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Letter to the Editor

Hearing Impairments in m.3243A>G Carriers may be due to an Impairment of Peripheral and Central Auditory Pathways

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Letter to the Editor

We read with interest the article by Uehara *et al*. on a retrospective cohort study of the clinical characteristics of m.3243A>G carriers and their association with hearing impairment [1]. m.3243A>G carriers with multisystem involvement had a lower body mass index (BMI) and more severe hearing loss than those who only suffered from hypoacusis or diabetes [1]. Two patients developed MELAS syndrome (mitochondrial encephalopathy, lactic acidosis, and stroke-like episode) [1]. It was concluded that early hearing loss may be a risk factor for systemic mitochondrial diseases, especially in lean individuals [1]. The study is interesting, but some points need to be discussed.

The first point is the retrospective design of the study [1]. Retrospective designs have several disadvantages, such as poor data quality, missing data, the inability to prove causality (only association), susceptibility to memory bias and selection bias, difficulties in controlling for confounding variables, and a generally lower level of evidence compared to prospective studies [2].

The second point is that the phenotype of the m.3243A>G variant may not only be determined by the heteroplasmy rate, but by several other factors such as the mtDNA copy number, the haplotype, tissue distribution and nuclear factors. These factors should be included before interpreting the results.

The third point is that the family history was positive for hearing loss in 3 patents, but it was not reported in how many patients the m.3243A>G variant was inherited from the mother and in how many it occurred spontaneously. Knowing whether the mutation was inherited or developed spontaneously is crucial to assess intra-familial phenotypic heterogeneity, to assess the intra-familial segregation, and for genetic counselling. We should know how many of the included female patients were in childbearing age and seeked genetic counselling.

The fourth point is that heteroplasmy rates were generally low and according to figure 1 19 patients had a heteroplasmy rate below 30% [1]. Did these patients with low heteroplasmy rate manifest only in the ears or also in other organs?

The fifth point is that the statement “early hearing loss may be a risk factor for systemic mitochondrial diseases, especially in lean individuals” cannot be derived from the index study, as only two patients progressed from hearing impairment and/or diabetes to MELAS. Based on only two patients, no general conclusions can be drawn that early hearing loss predicts progression to a multisystem disorder [1]. Before such a conclusion can be drawn, more comprehensive studies with a larger number of patients and homogeneous clinical symptoms are needed.

The sixth point is that hearing impairment in m.3243A>G carriers may not only be due to cochlear impairment, but also to involvement of the central nervous system, including lesions of the brainstem, reduced ability to localize sound sources, deficits in central auditory processing, structural lesions in the auditory cortex, or a stroke-like episode [3, 4]. Therefore, we should be aware of the results of central nervous system imaging, particularly magnetic resonance imaging of the brain. How many of the patients had a history of stroke-like episodes?

In summary, before drawing any general conclusions about hearing loss in carriers of m.3243A>G and its association with multisystem involvement, a larger number of patients with a homogeneous phenotype and genetic background should be studied.

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