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Letter to the Editor

# Impaired Hearing in MELAS

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To the Editor,

We read with interest the article by Crundwell et al[1] about 2 patients with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome who manifested clinically with bilateral sensorineural hearing impairment after speech development and significantly profited from unilateral implantation of a2 cochlea implant.[1] In patient 1 (53-year-old male), MELAS was found to be due to the variant m.3243A>G in *MT-TL1* and in patient 2 (47-year-old male), the genetic cause of MELAS was unknown.[1] The study is appealing but has some limitations that raise concerns which need to be discussed.

We disagree with the statement in the abstract that MELAS is the most common mitochondrial disorder (MID).[1] There are only few data available on the epidemiology of MIDs.[2] However, the few data reported in the literature and our own experiences suggest that non-syndromic MIDs prevail when compared with syndromic MIDs, such as MELAS.

Furthermore, we do not agree with the statement in the introduction that MELAS is characterized by myelopathy and respiratory insufficiency.[1] Myelopathy is not a typical phenotypic feature of MELAS and has been only rarely reported in these patients.[3] Myelopathy is more common in leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL), a syndromic MID, in which myelopathy is a pathognomonic feature of the disease.[4] Respiratory insufficiency may develop in MELAS only in the case of affection of the respiratory muscles, the brainstem, or the lungs.

It is contradictory to state that the diagnosis of MELAS was genetically confirmed and to state, at the same time, that the causative mtDNA variant is unknown in patient 2.

A further limitation of the study is that the heteroplasmy rate of the variant m.3243A>G in patient 1 was not provided. Heteroplasmy rates are usually high in clinically affected tissues. There are indications that high heteroplasmy rates can be found in cochlea specimens of deceased patients with MELAS.[5] They can vary significantly between tissues and patients and are responsible for the phenotypic heterogeneity of MID patients.

We disagree with the statement that patients with a poor prognosis are not prudent to receive a cochlea implant. Assessing the prognosis in MELAS patients is difficult and relies not only on heteroplasmy rates but also on mtDNA copy numbers, haplotype, the family history, and whether the causative variant occurred sporadically or had been inherited.

We also disagree with the statement that the progression of hearing impairment is related to the severity of the mitochondrial disorder. Due to the peculiarities of mitochondrial genetics, there are patients carrying the m.3243A>G variant who present with hearing impairment without other phenotypic features or hearing impairment is associated with only mild clinical manifestations.

We should be told why it took 1 year for patient 1 to objectify a positive effect of the cochlea implant.

Overall, the interesting study has some limitations and inconsistencies which challenge the results and their interpretation. Addressing these issues would strengthen the conclusions and could increase the status of the study. Since MELAS manifests in the brain and since cochlea implants forbid cerebral MRI, it is crucial to perform cerebral MRI prior to the implantation.

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## Author's Response

We are grateful for the interest in our article and for taking the time to write the letter to the editor. Below we have address the queries highlighted.

The statement in the abstract "Melas is the most common mitochondrial disorder" was taken from Handzel et al., 2020[1] who states "MELAS syndrome is the most common maternally inherited mitochondrial disease." After reviewing this we correct our initial abstract to MELAS is one of the more common mitochondrial syndromes, but pathogenic mtDNA variants are a more common cause of disease.

The statement in the introduction that MELAS is characterised by myelopathy and respiratory insufficiency was taken from Yasamura et al., 2003[2] who states "As the name suggests, the main features are mitochondrial myelopathy, encephalopathy, lactic acidosis and stroke-like episodes." We are happy to remove myelopathy from our list but feel respiratory issues are appropriately mentioned.

The letter to the editor felt it is contradictory to state that the diagnosis MELAS was genetically confirmed and to state at the same time that the causative mtDNA variant is unknown in patient-2. Upon review we can see that this may appear contradictory and wish to clarify that the causative mtDNA variant is unknown to the authors in Case 2. Data for the two cases was collected retrospectively from patient report and available medical records. In Case 1 the variant was recorded in the patients medical records however heteroplasmy rate of the variant m.3243A>G in patient-1 was not available to the authors. In Case 2, the patient confirmed the diagnosis of MELAS was made following genetic testing but they were unable to recall the variant. The results of this testing was not available to the authors.

The statement that patients with a poor prognosis are not prudent to receive a cochlear implant was taken from Chinnery et al., 20003[3] who state "it may not be prudent to invest in a cochlear implant in a patient with very poor prognosis from the outset". Of course, this has to be reviewed on a case by case basis, depending on the severity of the disease, and the CNS involvement level. This statement should be added.

The statement that the progression of hearing impairment is related to the severity of the mitochondrial disorder is referenced from Di Stadio et al., 2018[4] who state "Hearing disorders in MELAS are progressive and related to the severity of the mitochondrial disorder". We have further reviewed Di Stadio et al.[4] and do not feel the references they use substantiate this claim. We agree there is a spectrum of hearing loss with MELAS from mild to profound and there does not appear to be a strong correlation with heteroplasmy levels or other clinical symptom severity.

The letter asks why it took 1y for case-1 to objectify a positive effect of the cochlear implant. Within the clinical pathway our patients undergo several objective assessments of their cochlear implant outcomes. As part of commissioning requirements a battery of tests is completed at the 1 year stage with every patient. At other stages of the care pathway the number of tests completed at each visit is influenced by several factors. In case 1 aided soundfield testing was completed 2 weeks, 1 month, 2 months, 4 months and 12 months post switch-on. Average aided results of 25dB HL were recorded consistently over all of the visits. ASSE phoneme discrimination was first tested after 2 weeks, and the patient scored (20/20) 100%. Rather than reporting multiple test results for each case, to keep the article succinct, the authors chose to report the results from the 1 year review.

We hope this adequately answers the letter to editor queries, and appreciate the interest in our case reports.

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