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Case report

SANDO: Two novel mutations in POLG1 gene

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Abstract

Sensory ataxia with neuropathy, dysarthria and ophthalmoparesis represent the clinical triad of SANDO, a specific mitochondrial phenotype first reported in 1997 in association with multiple mitochondrial DNA deletions and mutations in *POLG1* or more rarely in the C10orf2 (twinkle-helicase) gene. We report a 44-year-old man with SANDO who harboured two novel mutations (P648R/R807C) in the POLG1 gene.

Keywords: SANDO; Sensory ataxic neuropathy; Dysarthria; Ophthalmoparesis; POLG1 gene

1. Introduction

The clinical triad of sensory ataxic neuropathy, dysarthria and ophthalmoparesis (SANDO) was first proposed in 1997 as an unique mitochondrial phenotype associated with multiple mtDNA deletions [1]. This clinical picture was initially described in four sporadic unrelated patients with adult onset of severe sensory ataxic neuropathy in association with dysarthria and chronic progressive external ophthalmoplegia. The patients had ataxic gait, loss of distal proprioception and vibration, areflexia on the lower limbs, positive Romberg sign and electrophysiologic and pathologic evidence of a peripheral axonal neuropathy. Skeletal muscle biopsy showed myopathic changes with centralized nuclei and ragged-red fibers. Molecular analysis in muscle and peripheral nerve detected multiple mitochondrial DNA (mtDNA) deletions but the genes responsible were not further investigated. More recently, mutations in the POLG1 (DNA polymerase-γA) [2–4] and the C10orf2 gene (Twinkle helicase) [5] genes have been described (Table 1).

2. Clinical case

A 44-year-old man presented at age 39 progressive bilateral ptosis, unsteadiness gait and muscle weakness with difficulty in dressing and lifting objects. Three years later he noticed dysphagia and diplopia and sought medical advice. Neurological examination revealed droopy eyes which worsened after repeated eye movements and external ophthalmoparesis with diplopia on horizontal gaze. The patient also presented fluctuant dysarthria and dysphagia which worsened at the end of the day. There was distal limb muscles weakness with reduced deep tendon reflexes. Perception of vibration and position was absent below the iliac crests. Touch, pain and temperature senses were preserved. Signs of cerebellar dysfunction were also evident. Romberg sign was positive.

There was no history of neurological disease in the patient's family, although four sibs had died at birth of unknown cause.

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Table 1
Genotype expression and other data of different SANDO phenotypes

Author and year	Origin	Onset age (years)	Muscle biopsy	POLG 1 mutation	C10orf2 mutation
Van Goethem et al. (2003)	Belgium	19	Normal	R627W + A467T	
Van Goethem et al. (2004)	Finland	30	Normal	W748S + W748S	
Van Goethem et al. (2004)	G. Britain	20	Normal	W748S + A467T	
Winterthun et al. (2005)	Norway	23	Normal	Q947H/W748S	
Hudson et al. (2005)	Germany	36	Unknown		K319E
Present case	Portugal	39	RRF	P648R + R807C	

RRF, ragged red fibers.

Routine studies showed increased levels of seric creatine kinase (350 U/L; NL = <172) and pyruvate (0.29 mmol/L; NL = 0.03–0.10); normal levels of lactate (1.93 mmol/L; $n = 0.5$–2.2 mmol/L) and lactate:pyruvate ratio (6.65; $n < 25$). Cerebrospinal fluid (CSF) protein was 1 g/L. Negative anti-ganglioside and anti-neuronal antibodies, normal immunologic study and absence of toxic contact, excluded other possible etiologies of sensory neuronopathy. Fundoscopic and cardiac evaluations as well as brain magnetic resonance imaging (MRI) and audiometry were normal. Electromyography was normal, including single-fiber orbicularis oculi jitter test and repetitive motor nerve stimulation. Nerve conduction studies (NCS) showed normal motor response, but absence of median, ulnar and superficial peroneal nerve action potentials.

A superficial peroneal nerve biopsy (Fig. 1a) showed marked loss of large myelinated fibers, without bulbs, regenerative clusters or active Wallerian degeneration. Biopsies of the short lateral peroneal and deltoid muscle showed roughly 5% of red ragged fibers on the modified Trichome staining (Fig. 1b) most of which stained negative with cytochrome *c* oxidase (COX) reaction (Fig. 1c). Spectrophotometric analysis of respiratory chain enzyme complexes was also normal.

Southern blot analysis and long-range polymerase chain reaction showed multiple mtDNA deletions (Fig. 1d) in muscle. Direct sequencing of the coding exons of the *POLG1* gene showed that the patient harboured two heterozygous mutations, p.P648R and p.R807C in a conserved region of this gene. The coding sequences of *C10orf2* and *ANT1* were normal.

Our patient was treated with levocarnitine 1 g tid and coenzyme Q10 (ubiquinone) 30 mg tid without clinical improvement.

3. Discussion

The clinical phenotype in our patient fulfills the clinical triad of SANDO which occurred most likely in the absence of a family history. Previous reports suggests that SANDO is either sporadic [1] or inherited as an autosomal recessive [2] or dominant trait [5]. As the first described patients with SANDO [1], NCS and nerve biopsy suggests a sensory ganglionopathy with presumed preferential involvement of the dorsal root ganglia with axonal degeneration of the large-diameter sensory axons.

The identified mutations in POLG1 are new, occurred in highly conserved domains of the protein, were absent in ethnically matched 200 control chromosomes, and were associated with a typical mitochondrial phenotype in skeletal muscle. Interestingly, a p.R807P mutation has already been reported in three patients with PEO [6], one of whom also showed axonal sensorimotor polyneuropathy and dysphagia, but he did not completely satisfy a clinical diagnosis of SANDO.

The clinical outcome of mutations in POLG1 gene range from PEO, both in families with dominant or recessive inheritance [6] and sporadic cases [7], to juvenile ataxic syndromes with epilepsy [4], parkinsonism [8] and infantile Alpers syndrome [9]. Recently a mitochondrial recessive ataxia syndrome (MIRAS) has been described, with its allele (W748S+E1143G) being the most common genetic cause of inherited ataxia in Finland [10]. As in MIRAS, in our patient ataxia and peripheral ataxia neuropathy is present. However he lacks symptoms or signs of CNS degeneration such as cognitive impairment, nystagmus, epileptic seizures or MRI abnormalities. There is also clear evidence of mitochondrial disease in muscle biopsy, and multiple mtDNA deletions in muscle DNA Southern blot analysis.

Considering the broad range of phenotypes, it seems that phenotype relates to the functional effect of the combination of different mutations in POLG1 gene, rather to one specific mutation. However, additional genetic and epigenetic factors must be further investigated.

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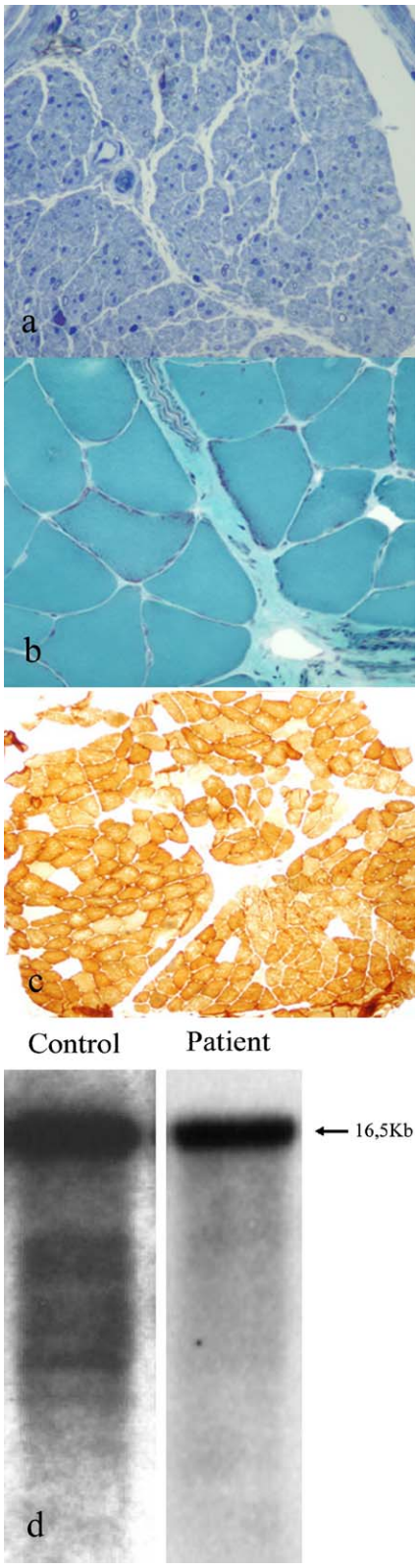

Fig. 1. Superficial peroneal nerve biopsy (resin section, toluidine blue) showing severe chronic axonal neuropathy (a). Modified Gomori trichome showing two ragged-red fibers (b). Cytochrome *c* oxidase reaction showing several negative fibers (c). Southern blot analysis of mitochondrial DNA showing multiple deletions (d).

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