SANDO syndrome in siblings: A familial case series of POLG-related disorder with variable age onset

Gaiola M[1], Passamonti M[1], Marcon M[2], Deluca C[3], Salvalaggio A[1], Corbetta M[1], Bello L[1], Pegoraro E[1], Minicuci GM[1]

[1]Dipartimento di Neuroscienze, Università degli Studi di Padova [2]Dipartimento di Neuroscienze, Ospedale Cazzavillan, Vicenza [3]Dipartimento di Neurologia, Ospedale San Bortolo, Vicenza

Introduction

POLG encodes the mitochondrial DNA polymerase essential for mitochondrial genome replication. Mutations in POLG are the most frequent cause of inherited mitochondrial disorders, affecting up to 2% of the population. They can result in early-onset mtDNA depletion syndromes or later-onset phenotypes due to mtDNA deletions (1). Clinical presentations vary widely and include the ataxia-neuropathy spectrum (ANS), which encompasses sensory ataxia, neuropathy, dysarthria, and ophthalmoplegia, known as SANDO. We report three siblings diagnosed with SANDO.

Case series

Case 1: A man developed symptoms at age 40 with progressive ataxia, ptosis and ophthalmoparesis, followed by dysphagia and dysarthria. Muscle biopsy revealed mitochondrial abnormalities, and EMG showed severe sensory axonal neuropathy. Genetic testing identified compound heterozygous POLG mutations (c.1399G>A and c.2243G>C), confirming SANDO. Treatment with ubidecarenone provided minimal benefit. The disease progressed with frequent falls and head trauma, epileptic seizures, and cognitive decline (memory, attention, visuospatial processing). He died at 60 due to complications of prolonged immobility.

Case 2: A 41-year-old woman with headache and anxiety–depressive disorder treated with valproate was evaluated for a 10-year history of progressive ataxia. Early involuntary movements and psychiatric symptoms suggested Huntington's disease. Brain MRI revealed bilateral bulbar hyperintensities, consistent with SANDO/PAPT spectrum, and EMG confirmed severe sensory axonal neuropathy. Examination showed ataxia, dysarthria, ptosis, ophthalmoparesis, and jerky limb and head movements. After her brother's diagnosis, genetic testing confirmed the same POLG mutations. Valproate was discontinued. Ataxia worsened progressively, and she became bedridden within a few years

Case 3: A 56-year-old man with bronchial asthma presented with imbalance and dysarthria. CT detected a left fronto-orbital lesion, resected and confirmed as meningioma. Neurological examination showed mild dysarthria, ophthalmoparesis, and ataxia. Following his siblings' diagnoses, genetic testing confirmed the same compound heterozygous POLG mutations

Motor NCS

Nervo / Posizioni	Muscle	Latency ms	Amplitude mV	Amp % %	Duration ms	Segmenti	Distance mm	Lat Diff ms	Velocity m/s
D Tibiale - AH									
Ankle	AH	3,80	18,5	100	5,31	Ankle - AH			
Pop fossa	AH	14,01	10,5	57	6,04	Pop fossa - Ankle	405	10,21	40
L Tibiale - AH									
Ankle	AH	3,02	16,0	100	6,72	Ankle - AH			
Pop fossa	AH	13,75	10,1	63,3	7,50	Pop fossa - Ankle	425	10,73	40

Sensory NCS

Nervo / Posizioni	Rec. Site	Onset Lat ms	Peak Lat ms	NP Amp µV	PP Amp µV	Segmenti	Distance mm	Dig-Polso m/s	Vel. m/s
D Surale									
Caviglia	Polpaccio	NR	NR	NR	NR	Caviglia - Polpaccio			
L Surale									
Caviglia	Polpaccio	NR	NR	NR	NR	Caviglia - Polpaccio			
L Peroneo superficiale									
Gamba	Dorso del piede	NR	NR	NR	NR	Gamba - Dorso del piede			
D Peroneo superficiale									
Gamba	Dorso del piede	NR	NR	NR	NR	Gamba - Dorso del piede			
L Ulnare - Digit V									
Wrist	Dig V	2,29	3,02	0,95	3,1	Wrist - Dig V	120	52,4	52,4

Fig.1 NCS: length-dependent axonal sensory polyneuropathy

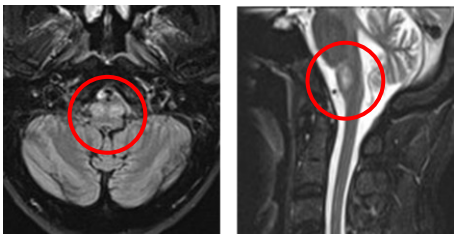

Fig. 2 MRI section showing bilateral hyperintensity of the medulla oblongata

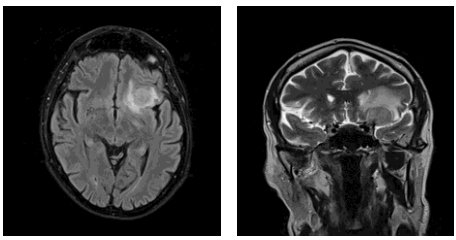

Fig. 3 MRI section showing a left fronto-orbital lesion: meningioma.

Conclusions

SANDO syndrome is a rare POLG-related disorder with autosomal recessive inheritance. We described a family in which all three siblings carried the same compound heterozygous mutation. Although autosomal recessive inheritance is suspected in this family, genetic testing of the parents was not available; therefore, it remains undetermined whether the compound heterozygous mutations were in cis or in trans.

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