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Short Commentary

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POLG1/ANT1-Related SANDO is a Multisystem Mitochondrial Disorder

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In a recent article Kirschenbaum et al., described a 50 years female with sensory ataxic neuropathy with dysarthria and ophthalmoplegia (SANDO) syndrome due to the mutation c.467A>T in the *POLG1* gene [1]. SANDO, first described by Fadic et al. in 1997 [2], is clinically characterized by the triad of sensory ataxic neuropathy, dysarthria, and ophthalmoparesis [3]. We have the following comments and concerns.

The patient died suddenly from cardiac arrest [1]. Was the individual history positive for palpitations, syncopes, or episodes of heart failure? Was the family history positive for sudden cardiac death (SCD) as has been previously reported [4]? Did the patient undergo cardiologic work-up before decease? Was a Holter-ECG recorded or an echocardiography carried out? Did the patient undergo cardio-pulmonary resuscitation? Was there any indication on autopsy for the presence of left ventricular hypertrabeculation/noncompaction (LVHT) most frequently found in mitochondrial disorders and complicated by stroke/embolism, heart failure, ventricular arrhythmias, or SCD [5]. Since SANDO may go along with anxiety [6] it would be interesting to know if the patient had died suddenly from the complications of Takotsubo syndrome (TTS), also known as acute stress cardiomyopathy.

The authors suspect histological and histochemical changes in the muscle [1]. Did the patient manifest with clinical features of myopathy other than ptosis or external ophthalmoplegia? Did she complain about muscle cramps, easy fatigability, or exercise intolerance? Was the muscle investigated at autopsy?

The patient was compound heterozygous for two *POLG1* variants, c.1399G>A and c.2243G>C [1] as has been previously reported [6]. Were the mutations hereditary or sporadic? Were the parents or siblings investigated for the two *POLG1* variants? Were any other first-degree relatives investigated neurologically or for the mutations?

Patients with SANDO typically show cerebellar atrophy, and fissures and hyperintense lesions in the olivary nuclei, cerebellar white matter, and the dorsomedial thalami [7]. Did the patient undergo a second cerebral imaging for follow-up and were these typical abnormalities detectable on MRI? Did any other of the mutation carriers in the family undergo cerebral imaging?

The patient received immunoglobulins [1]. Which was the rationale to apply this compound? Were there any clinical or chemical indications for the presence of an immune neuropathy? Immunoglobulins have not been reported previously to exhibit a beneficial therapeutic effect in SANDO.

SANDO may be associated with multiple deletions of the mtDNA [8, 9]. Was any tissue investigated for the presence or absence of secondary mtDNA deletions?

Overall, this interesting case and the review of the literature show that SANDO is indeed a multiorgan disorder and not restricted to the cerebrum, peripheral nerves, and the extraocular muscles. Detection of an index case with SANDO requires extensive investigations of other first-degree family members.

Table 1: Phenotypic features of SANDO.

	Manifestation	Mutated gene	Reference
Central nervous system	Dysarthria	none	[7]
	Dysphagia	*ANT1/POLG1*	[4]
	Tremor	*POLG1*	[10]
	Cognitive impairment	*POLG1*	[10]
	Dementia	*POLG1*	[10]
	Epilepsy	none	[11, 12]
	Olivary degeneration	*POLG1*	[13]
	Parkinsonism	*POLG1*	[14]
	Headache	*POLG1*	[12]
	Lactate elevation	*ANT1/POLG1*	[4, 12]
	Depression	*POLG1*	[6]
	Anxiety	*POLG1*	[6]
Eyes	Visual impairment	*POLG1*	[10]
Ears	Impaired hearing	*ANT1/POLG1*	[4]
Endocrine organs	Early menopause	*POLG1*	[6]
Heart	Sudden cardiac death	*POLG1*	[1]
Gastrointestinal tract	Constipation (MNGIE-like)	*POLG1*	[6]
Peripheral nerves	Sensory ataxia	*POLG1*	[10]
	Gait disturbance/falls	*ANT1/POLG1*	[4]
	Sensory-motor neuropathy	*POLG1*	[10]
Muscle	Ptosis	*POLG1*	[6]
	Ophthalmoparesis	*POLG1*	[10]
	Quadruparesis	*ANT1/POLG1*	[4]
	Muscle cramps	*POLG1*	[6]
	Lactic acidosis	*ANT1/POLG1*	[4]

Conflict of Interest

There are no conflicts of interest. Both authors contributed equally.

Ethical approval

The research has been given ethical approval.

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