damaging, and Align-GVGD Class C0). The patient also carried an *MYH7* pathogenic variant (c.3134G>A, p.Arg1045His), segregating in families with cardiomyopathy,²⁻⁴ but without abnormal cardiac findings. Targeted mutational analysis in an asymptomatic sister with normal neurologic examination demonstrated only the whole *HEXB* gene deletion, supporting the *trans* status of the patient's *HEXB* variants. This sister also carried the *MYH7* variant without clinical correlate and normal ECG and echocardiogram. The remaining relatives in the Philippines were unavailable for evaluation.

Discussion

Adult-onset SD appears to be rare in the Filipino population. The atypical asymmetric pattern of weakness from LMN disease and the whole *HEXB* gene deletion occurring in compound heterozygosity with an established pathogenic missense variant are novel clinical and genetic findings, respectively. Coexistence of an independent *MYH7* pathogenic variant is not reported in SD. Thus, our patient harbors pathogenic variants in 2 genes causative of rare disorders (double trouble), both potentially involving the neuromuscular system.

Hereditary adult-onset LMN disorders encompass various disorders, including SD, Tay-Sachs disease, 5q- and non-5q-SMA, Kennedy disease, and familial ALS. Adult-onset SD is

Figure 2 Muscle Biopsy Findings in Adult-Onset Sandhoff Disease



Hematoxylin and eosin-stained section (A) demonstrates a group of atrophic muscle fibers (arrow). The atrophic fibers overreact for nonspecific esterase (B) and in ATPase-reacted section at pH 4.3 (C) are of both histochemical type (type 1 fibers are dark), indicating denervation atrophy. ATPase-reacted section at pH 4.6 (D) demonstrates grouping of both type 1 (dark) and type 2A (light) muscle fibers, consistent with reinnervated skeletal muscle (magnification: $\times 20$, A-C; $\times 5$, D). There was no evidence of muscle lysosomal dysfunction by acid phosphatase or LAMP2 staining (not shown).

uncommon. Retrospective review of clinically and biochemically characterized adult-onset SD cases combined from a French cohort and the literature identified only 17 patients carrying 14 unique *HEXB* variants (frequently p.Arg505Glu in homozygosity).¹ Among LMN presentations, weakness is classically symmetric, beginning in quadriceps and psoas muscles and later involving the upper limbs, predominantly triceps. Our patient had clearly asymmetric LMN disease, although predominantly involved muscles typically affected in SD. Most patients with SD display generalized cerebellar atrophy, often with minimal to no cerebellar symptoms or signs associated, as in our patient (Figure 1).

Pathogenic variants in *MYH7* causative of cardiomyopathy cluster in the head and neck domain of the protein.⁵ Those causative of skeletal myopathy with or without cardiomyopathy localize to the distal rod domain, although exceptions occur.⁵ The patient's *MYH7* pathogenic variant (p.Arg1045His) in the distal neck domain could explain hypertrophic cardiomyopathy and congestive heart failure in the brother and mother, respectively. However, this variant had no cardiac correlate in the proband and her sister, suggesting low- or age-related penetrance, well described in *MYH7*-related cardiomyopathies.⁶ *MYH7* pathogenic variants can cause skeletal myopathy; however, this specific variant is not reported with skeletal myopathy, and no definite myopathic features were demonstrated on muscle biopsy (Figure 2). Nevertheless, we cannot exclude that the *MYH7* variant could contribute to the patient's weakness. Indeed, the *MYH7* myopathologic spectrum comprises varied findings (congenital fiber-type disproportion, hyaline bodies staining for slow heavy chain myosin, and cores/minicores) including nonspecific features.⁷

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Appendix Authors

| Name | Location | Contribution |
|-----------------------------------|---|--|
| Grayson Beecher, MD | Division of Neuromuscular Medicine, Department of Neurology, Mayo Clinic, Rochester, MN | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data; and additional contributions: contributed to the clinical diagnosis |
| Teerin Liewluck, MD | Division of Neuromuscular Medicine, Department of Neurology, Mayo Clinic, Rochester, MN | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data; and additional contributions: performed and evaluated electrodiagnostic studies |
| Margherita Milone, MD, PhD | Division of Neuromuscular Medicine, Department of Neurology, Mayo Clinic, Rochester, MN | Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data; and additional contributions: contributed to the clinical diagnosis, evaluated muscle pathology, and supervised manuscript preparation |

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