Sarcouncil Journal of Medicine and Surgery

**ISSN(Online): 2945-3534**

Volume- 04| Issue- 03| 2025

**Letter to the Editor** **Received:** 11-02-2025 | **Accepted:** 23-02-2025 | **Published:** 03-03-2025

# When Assessing the Type of Hearing Loss in Mitochondrial Disorders, the Particularities of Mitochondrial Genetics must be taken into Account

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**Keywords:** mtDNA, mitochondrial disorders, hearing loss, m.3243A>G, audiology.

## LETTER TO THE EDITOR

We read with interest the article by Koohi, *et al*., on a cross-sectional and observational study of the nature of hearing loss in 72 patients with primary mitochondrial disorder (MID) using a battery of audiologic tests, including pure tone audiometry (PTA), tympanometry, acoustic reflex threshold (ARS) determination, rapid speech in noise test (QSIT), listening in spatial sounds and sentences test (LISN-S), brainstem audiometry (ABR), and distortion product of autoacoustic emissions (DPOAE) [Koohi, N. *et al*., 2024]. Among MID patients with the mtDNA variants m.3243A>G/T (n=41), other mtDNA variants (n=18) or nDNA variants in *POLG1* (n=2), *SURF1* (n=1), *RNASEG1* (n=1) and OPA1 (n=1), as well as in seven genetically unconfirmed MID patients, PTA thresholds were elevated, LISN-S test showed deficits in spatial processing, and ABRs were abnormal in carriers of m.3243A>G/T [Koohi, N. *et al*., 2024]. It was concluded that personalized, genotype-specific hearing testing and targeted treatment strategies that address both cochlear and neural/central hearing deficits in MID are needed [Koohi, N. *et al*., 2024]. The study is noteworthy, but some points should be discussed.

The first point is that an article entitled "beyond the cochlea: exploring the multifaceted nature ...." expects to report the results of what really lies beyond, including the brain. Surprisingly, cerebral imaging was not reported in any of the 72 patients included [Koohi, N. *et al*., 2024]. Although the lack of a cerebral MRI scan was cited as a limitation of the study, it is incomprehensible why the study was conducted without imaging of the cerebral auditory pathways and cortical imaging of hearing. Especially considering the fact that MIDs often manifest in the central nervous system (CNS) [Finsterer, J, 2006; Lax, N. Z. *et al*., 2017] and the inclusion of carriers of the m.3243A>G/T variant in particular, it is conceivable that at least in some of the included patients the hearing impairment is due to a retrocochlear CNS lesion and not a cochlear lesion. Morphological examinations are required to determine whether the neural/central hearing impairment is due to a functional or morphological impairment of the central auditory pathway or the cortical representation of hearing.

The second point is that the phenotypic appearance of pathogenic mtDNA variants may depend not only on the location of the mutation within the mtDNA and the type of mutation, but also on the heteroplasmy rates in different affected or unaffected tissues, on the mtDNA copy number, on the haplogroup and accompanying polymorphisms, and on the genetic background of the nucleus. However, these influencing factors were neither mentioned in the methods section nor in the limitations.

Thirdly, it is incomprehensible why seven patients were included in the study in whom the diagnosis of MID was not genetically confirmed. Since histologic and immunohistologic findings cannot clearly confirm that the abnormalities are due to a genetic defect, the seven patients should have been excluded from the analysis. Even if biochemical tests indicate impaired function of a respiratory chain complex, this does not clearly confirm that the underlying etiology is genetic [Pyle, A. *et al*., 2015].

The fourth issue with the study is that interobserver variability was not calculated, nor were test-retest reliability studies or follow-up studies conducted. To assess how reliable the test results of the single tester were, it would have been necessary to compare them with those of another tester. Although the study design was cross-sectional, it would have been interesting to test all patients a second time to also calculate the test-retest reliability of the tests used and determine whether hearing impairment progresses.

In summary, this interesting study has limitations that put the results and their interpretation into





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DOI- https://doi.org/10.5281/zenodo.14962931

perspective. Removing these limitations could strengthen the conclusions and reinforce the message of the study. All open questions need to be clarified before readers uncritically accept the conclusions of the study. Before drawing definitive conclusions about the nature of hearing loss in MID patients, parameters representing the specific features of mitochondrial genetics and their influence on auditory pathway impairment in MID need to be considered.

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**Source of support:** Nil; **Conflict of interest:** Nil.

**Cite this article as:**
Finsterer, J. "When Assessing the Type of Hearing Loss in Mitochondrial Disorders, the Particularities of Mitochondrial Genetics must be taken into Account." *Sarcouncil Journal of Medicine and Surgery* 4.3 (2025): pp 3-4.





**Publisher: SARC Publisher**