

Enhancement of cranial nerves, conus medullaris, and nerve roots in POLG mitochondrial disease

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A 20-year-old female patient was admitted to our department due to ptosis, double vision, and difficulty walking. The symptoms had evolved during the course of 2 months. She had never been very athletic and was described as always having been a “slow runner,” but otherwise her previous history was unremarkable. There was no family history of neurologic disease. There were no preceding triggering factors such as infections, fever, or physical stress, and the patient did not take valproate. On examination, she had bilateral external ophthalmoplegia and ptosis, grade 4 proximal and distal paresis in the lower extremities, grade 4 distal paresis in the upper extremities, distal sensory loss (for all sensory modalities), and sensory ataxia. After several months, she started experiencing a very slow improvement, which is—at the present moment—still incomplete.

MRI showed enhancement of the oculomotor nerves, the conus medullaris, the adjacent leptomeninges, and the cauda equina nerves. In the course of 1½ years, 5 MRI scans of the brain and medulla were performed, and the findings were stationary and independent of the acute decline. The radiologic findings were present before a lumbar puncture was performed.

Electroneuronography showed signs of an axonal neuropathy mainly affecting the lower extremities. CSF examination revealed a mild pleocytosis (7 cells) [reference <5 cells/mm³], elevated protein (22 mg/dL) [reference 20–50 mg/dL], and elevated lactate (3.3 mmol/L) [reference 1.2–2.1 mmol/L]. Several repeat CSF examinations were performed and showed the same abnormalities. CSF was negative for viruses and bacteria including *Borrelia burgdorferi*, syphilis, and tuberculosis. CSF cytology and flow cytometry were performed on 3 consecutive samples and revealed no tumor cells. Blood samples showed normal thyroid and liver functions tests and were negative for HIV serology, hepatitis B and C serology, tuberculosis (QuantiFERON test), syphilis, monoclonal protein, anti-nuclear antibody, antineutrophil cytoplasmic antibodies, antiphospholipid antibodies, angiotensin-converting enzyme, paraneoplastic antibodies, aquaporin-4 antibodies, contactin-1 and neurofascin-155 antibodies, ganglioside antibodies (incl.GQ1B), and acetylcholine receptor antibodies. Serum lactate was not measured. PET CT showed no abnormalities.

The clinical phenotype was compatible with sensory ataxic neuropathy, dysarthria, and ophthalmoparesis. Genetic testing revealed that she was compound heterozygous for 2 pathogenic polymerase gamma 1 (POLG) variants (c.2243G>C and c.2391G>T) located on chromosome 15. Parental DNA testing showed that the POLG variants were in trans position and therefore responsible for the clinical phenotype. The POLG gene is essential for the function of the only DNA polymerase that is active in mitochondria and can replicate in mitochondrial DNA (figures 1 and 2).

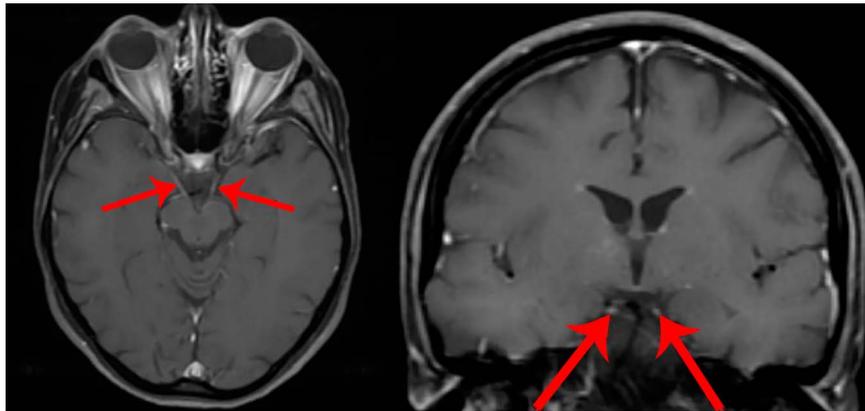
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Figure 1 Contrast-enhanced T1-weighted axial and coronal fat-saturated images showing bilateral smooth enhancement of the oculomotor nerves (arrows)



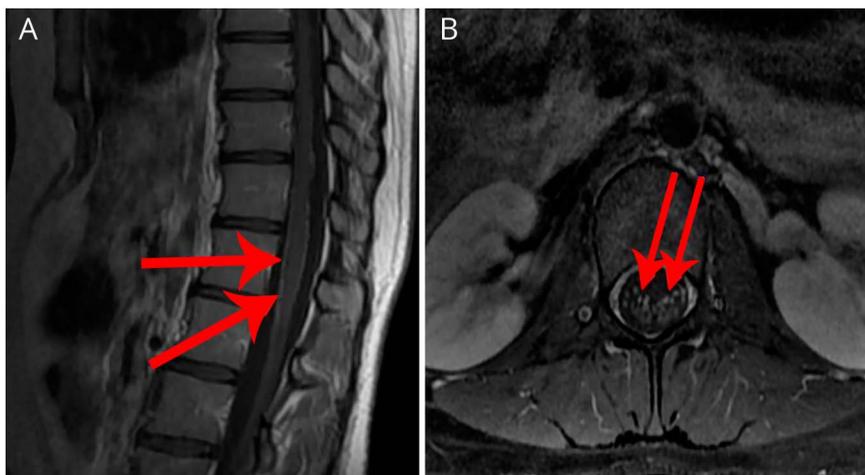
There has been only 1 previous report of abnormal nerve enhancement in mitochondrial disease. That report involved an infant patient with POLG variants whose MRI showed oculomotor nerve and cervical root enhancement.¹ The pattern of enhancement in our patient (involving the cranial nerves, conus medullaris, and cauda equine nerve roots) is rare and usually not associated with mitochondrial disease. We believe that the patient has been thoroughly investigated and has been followed clinically for more than 1 year without emergence of symptoms compatible with a systemic condition such as an autoimmune or neoplastic disorder. Therefore, it is considered likely that the MRI findings are caused by the mitochondrial disorder, although a peripheral nerve or nerve root biopsy was not performed.

POLG-related disorder can be associated with MRI changes of the brain parenchyma. A review of 136 patients with

POLG-related epilepsy showed that stroke-like lesions were the most prevalent abnormalities (43%), followed by thalamic (37%), cerebellar (17%), basal ganglia (14%), and cerebral white matter (7%) lesions. Generalized atrophy was also prevalent (28%). No such lesions were found in our patient.²

The differential diagnoses for nerve root and conus medullaris enhancement are very broad and include infectious, autoimmune, and neoplastic disorders.³ Mitochondrial disease is a very rare cause of nerve enhancement. The reason for the enhancement is not known, and it is unclear whether it is a distinguishing property of POLG variants or whether the enhancement is to be found in other mitochondrial variants as well. Routine use of contrast in the radiologic evaluation of patients with neurologic manifestations of mitochondrial disease could help elucidate this.

Figure 2 Contrast-enhanced sagittal T1-weighted and axial fat-saturated images showing enhancement of the conus medullaris (A) and cauda equina nerve roots (B) (arrows)



With this case, we wish to highlight that POLG-associated mitochondrial disorder should be included as a differential diagnosis in patients with enhancement of the cranial nerves, nerve roots, and the conus medullaris.

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Disclosure

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Name	Location	Role	Contribution
Michael Bayat, MD	Aarhus University Hospital	Author	Designed and conceptualized the study and drafted the manuscript
Yousef Yavarian, MD	Aalborg University Hospital	Author	Data collection and analysis (radiology)
Allan Bayat, MD	Danish Epilepsy Centre, Dianalund	Author	Drafting and revision of the manuscript
Jakob Christensen, MD	Aarhus University Hospital	Author	Drafting and revision for intellectual content

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