POLG mutations associated with remitting/relapsing neurological events

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ABSTRACT

Recent experimental data underline the relationship between mitochondria and immune function. Clinical reports of patients presenting with mitochondrial dysfunction associated with dysimmune responses in the central nervous system reinforce this new concept. We describe the first case of a woman presenting with symptoms related to a novel compound heterozygous mutation of the mitochondrial polymerase γ (*POLG*) gene, associated with neurological events suggestive of a demyelinating process. Clinical examination revealed bilateral ptosis, progressive external ophthalmoplegia and axonal sensitive polyneuropathy suggestive of a mitochondrial disease. In line with this, muscle biopsy showed ragged red fibers, and sequencing of *POLG* revealed two heterozygous mutations. In addition, the patient exhibited relapsing neurological symptoms, and cerebral and spinal MRI mimicking multiple sclerosis. This patient stresses the relationship between mitochondrial dysfunction and inflammation. Recent studies suggest that targeting mitochondrial dysfunction could provide benefits in treating some inflammatory diseases.

1. Introduction

Mutations of the mitochondrial polymerase γ (*POLG*) gene are responsible for a broad clinical spectrum of mitochondrial disorders with a predominant recessive mode of inheritance.[1,2] We report a patient presenting with bilateral ptosis, progressive external ophthalmoplegia (EO) and chronic axonal sensory polyneuropathy associated with episodes of optic neuritis, facial hypoesthesia and myelitis. Serial cerebral and spinal MRI revealed multiple sclerosis (MS)-like lesions. Sequencing of *POLG* found two recessive pathogenic mutations.

2. Case report

A 59-year-old woman was referred to our unit for neuro-ophthalmological disorders.

Her medical history began at age 39 with a bilateral progressive ptosis. Blood analyses, including anti-acetylcholine receptor antibodies, were negative. Electroneuromyogram (EMG) showed a chronic axonal sensory polyneuropathy with normal neuromuscular transmission. At age 49, diplopia with EO appeared and progressively worsened. At age 59, a mitochondriopathy was suspected because of bilateral ptosis, complete EO, sensory ataxia, proximal muscular deficit, and presence of hyperlactacidemia and axonal sensory polyneuropathy on a second EMG. A deltoid muscle biopsy revealed typical features of mitochondrial myopathy (Fig. 1). Long-range polymerase chain reaction (PCR) of muscle mitochondrial (mt) DNA showed multiple DNA deletions and real-time PCR found a decrease of mtDNA copy number. The genetic search for mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) and myoclonic epilepsy with ragged red fibers was negative. Sequencing of *POLG* found two recessive mutations: one novel (c.1190C>T) and one already known (c.2564T>C)[1] which was found in the mother of the patient, but not in her sister; both were asymptomatic. We did not genotype the deceased father.

In addition to symptoms related to *POLG*, the patient experienced, at 51 and 56 years of age respectively, acute visual loss (left eye) with central scotoma and acute blurred vision (right eye) with retro-ocular pain, both improving after intravenous methylprednisolone. At age 57, a hypoesthesia in the left trigeminal territory resolved spontaneously. Four months later, she presented with hypoesthesia of the left lower limb related to a thoracic myelitis (Fig. 2A). At age 59, optical coherence tomography showed bilateral papillary loss of nerve fibers. Blood tests, including neuromyelitis optica antibodies, were normal. The patient always refused lumbar puncture for cerebrospinal fluid analysis. Brain MRI was suggestive of a condition mimicking MS and showed that lesion load varied with time (Fig. 2B–E).

3. Discussion

We report a patient with symptoms related to a novel compound heterozygous mutation of *POLG* associated with remitting/relapsing neurological events suggestive of an MS-like disease.

Our patient presented clinical, biological, electrophysiological and histological features typical of mitochondriopathy related to *POLG* mutations.[1,2] Sequencing of the *POLG* found a mutation already known as deleterious (c.2564T>C)[1] and a novel c.1190C>T mutation, now classified as deleterious according to following criteria: association with a known deleterious mutation and co-segregation with the disease within the family; significant depletion and multiple deletions of muscle mtDNA; pathogenic status of the mutation as evidenced by the great inter-species conservation and by its absence in 250 patients and 100 controls.

In addition to *POLG* mutations, our patient presented with four clinical events mimicking MS on clinical and radiological grounds.[3]

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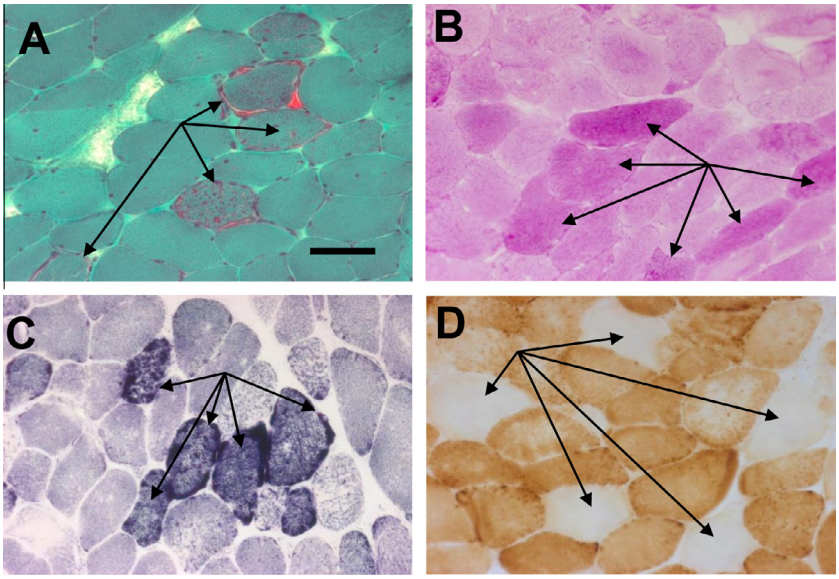

Fig. 1. Aspects of mitochondriopathy on histological analysis of muscular biopsy. (A) Ragged-red fibers on Gomori trichrome staining, (B) positive periodic acid-Schiff staining showing pathological glycogen accumulation, (C) succinate dehydrogenase staining indicating an unusual accumulation of subsarcolemmal mitochondria, and (D) 10% negative cytochrome *c* oxidase (COX) staining reflecting a deficit in mitochondrial COX enzyme. Black arrows indicate abnormal staining. Scale bar in A (100 μm; original magnification × 20) also applies in B–D. This figure is available in colour at www.sciencedirect.com.

Recently, *POLG* variations associated with clinically isolated syndrome have been reported.[4]

Primary mitochondrial diseases due to mtDNA or nuclear DNA mutations have been implicated in white matter lesions suggestive of a central nervous system inflammatory pathology.[5] Recent data suggest that mitochondrial dysfunction might favour an inappropriate immune response[6] such as in Leber hereditary optic neuropathy and in optic atrophy type 1 gene mutations,[7] both disorders having been reported with MS-like disease characteristics.[8,9]

The polymerase gamma encoded by *POLG* is the only polymerase able to replicate and repair mtDNA, therefore any *POLG* mutation may induce deleterious effects on mtDNA synthesis and consequently result in a mitochondrial dysfunction. Moreover, mitochondrial gene defects could potentiate mitochondrial dysfunction induced by reactive oxygen and nitrogen species in inflammatory lesions and therefore increase the vulnerability of energy-demanding demyelinated axons.[5,6] This suggests that targeting mitochondrial dysfunction could have benefit in treating some inflammatory disease.[10]

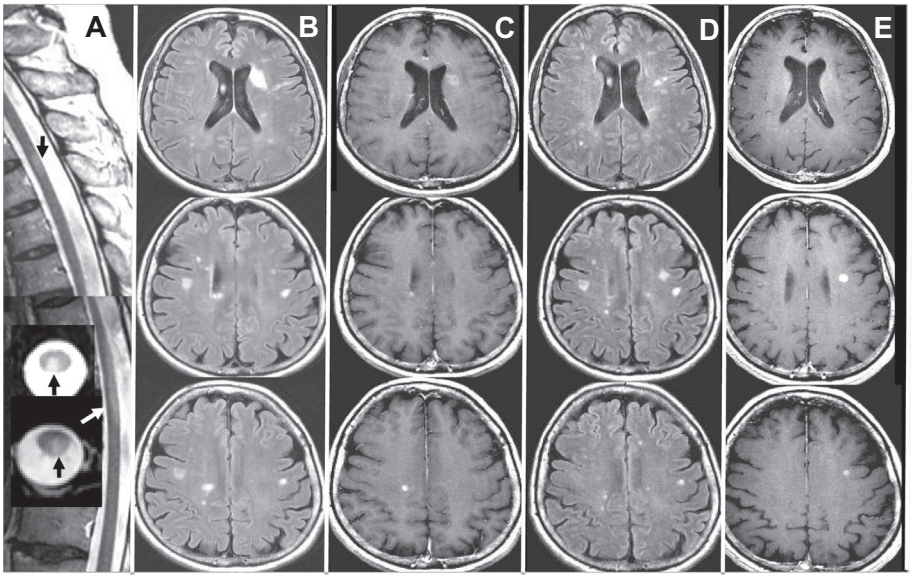

Fig. 2. (A) Fluid-attenuated inversion recovery (FLAIR) MRI sagittal sequences (inserts: axial sequences) of the spinal cord showing two thoracic hyperintensities (black and white arrows; taken when the patient was 58 years old). Axial (B) FLAIR MRI showing multiple white matter hyperintensities, with (C) post-gadolinium T1-weighted sequences showing two enhanced lesions (56 years old). Axial (D) T2–FLAIR MRI showing increased lesion load with (E) post-gadolinium T1-weighted sequences showing a new active lesion and disappearance of previous gadolinium enhancement (58 years old).

Conflict of interest/disclosure

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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