

ORIGINAL RESEARCH

Temporal bone histopathology in MELAS syndrome

Ophir Handzel¹  | Omer J. Ungar² | Dan J. Lee³ | Joseph B. Nadol Jr³ 

¹Cochlear Implant Center, Department of Otolaryngology/Head, Neck & Maxillofacial Surgery, Tel-Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Israel

²Department of Otolaryngology/Head, Neck & Maxillofacial Surgery, Tel-Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Israel

³Otopathology Laboratory, Department of Otolaryngology-Head and Neck Surgery, Massachusetts Eye and Ear, Harvard Medical School, Boston, Massachusetts

Correspondence

Ophir Handzel, The Cochlear Implant Program, Department of Otolaryngology Head and Neck and Maxillofacial Surgery, Tel-Aviv Sourasky Medical Center, Tel-Aviv University, 6 Weizmann St., Tel-Aviv 6423906, Israel, Sackler Faculty of Medicine, Tel-Aviv University.
Email: ophir.handzel@ozen.co.il

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Abstract

Objectives: Describe the histopathology of the temporal bones in MELAS (myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) syndrome. The syndrome results from a known point mutation in mitochondrial DNA.

Methods: Histopathology analysis of a pair of temporal bones from the oldest surviving MELAS syndrome temporal bone donor. Histopathologic findings were correlated with known premortem clinical data.

Results: The inner ears showed severe but incomplete atrophy of the stria vascularis for the length of the cochleae. In contrast, the organ of Corti and inner hair cells appeared intact with some loss of outer hair cells. Other than moderate loss at the basal turn, spiral ganglion cells numbers were normal. The vestibular neuroepithelium was mostly normal with the exception of moderate degeneration of the macula sacculi and partial collapse of the saccular wall on the right. The cerebral cortex had infarct-like lesions with adjacent gliosis.

Conclusion: This is an analysis of the oldest patient with MELAS syndrome to date, an addition to only two previously published patients. It supports the notion that hearing loss is a result of dysfunction of the stria vascularis and not loss of hair cells or neurons. Patterns of vestibular pathology are in agreement to in-vivo measurements. These findings support auditory rehabilitation with cochlear implants and may be relevant to hearing loss due to other mitochondrial mutations.

Level of evidence: 4

KEYWORDS

genetics, MELAS syndrome, otology, otopathology, sensorineural hearing loss

1 | INTRODUCTION

Hearing loss is common, and genetic abnormalities are a frequent cause. Mutations in mitochondrial DNA (mtDNA) are responsible for close to 1% of prelingual congenital deafness and approximately 5% of post lingual hearing loss in Caucasians.¹ Mutations in mtDNA can cause both syndromic and isolated hearing loss.

MELAS is a syndrome typified by mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes.² Although a number of mutations can cause the syndrome, the majority (80%) are caused by a point mutation of alanine and guanine at 3243.³ MELAS syndrome is the most common maternally inherited mitochondrial disease.

The goal of this article is to describe the histopathology of the temporal bones, in a patient with MELAS syndrome, and discuss the broader implications on mitochondrial hearing loss.

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2 | METHODS

2.1 | Temporal bone acquisition

Temporal bone specimens were obtained in compliance with Human Subject Assurance No. FWA00006221 (exemption 4) from the Massachusetts Eye and Ear Infirmary.

2.2 | Temporal bone preparation and light microscopy

Both temporal bones are available for study. The time elapsed between the death of the donor to tissue fixation was 21 hours. The specimens were fixed in 10% formalin, decalcified with ethylene diamine tetra-acetic acid (EDTA), dehydrated in graded alcohols, and embedded in celloidin. Serial sections 20 μ m thick were cut in the axial (horizontal) plane. Every tenth section was stained with hematoxylin and eosin (H&E) and mounted on glass slides. For analysis and quantification of cellular elements two-dimensional reconstruction of the cochlea was done. Neurons were counted by identification of their nucleoli under 400 \times magnification. A correction factor of 0.9 was applied to the counted number of neurons to account for the possibility of double counting in two consecutive sections.⁴

3 | RESULTS

3.1 | Clinical history

A 42-year-old man first experienced hearing loss at the age of 25. The hearing loss was progressive and worse on the right. He used hearing aids, but an audiogram is not available. None of nine other siblings had a history of hearing loss or other mitochondria-related diagnoses. At the

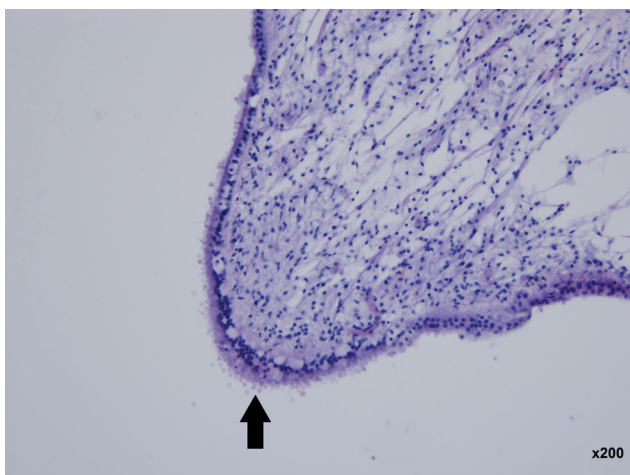


FIGURE 1 Post mortem changes: vesiculation in the neuroepithelium of the ampulla of the lateral semi-circular canal. Left ear. (hematoxylin and eosin staining $\times 200$ magnification)

age of 40, he developed systemic illness with headache, malaise, and fatigue for a week, followed by an acute onset of expressive aphasia. His language gradually improved. MRI demonstrated a left temporoparietal lesion and later subsided. The following month he had a tonic-clonic seizure. These manifestations were preceded by subtle changes in personality and behavior. The combination of these symptoms with the patient's short stature and family history of type 1 diabetes raised the suspicion for MELAS syndrome. He tested positive for mtDNA mutation 3243A>G. He died at the age of 42 of respiratory failure.

3.2 | Histopathological findings

Preservation of the temporal bones was good despite the 21 hours elapsed between death and fixation of tissue. Minor vesiculation of

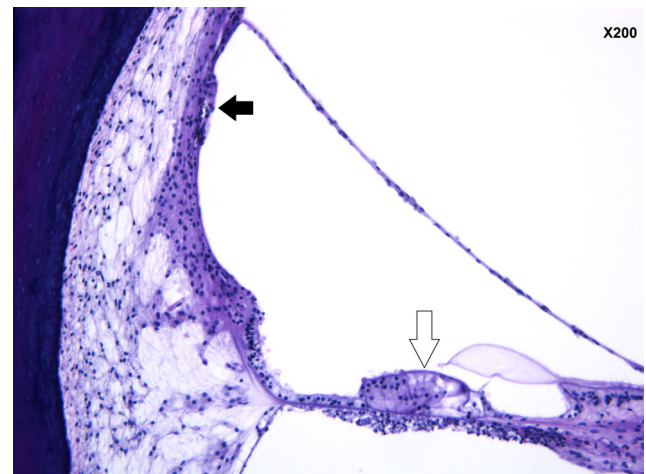


FIGURE 2 Severe atrophy of the stria vascularis (black arrow). Preservation of the organ of Corti (white arrow). Left ear, ascending basal turn. (hematoxylin and eosin staining $\times 200$ magnification)

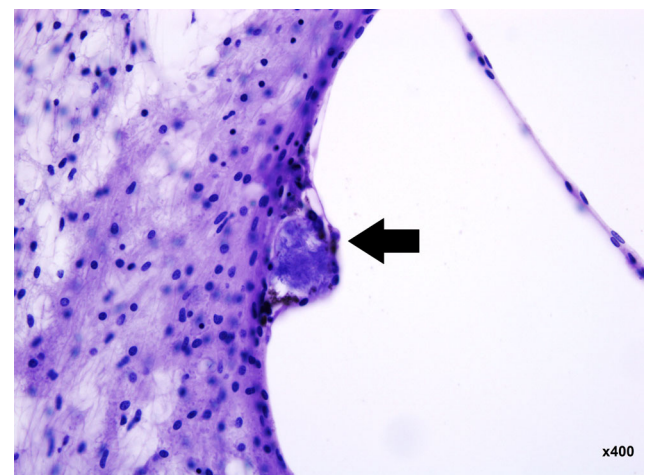


FIGURE 3 Basophilic inclusion cyst in the stria vascularis of the ascending basal turn of the left ear. (hematoxylin and eosin staining $\times 400$ magnification)

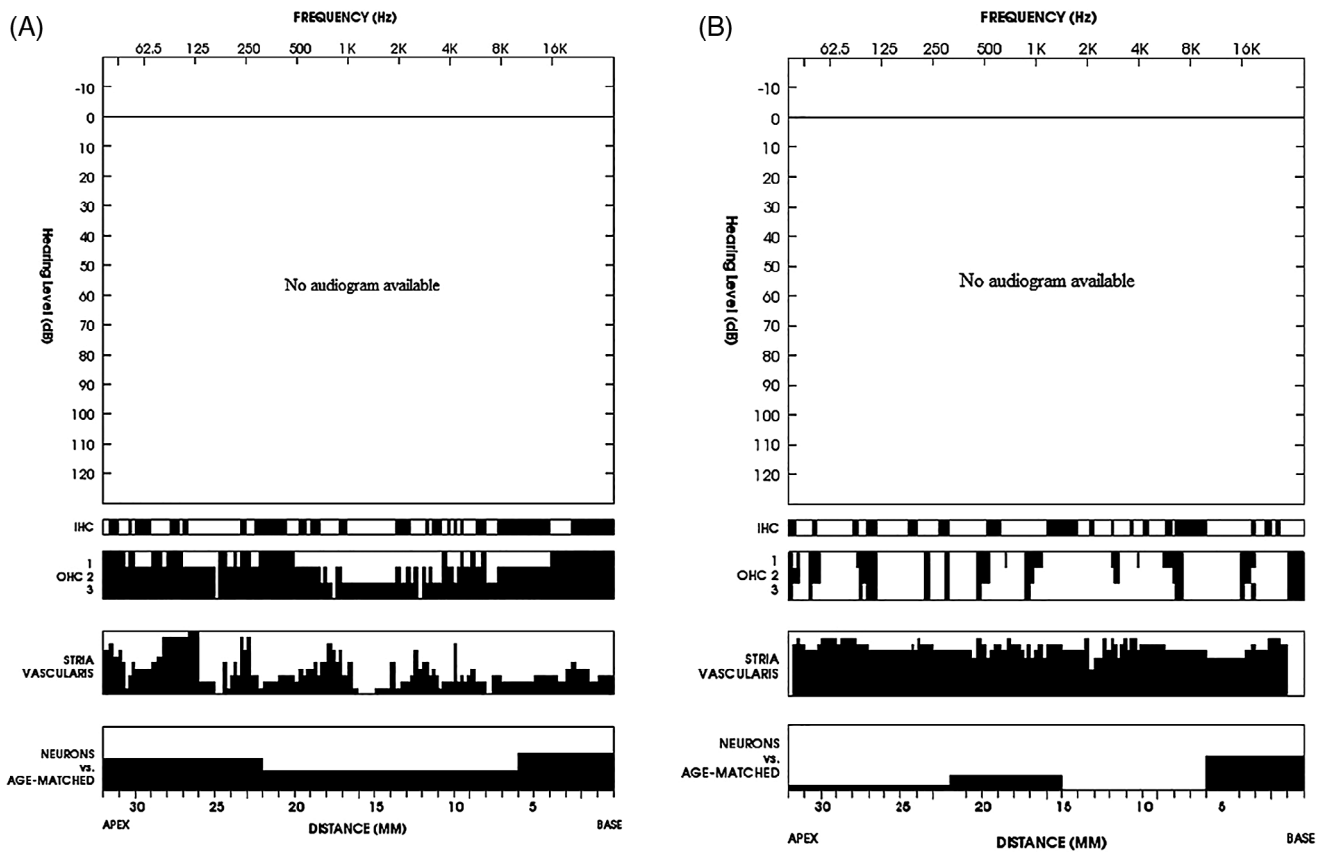


FIGURE 6 Cytocochleogram of the right (A) and left ear (B). Graphic display of the findings: atrophy of stria vascularis was the most prominent pathology. Black symbols a missing cochlear component

Hearing loss is present in 30%-75% of patients with MELAS syndrome.⁸ It typically presents before the age of 40 and can vary from mild loss to severe loss meeting the criteria for cochlear implantation. About 20% of patients with MELAS syndrome have severe to profound sensorineural hearing loss. Hearing loss is symmetric, commonly starts at the high tones progressing to involve the mid- and low tones. However, it can be the same across frequencies. Hearing loss can be the first and initially the only manifestation of MELAS syndrome. The diagnosis of a mitochondrial cause for hearing loss can have several clinical implications such as avoidance of exposure to noise and aminoglycosides. In the case presented hearing loss was the sole symptom of MELAS syndrome for more than a decade. In a family with no history of either hearing loss or mitochondrial disease, a patient with such long duration of deafness is unlikely to be identified with mitochondrial deafness. The patient died at the age of 42 years. Previous descriptions of temporal bone histopathology are of patients who died at the age of 23 and 30 years, making the reported case the oldest one with MELAS syndrome.^{9,10}

The main histopathology finding in the studied case is severe atrophy of the stria vascularis in both cochleae with preservation of the organ of Corti and most spiral ganglion neurons. Spiral ganglion population exceeded 50% of the normal age-matched complement even in the worse hearing right ear. By itself, this level of neuronal population usually is not associated with pure-tone thresholds shifts.

These observations were seen in two previously reported temporal bones.^{9,11} Why do the various cochlear cells demonstrate such a wide variability in the impact of the mutation on their survival? Processed temporal bones were used to correlate the mutation rate in various cochlear cells with the extent of damage seen. LASER capture can allow harvesting of a single cell from the cochlea. The rate of mutated mtDNA as a fraction of the total mtDNA in cochlear cells was measured. No correlation between the rate of mutated cell and cellular damage was detected.^{9,11} Conceivably, different cochlear tissues have different energy needs, and the stria vascularis could be more sensitive to mitochondrial injury as compared to other cochlear cells. Alternatively, damage to the stria vascularis may not be a primary event but rather a secondary one. The production of cytochrome oxidase complex 4 is modified, resulting in an increase in ROS that induce cochlear damage. ROS acts differently on different structures of the cochlea, possibly explaining the variability in intracochlear damage.

Treatment of mitochondrial disease is challenging. Deficiency in coenzyme Q10, is the only condition that is ameliorated with dietary supplements. For MELAS, arginine and citrulline can provide some symptomatic relief. The patient reported herein was treated with these supplements.¹² Both arginine and citrulline act as nitrous oxide precursors. Their administration can result in increased nitrous oxide availability and may lessen the stroke-like episodes typical of MELAS

syndrome. While great advancements are made with treatment of nuclear genetic defects, gene therapy for suppressing or replacing mutated mtDNA is not feasible at this stage. Hearing loss in MELAS can be helped with hearing aids. If hearing worsens to nonaidable level, cochlear implantation can be considered. Despite the ubiquitous insult to the central nervous system in MELAS syndrome, cochlear implantation can be effective.¹³⁻¹⁶

Based on the observed findings of good preservation of auditory neurons effective stimulation with a cochlear implant could be expected. This finding may have implications for patients with hearing loss associated with other mitochondrial disease.

In summary, MELAS syndrome is caused by a point mutation in mtDNA. The most significant cochlear pathology is atrophy of the stria vascularis with good preservation of the organ of Corti and spiral ganglion neurons. These observations have implications for the rehabilitation of hearing loss in this and other mitochondrial diseases.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

ORCID

Ophir Handzel  <https://orcid.org/0000-0002-6905-3034>

Joseph B. Nadol Jr  <https://orcid.org/0000-0002-4033-3104>

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