LETTER TO THE EDITOR

Expanding the phenotype of SORD mutation

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We read with great interest the recent article by Cortese et al. titled "Genotype and phenotype spectrum of Charcot-Marie-Tooth (CMT) disease due to mutations in the sorbitol dehydrogenase (SORD) gene" [1]. This work significantly enhances our understanding of CMT-SORD neuropathies—an autosomal recessive disorder resulting from SORD mutations that cause toxic sorbitol accumulation in peripheral nerves [2].

In this context, we report an atypical case that expands the clinical spectrum of SORD-associated neuropathy. The patient, previously healthy with no family history of neuropathy or consanguinity, first exhibited motor impairments during adolescence (e.g., difficulties with rope climbing and motor coordination). At the age of 30, he was referred for a progressive muscle atrophy, gait disturbances, and falls, accompanied by pes cavus and Achilles tendon contractures. Initial investigations included electromyography (EMG), which revealed both myogenic and neurogenic abnormalities, and a biological assessment showing creatine phosphokinase (CPK) levels at 1000 UI/L. A muscle biopsy of the gastrocnemius was performed, and the overall clinical picture was suggestive of spinal CMT. Genetic testing for *PMP22* gene duplication was negative.

Over time, the patient's condition evolved: while distal retractions remained relatively stable, a proximal motor decline emerged, leading to further evaluation at age 54. At that stage, clinical signs were indicative of pyramidal tract irritation (brisk reflexes, an extended reflexogenic zone, a positive Babinski sign, and significant Achilles contractures at -40°). A comprehensive workup—including tests for mitochondrial disorders, autoimmune markers (anti-GAD, anti-RACH, anti-MUSK), peroxisomal disorders, and mutations in *SMN1*, *HSPB1*, and *HSPB8* genes—returned normal results. Muscle MRI revealed a neurogenic pattern with approximately 50% fat infiltration, predominantly affecting the pelvis and thighs (Figure 1A), and EMG confirmed a mixed pattern (myogenic in proximal muscles, neurogenic in distal ones) (Figure 1B.1A). Brain MRI showed multiple enlarged perivascular spaces and atypical white matter hyperintensities, particularly in the temporal poles (Figure 1C). Although magnetic resonance spectroscopy did not reveal a lactate peak (1.3 ppm), a distinct peak between 3.7 and 3.8 ppm was detected, suggesting the accumulation of an abnormal metabolite (Figure 1D).

A muscle biopsy of the left deltoid indicated chronic denervation without respiratory chain defects. Elevated fasting sorbitol levels (295.7 µmol/L), combined with the identification of a homozygous c.757delG mutation in the *SORD* gene, confirmed the diagnosis of CMT-SORD.

The patient exemplifies several atypical features in SORD-associated neuropathy. The initial presence of both myogenic and neurogenic changes, along with an unusually high CPK, suggests that early muscle involvement may be more pronounced than previously recognized [7]. The later appearance of central signs (brisk reflexes and positive Babinski) and MRI abnormalities challenges the classic view of CMT as a purely peripheral disorder and raises the possibility of a broader neurodegenerative process, potentially overlapping with conditions like juvenile amyotrophic lateral sclerosis (JALS) as reported by Bernard et al. [4].

We propose that sorbitol level measurement should be integrated into the diagnostic workup for patients with motor symptoms (suspected CMT or dHMN)—even when central signs or brain MRI abnormalities are present—to improve diagnostic accuracy and potentially guide therapeutic strategies aimed at modulating sorbitol metabolism, such as aldose reductase inhibitors [3,5,6]. Future studies are needed to elucidate the underlying mechanisms linking sorbitol accumulation to neurodegeneration and to determine the full clinical impact of *SORD* mutations. Sorbitol accumulation seems having deleterious effects on both peripheral (neurogenic / myogenic patterns) and central nervous systems (white matter changes and enlarged perivascular spaces, pyramidal syndrome).

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author.

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Competing interests

The authors declare that they have no competing interests

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Figure legend

Figure 1 Multimodal evaluation of a patient with SORD-related CMT. [**A**(**i**–**iii**)]: Axial FLAIR. Muscle MRI demonstrating diffuse muscular atrophy with a neurogenic pattern. The imaging reveals widespread reduction in muscle bulk, indicative of chronic denervation and reinnervation changes that correlate with the clinical presentation of neuropathic weakness. [**B**(**i**)] Needle electromyography tracing of the right deltoid: myogenic abnormalities are found, characterized by low-amplitude, short-duration and polyphasic motor unit potentials with early recruitment. For the left anterior tibial muscle [**B**(**ii**)], neurogenic pattern is found, shows polyphasic motor unit potentials with increased amplitude and duration, along with reduced recruitment. (**C**) Axial FLAIR MRI demonstrating numerous enlarged perivascular spaces associated with an atypical leukoencephalopathy predominantly involving the temporal lobes. (**D**) Brain spectroscopy showing a peak between 3.7 and 3.8 ppm, with no lactate peak at 1.3 ppm.

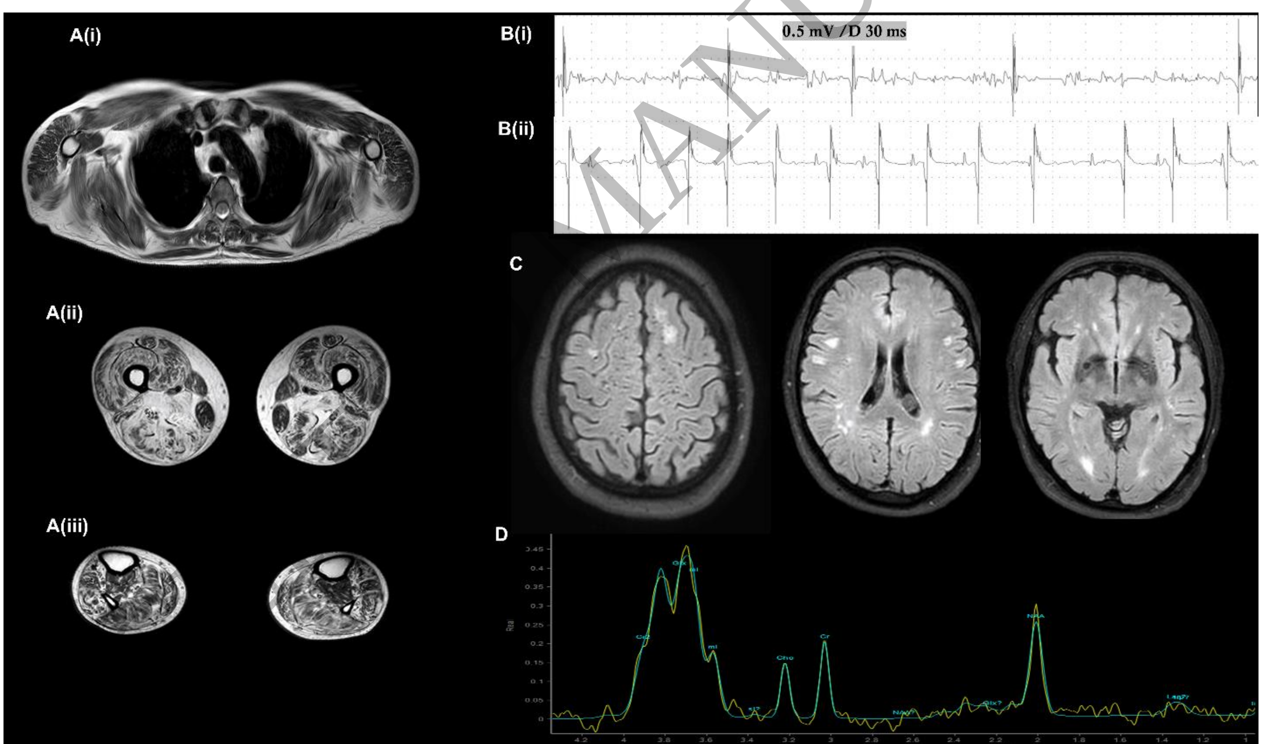

Figure 1
166x98 mm (DPI)