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A COA8 homozygous mutation presenting as a demyelinating CMT with leukopathy

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Patients with cytochrome c oxidase (COX) deficiency exhibit clinical heterogeneity, with the onset of symptoms ranging from infancy to adulthood. COA8-related disorders typically present in childhood with acute symptoms and cavitating posterior leukoencephalopathy, though milder, muscle-predominant forms have recently been reported.

We describe a 54-year-old woman with a pauci-symptomatic demyelinating sensorimotor neuropathy (25-30 m/s in the lower limbs, 30-40 m/s in the upper limbs). Neurological examination showed short stature, preserved motor function, hammer toes, mildly high-arched feet, mild dysmetria without lateralization, and distal hypoesthesia with intact proprioception and vibration sense. Further investigations revealed a history of migraines, hearing loss, early menopause, and symmetrical posterior-predominant leukoencephalopathy.

Targeted NGS for hereditary neuropathies was unremarkable. The neurometabolic workup was negative, and there was no evidence to support a diagnosis of MNGIE.

Whole genome sequencing identified a homozygous COA8 mutation (c.476+1G>A), confirmed by diffuse COX deficiency and significantly reduced complex IV activity on muscle biopsy.

Historically, the only mitochondrial gene associated with both demyelinating neuropathy and leukoencephalopathy was TYMP (MNGIE). Later, CMT4K (SURF1) was described, as well as rare cases involving mutations in POLG, RRM2B, and DARS2 (which more commonly cause axonal neuropathies), as well as COA8.

Brain MRI can be useful in the genetic diagnosis of a demyelinating neuropathy, and the mitochondrial hypothesis should be considered when leukoencephalopathy is also present, especially in the context of other suggestive symptoms (in this case: migraine, deafness, short stature, early menopause).