LETTER TO THE EDITOR

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

POLG1 variants may secondarily affect mtDNA load and structure

JOSEF FINSTERER

Krankenanstalt Rudolfstiftung, Messerli Institute, Vienna, Austria

Keywords: mtDNA, respiratory chain, mitochondrial disorder, oxidative phosphorylation, multi-organ, *POLG1*.

Dear Editor,

With interest, we read the article by Bastian *et al.* about a 49-year-old male with a mitochondrial disorder (MID) manifesting as bilateral ptosis, chronic progressive external ophthalmoparesis (CPEO), dysphagia, and proximal limb muscle weakness with onset around the age of 35 years [1]. Work-up revealed the variant c.2864A>G in deoxyribonucleic acid (DNA) polymerase subunit gamma (*POLG1*) [1]. We have the following comments and concerns.

Missing in this report is an investigation of the mitochondrial DNA (mtDNA), since *POLG1* variants may secondarily result in either multiple mtDNA deletions or mtDNA depletion. In this respect, it is necessary to report the heteroplasmy rates of the probable mtDNA defects. Missing is also the information whether the *POLG1* variant occurred in the homozygous or heterozygous form. Additionally, we should be informed if the mother or any of the patient's siblings carried the variant.

Since immunohistology of the skeletal muscle revealed cytochrome *c* oxidase (COX)-negative fibers, it is quite likely that function of one or multiple respiratory chain complexes was impaired. Thus, we should be informed about the activity of respiratory chain complexes on biochemical investigations of the muscle homogenate.

Since the patient obviously had developed bulbar manifestations [1], we should know if there was dysarthria or affection of the tongue in addition to dysphagia and if dysphagia was complicated by aspiration and recurrent broncho-pulmonary infections. It should be also discussed if dysphagia was due to central nervous system involvement, due to affection of lower cranial nerves, or due to affection of the smooth muscle cells. In this respect, results of cerebral magnetic resonance imaging (MRI), nerve conduction studies, and video-cinematography should be provided.

Missing is also a prospective investigation of organs/systems not apparently clinically affected. Since MIDs are multisystem disorders in the majority of the cases [2], and manifest frequently not only in the brain and the muscles but also in the eyes, ears, endocrine organs, heart, lungs, gastrointestinal tract, kidneys, cartilage, skin, immune system, and bone marrow [3], we should be informed about the results of routine blood tests and about specific prospective investigations to rule out or confirm multisystem involvement in the index case.

According to our own experience, correction of ptosis is frequently only of limited effect and ptosis recurs after a certain time. For how long was ptosis surgery affective in the index case? It should be also mentioned if surgery was associated with any complications since it has been repeatedly reported that over- or under-correction of ptosis by the plastic surgeon may lead to xerophthalmia, conjunctivitis, scleritis, blepharitis, or even worsening of ptosis.

Affection of the skeletal muscles in MIDs frequently goes along with exercise intolerance and easy fatigability. We should be informed if any tests were carried out to assess if there was easy tiring. Additionally, we should know if serum lactate was elevated at rest or during mild exercise. The lactate stress test has been proven useful in the diagnostic work-up of patients with a MID and is technically easy to perform [4].

Overall, this interesting case could be more meaningful by providing more data about secondary mtDNA defects and heteroplasmy, about biochemical investigations, about prospective investigations for multisystem involvement, and by providing information about homo- or heterozygosity of the culprit variant, about the result of ptosis surgery, and about the results of the lactate stress test.

Conflict of interests

There is no conflict of interests.

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Corresponding author
Josef Finsterer, MD, PhD, Krankenanstalt Rudolfstiftung, Messerli Institute, Postfach 20, 1180 Vienna, Austria; Phone +43–1–7116572085, Fax +43–1–71165, e-mail: fifigs1@yahoo.de

Received: July 5, 2019

Accepted: November 9, 2019