**POLG1-Related Retinopathy in Non-Syndromic Multisystem Mitochondrial Disorder**

**Abstract:**

Keywords: MELAS, stroke, stroke-like episode, mtDNA, respiratory chain, mitochondrial.

**LETTER TO THE EDITOR**

With interest we read the article by Sanderson, K. G. et al., (2020) about a 14yo Indian male with sensory ataxic neuropathy, dysarthria, and ophthalmoplegia (SANDO) plus syndrome due to the previously reported variant c.911T>G in *POLG1*, who was described as the first documented case with generalised rod ON-bipolar dysfunction but electronegative electroretinography (ERG) (Sanderson, K. G. et al., 2020). We have the following comments and concerns.

We do not agree with the diagnosis of SANDO (Sanderson, K. G. et al., 2020). SANDO is characterised by sensory neuropathy, dysarthria, and ophthalmoplegia. However, the index patient had cyclic vomiting syndrome, anorexia, developmental delay (speech at age 2y), epilepsy (treated with oxcarbazepine (OXC)), myopathy affecting the extra-ocular, limb and respiratory muscles (ophthalmoparesis, ptosis, quadraparesis with contractures, respiratory insufficiency), sleep apnoea syndrome, and dysphagia requiring nutrition via a G-tube (Sanderson, K. G. et al., 2020). The patient did not fulfil the diagnostic criteria for SANDO, since he was not described as having ever developed the cardinal phenotypic features sensory neuropathy and dysarthria (Sanderson, K. G. et al., 2020). We should know the results of the clinical neurological exam at the last follow-up and the results of nerve conduction studies.

POLG1 mutations may secondarily cause reduction of the mtDNA copy number (mtDNA depletion) (Paramasivam, A. et al., 2019). Thus, we should know if there was mtDNA depletion and to which degree the mtDNA copy number was reduced.

There is a discrepancy between the description of the phenotype in the case report section and the discussion. In the case report section nothing is mentioned about headache or hypotonia. Surprisingly, the discussion indicates that the patient additionally had sporadic headache since age 2y, and hypotonia from the age of 4y.

The patient was diagnosed with sleep apnoea syndrome (SAS). However, the patient was reported to have experienced weight loss and affection of the respiratory muscles. Is it conceivable that SAS was rather chronic respiratory failure due to affection of respiratory muscles? We should know the results of sleep laboratory findings and of cerebral MRI to see if there was brainstem involvement in the disease.

The patient presented with chronic coughing. We should know the cause of chronic coughing. Is micro-aspiration conceivable or was it due to heart failure? Since POLG1-related disorders may go along with cardiomyopathy (Verhoeven, W. M. et al., 2011), it is crucial that the results of echocardiography and long-term ECG recordings are presented. Additionally, we should know the serum levels of creatine-kinase, lactate, and proBNP.
Since POLG1 variants may manifest with optic atrophy (Felhi, R. et al., 2019), we should know the results of visually-evoked potentials (VEPs) and the magnetic resonance imaging (MRI) of the optic nerve. Though only rarely reported, POLG1 variants may also go along with retinopathy, particularly pigmented retinopathy (Fonzo, A. D. et al., 2003).

OXC is potentially mitochondrion-toxic and may have an adverse effect on the mitochondrial metabolism (Finsterer, J. 2017). We should know the daily dosage and serum levels, and if any side effect developed. The patient additionally received coenzyme-Q (CoQ), lipoic acid, and L-carnitine since the age of 9y (Sanderson, K. G. et al., 2020) but the mitochondrial disorder (MID) was diagnosed not earlier than at age 10y. Which was the rationale for prescribing antioxidants and cofactors in the absence of a documented MID at that time?

Overall, this interesting case of a POLG1-related mitochondrial disorder (MID) has a number of shortcomings, which need to be addressed before drawing final conclusions. The patient had no SANDO but rather an early-onset, non-syndromic, multisystem, POLG1-related MID, manifesting in the brain, skeletal muscle, intestines, and the eyes.

REFERENCES