

## Letter to the Editor

# Assessment of Audiological and Vestibular Involvement in Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-Like Episodes Requires in-Depth Background Information

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Dear Editor,

With great interest we have read the article by Hougaard et al. <sup>[1]</sup>, which presents a study on 8 patients with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) who underwent audiological (pure-tone audiometry and standard speech audiometry) and vestibular testing (dizziness handicap inventory, ocular vestibular-evoked myogenic potential testing, cervical vestibular-evoked myogenic potential testing, and video head impulse test). These tests revealed that all the patients had involvement of their audiological and vestibular organs but did not have cochlear or vestibular nerve involvement <sup>[1]</sup>. We have the following comments and concerns.

The first shortcoming of the study is that the selection of patients is unclear. The inclusion criteria were the diagnosis of MELAS or maternally inherited diabetes and deafness (MIDD) or a carrier status of the m.3243A>G variant, which is in disagreement with the title. Furthermore, because MELAS may be caused by several different mutations in several different mtDNA or nDNA-located genes, <sup>[2]</sup> it is conceivable that all the 8 patients carried a different mutation. Therefore, it is crucial to specify if the causative mutation was truly known in each patient and to mention which mutation was identified in each of them.

The second shortcoming is that the entire phenotypic spectrum has not been provided. MELAS is usually a multisystem disease; therefore, the study must specify how many patients were diagnosed with MELAS or MIDD and which organs or tissues were affected in addition to the audiological and cochlear organs. Because hearing impairment and systemic or non-systemic vertigo may be due to involvement of the peripheral nerves or due to central nervous system (CNS) affection associated with reduced thickness of the auditory cortex, <sup>[3]</sup> CNS imaging and nerve conduction studies should be provided to recognize how many patients had involvement of the CNS and how many had neuropathy due to diabetes, renal insufficiency, thyroid dysfunction, or simply due to primary peripheral nerve affection.

The third shortcoming of the study is that heteroplasmy rates of mtDNA mutations were not provided. It is well appreciated that the phenotype in mtDNA mutation carriers may depend on heteroplasmy rates via epigenetic influences on the histone acetylation or mtDNA/nDNA transcription <sup>[4]</sup>. Therefore, heteroplasmy rates must be determined in hair follicles, skin fibroblasts, blood lymphocytes, muscle, buccal mucosa cells, and urinary epithelial cells. Heteroplasmy rates must be correlated with the results of each audiological and vestibular test.

The fourth shortcoming of the study is that the current medication that was regularly taken by each patient was not specified. Considering that drugs may strongly influence the phenotype of mitochondrial disorders (MIDs), <sup>[5]</sup> it is crucial to know

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the compounds that the 8 patients were regularly taking. Several drugs (e.g., antiseizure drugs) are well-known for their potential mitochondrion toxicity<sup>[5]</sup> why they may strongly influence the clinical presentation.

The fifth shortcoming is that the family history of the patients was not provided. Because MIDs due to mtDNA variants are inherited via the maternal line in approximately 75% of the patients, it is crucial for interpreting the results and genetic counseling to determine which other first degree relatives carried the causative mtDNA/nDNA variant or presented with clinical manifestations.

Overall, this interesting study could be more meaningful if the above mentioned shortcomings were addressed to assess the test results in the light of the genetic background, the family history, the individual phenotypic expression, the multisystem involvement, and the influence of the medication taken by these patients.

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