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Letter to the Editor

One Swallow doesn't make a summer

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We read with interest Sun *et al's* article about a 42-year-old female with mitochondrial encephalopathy, lactic acidosis, and stroke-like episode (MELAS) syndrome, phenotypically characterized by short stature, bilateral impaired hearing, cardiomyopathy, diabetes, renal insufficiency, and recurrent episodes of headaches, dizziness, vomiting, tremors, diplopia, and blurred vision [1]. The patient received consecutive cochlear implants (CIs) at age 42, resulting in significant progressive improvements in objective speech recognition, such as mono- and di-syllabic words according to the SSQ-TW, subjective spatial hearing, and sound qualities during a 12-month follow-up [1]. The study is excellent, but some points need discussion.

The first point is that the general conclusions that MELAS patients who receive bilateral CIs can achieve satisfactory speech recognition, spatial hearing, and sound quality after CI is not justified [1]. Such conclusions cannot be drawn from an individual case. In order to draw general conclusions about the effect of a treatment, an appropriate design with an appropriate number of participants is essential.

A second point is that the heteroplasmy rate of 29.5% is quite low suggesting that impaired hearing in the index patient could be due to a cause other than the m.3243A>G variant. In addition to the panel test for mutations in genes associated with impaired hearing, were alternative causes of impaired hearing such as side effects of ototoxic medications, diabetes, trauma to the ear or head, work-related ototoxic chemicals, viral infections, and acoustic trauma appropriately ruled out?

A third point is that the phenotype is influenced not only by heteroplasmy rates in affected and unaffected tissues, but also by mtDNA copy numbers, polymorphisms, and nuclear genes. We should know whether mtDNA sequencing or WES found additional variants that could explain the phenotype? Was the mtDNA copy number increased?

A fourth point is that MELAS is not characterized by "ischemic changes in the cerebral cortex", as stated in the introduction [1]. The pathognomonic phenotypic feature of MELAS is the stroke-like episode (SLE), which manifests on cerebral imaging as stroke-like lesion (SLL) [2]. SLLs are not ischemic in nature and not due to focal hypoperfusion. Therefore, we should know whether the "neurological episodes" described in the index patient were due to SLLs or not. Was the patient ever subjected to cerebral imaging during any of these episodes? Was an EEG ever recorded during these episodes? SLEs often manifest with clinical or subclinical seizures [3].

A fifth point is that the cause of hearing impairment in MELAS is unknown and not certain to be due to ATP deficiency, as stated in the introduction [1]. In addition to ATP deficiency several other speculations have been made about the aetiology, such as oxidative stress, apoptosis of hair cells or stria vascularis, electrolyte imbalances, and impaired mitochondrial dynamics and reproduction.

A sixth point is that the mother's genotype and phenotype were not adequately described. Did the mother also carry the m.3243A>G variant? Did she have the same phenotype as the index patient? In particular, did she also suffer from impaired hearing?

A seventh point is that the type of anaesthesia during CI implantation has not been described in detail [1]. Did the patient undergo general anaesthesia with volatile anaesthetics or receive ketamine or propofol intravenously?

In summary, the excellent study has limitations that should be addressed before final conclusions are drawn. Before concluding that bilateral CIs are generally beneficial for MELAS patients, appropriately designed and powered studies are needed.

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Statement of Ethics: A) The study was approved by the institutional review board (responsible: Finsterer J.) at the 4th February 2024. b) Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Data availability statement: Data that support the findings of the study are available from the corresponding author.

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Compliance with Ethics Guidelines: This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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