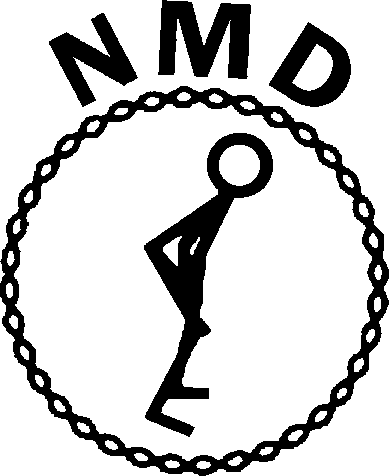
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Case report

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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 mitochon- drial 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.

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

1. Introduction

The clinical triad of sensory ataxic neuropathy, dys- arthria and ophthalmoparesis (SANDO) was ﬁrst pro- posed in 1997 as an unique mitochondrial phenotype associated with multiple mtDNA deletions [[1]](#_bookmark1). This clin- ical picture was initially described in four sporadic unre- lated 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 vibra- tion, 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-cA) [[2–4]](#_bookmark1) and the C10orf2

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gene (Twinkle helicase) [[5]](#_bookmark1) genes have been described ([Table 1](#_bookmark0)).

1. 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 move- ments 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-ganglio- side and anti-neuronal antibodies, normal immunolog- ic study and absence of toxic contact, excluded other possible etiologies of sensory neuronopathy. Fundo- scopic 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. 1](#_bookmark4)a) 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. 1](#_bookmark4)b) most of which stained negative with cytochrome *c* oxidase (COX) reaction ([Fig. 1](#_bookmark4)c). Spectrophotometric analysis of respiratory chain enzyme complexes was also normal.

Southern blot analysis and long-range polymerase chain reaction showed multiple mtDNA deletions ([Fig. 1](#_bookmark4)d) 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.

1. 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]](#_bookmark1) or inherited as an autosomal recessive [[2]](#_bookmark1) or dominant trait [[5]](#_bookmark1).

As the ﬁrst described patients with SANDO [[1]](#_bookmark1), NCS and nerve biopsy suggests a sensory ganglionopathy with presumed preferential involvement of the dorsal root ganglia with axonal degeneration of the large-diam- eter 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. Interest- ingly, a p.R807P mutation has already been reported in three patients with PEO [[6]](#_bookmark1), 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]](#_bookmark1) and sporadic cases [[7]](#_bookmark2), to juvenile ataxic syndromes with epilepsy [[4]](#_bookmark1), parkinson- ism [[8]](#_bookmark3) and infantile Alpers syndrome [[9]](#_bookmark5). 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]](#_bookmark6). 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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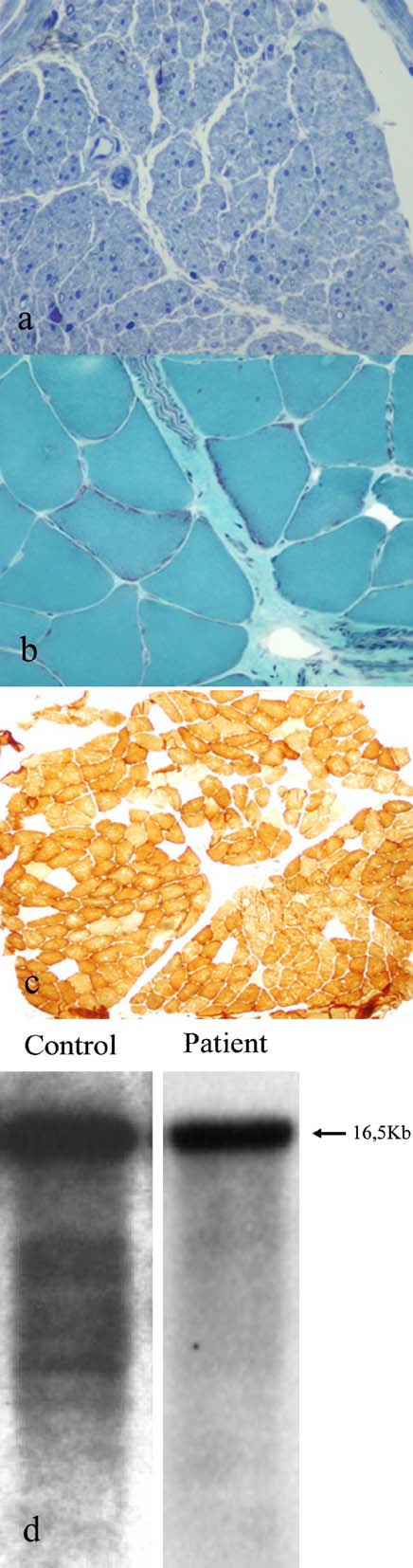


Fig. 1. Superﬁcial peroneal nerve biopsy (resin section, toluidine blue) showing severe chronic axonal neuropathy (a). Modiﬁed Gomori trichome showing two ragged-red ﬁbers (b). Cytochrome *c* oxidase reaction showing several negative ﬁbers (c). Southern blot analysis of mitochondrial DNA showing multiple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

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