POLG mutation causing PEO and sensory polyneuropathy with a myasthenic-like onset

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Objective

We report a case of a 58-year-old patient who developed palpebral ptosis, diplopia and fluctuating dysphagia 3 weeks after SARS-Cov-2 infection. Initially diagnosed with seronegative myasthenia gravis (MG) with concomitant axonal neuropathy, due to the lack of improvements from treatments and the persistence of symptoms, he was diagnosed with a genetic disease.

Materials

Assessments included cerebrospinal fluid analysis (neurofilaments, inflammatory cytokines, autoantibody panel), blood analysis (microbiological and metabolic analysis, tumor and tissue damage markers); MRI and CT; EMG and autonomic testing. The genetic assessment completed the diagnostic workup.

Method

The diagnostic workup was initially oriented to confirm the initial suspect of MG (ptosis, diplopia, fluctuating swallowing, fatigability). Repetitive nerve stimulation of the facialis nerve was normal; single fiber EMG of the frontalis muscle showed increased jitter. The low response to therapy (cholinesterase inhibitors, immunomodulatory therapy) and the concomitant polyneuropathy symptoms (worsening distal paraesthesia with painful/thermic sensory impairment at lower limbs, appeared three years before the ocular motility impairment), introduced us to reconsider the diagnosis: ocular symptoms were attributed to a possible chronic progressive external ophthalmoplegia (PEO). After excluding other causes (inflammatory, autoimmune, infective, neoplastic and deficient causes) the genetic test was decisive to define the diagnosis.

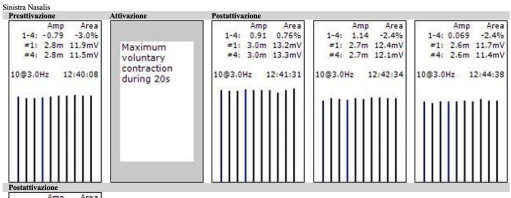

Fig. 1: RNS

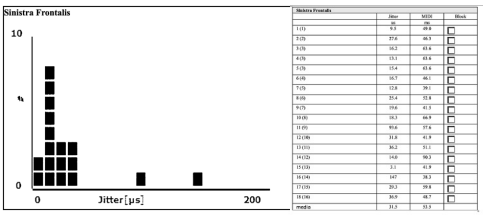

Fig. 2: Single fiber EMG

sensitiva				
	lat	cv	distanza	amp
	ms	m/s	mm	uV
Peroneus superfic Sensitiva Sinistra				
Calf - Med. Dor. Cutan.	--			--
Peroneus superfic Sensitiva Destra				
Calf - Med. Dor. Cutan.	--			--
STC Sensitiva Sinistra				
POLSO - I DITO RAD	1.99	55.3	110	3.5
POLSO - III DITO MED	3.16	47.5	150	2.8
POLSO - V DITO ULN	2.34	53.4	125	5.8
Suralis Sensitiva Sinistra				
Mid. lower leg - Lat. Malleolus	--			--
Suralis Sensitiva Destra				
Mid. lower leg - Lat. Malleolus	--			--

Fig. 3: ENoG

Results

We identified a compound heterozygous mutation (c.428C>T and c.3311C>G) of the nuclear POLG gene. Compound heterozygosity was verified by segregation analysis. A diagnosis of mitochondrial disease caused by POLG mutation was made, featuring PEO and axonal sensory polyneuropathy as main features. Treatment with ubidecarenone was started.

Discussion

Here we report a case of coexisting and apparently unlinked symptoms, i.e. progressive ocular motility impairment and sensory polyneuropathy. The clinical presentation and initial diagnostic workup were misleading. The emergence of atypical features such as the absence of response to treatment for MG and the presence of a polyneuropathy mandated the reconsideration of the diagnosis. POLG encodes the mitochondrial DNA (mtDNA) polymerase gamma, responsible for replication of the mitochondrial genome. POLG mutations can cause several syndromes, including PEO [1] and peripheral neuropathy [2]. Single fiber EMG is highly sensitive but not specific for MG, with evidence of increased jitter in mitochondrial myopathies [3].

Conclusions

This case report underlines the importance of keeping a broad differential diagnosis in mind, especially in the presence of atypical features or unexplained absence of treatment response. In the correct clinical context, genetic analysis can contribute to the diagnostic process and suggest specific treatments.

Rererences:

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[3] D. A. Krendel, D. B. Sanders, and J. M. Massey, "Single fiber electromyography in chronic progressive external ophthalmoplegia," Muscle Nerve, vol. 10, no. 4, pp. 299–302, May 1987, doi:10.1002/mus.880100404.