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# Sensorineural hearing loss in MELAS syndrome

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**Abstract**
A case of sensorineural hearing loss (SNHL) in MELAS syndrome, a variety of mitochondrial cytopathy, is presented. Mitochondrial cytopathies have gone almost unreported in the otolaryngology literature, despite evidence from a recent review that about 60 per cent of such patients suffer from SNHL (Gold and Rapin, 1994). The same review revealed that only one of 117 case reports in the period 1984–1993 contained an audiogram (Swift and Singh, 1988), and none presented sequential audiograms. However, audiometry has since been published on 23 members of a family with a mitochondrial point mutation causing only sensorineural hearing loss with no other symptoms (Vernham *et al.*, 1994). We present a case of mitochondrial cytopathy three years after diagnosis with two sequential audiograms.

**Key words: Cytopathy, mitochondrial; Hearing loss, sensorineural**

## Introduction

Mitochondrial cytopathies are a group of rare congenital disorders of mitochondrial DNA (mtDNA). Familiar to neurologists, this group of diseases has received scant attention in the otolaryngology literature, with some notable exceptions (Swift and Singh, 1988; Gold and Rapin, 1994; Hartley and Ascott, 1994; Vernham *et al.*, 1994). This class of diseases includes Kearns-Sayre syndrome, as well as the so-called 'MERRF' (mitochondrial encephalopathy with ragged red fibres) and 'MELAS' (mitochondrial encephalopathy with lactic acidosis and stroke-like episodes) syndromes. These classifications are based on clinical and/or histological findings, however, considerable overlap of the syndromes is now recognized. The responsible genetic mutations were identified as recently as 1988 (Bindoff *et al.*, 1994).

Patients with a mitochondrial cytopathy may come to the otologist because of SNHL, which is known to be associated with about 60 per cent of cases (Gold and Rapin, 1994). The natural history is unknown, although our patient and those reported elsewhere experience steady deterioration of their symptoms over years (Vernham *et al.*, 1994).

According to the review by Gold and Rapin (1994), literature regarding SNHL may be biased by the delayed presentation which is associated with these slowly progressive disorders.

Mitochondrial cytopathies share several common features. They result from a genetic defect (deletion, point mutation, or duplication) of mtDNA which results in respiratory chain dysfunction. Animal studies reveal that the cochlea has high cellular energy demands, particularly in its basal turn, which may explain the susceptibility of the cochlea to this disease (Schneider *et al.*, 1987).

Unlike the Kearns-Sayre syndrome, which is usually sporadic, MELAS syndrome is usually inherited from maternal mtDNA (Harding, 1996). Like most of the mitochondrial cytopathies it is inherited from maternal mtDNA derived from the ovum; sperm do not contain mitochondria in their heads so paternal mtDNA is not transmitted to the embryo. Therefore, children of either sex can potentially inherit the disease, but only females can pass it on.

Although the pathophysiological basis of MELAS remains unclear, a point mutation in the tRNA gene of mtDNA has been identified in 80 per cent of patients (Harding, 1996).

## Case report

A 38-year-old woman was referred to a neurologist because of her eight-year history of progressive bilateral ptosis. Eight years earlier she had developed non-insulin-dependent diabetes mellitus and she had a significant obstetric history including four miscarriages, two neonatal deaths and one live birth. Bilateral ptosis and bilateral internuclear ophthalmoplegia with limitation of adduction of both eyes were elicited. There were pigmented areas on both retinae and generalized musle wasting. Height was 147.5 cm and intellect was normal. On closer questioning she admitted to a two-year history of progressive hearing loss, worse on the right. Mitochondrial cytopathy was suspected. Confirmation was made by muscle biopsy, which demonstrated the so-called 'ragged-red fibres'. These represent accumulated mitochondria adjacent to the cell membrane, giving it a ragged edge that stains red with the Gomori trichrome method (Bindoff *et al.*, 1994). MELAS syndrome was subsequently diagnosed by the presence of the characteristic point mutation.

An ENT opinion was later requested. The patient denied any history of familial hearing loss, childhood ear infections, noise trauma, tinnitus, or vertigo. Otoscopy was normal, as were cerebellar tests. Weber's tests localized to the left. The pure-tone audiogram is shown in Figure 1. Our case did not demonstrate the preponderance of the hearing loss for high frequencies seen in other reports

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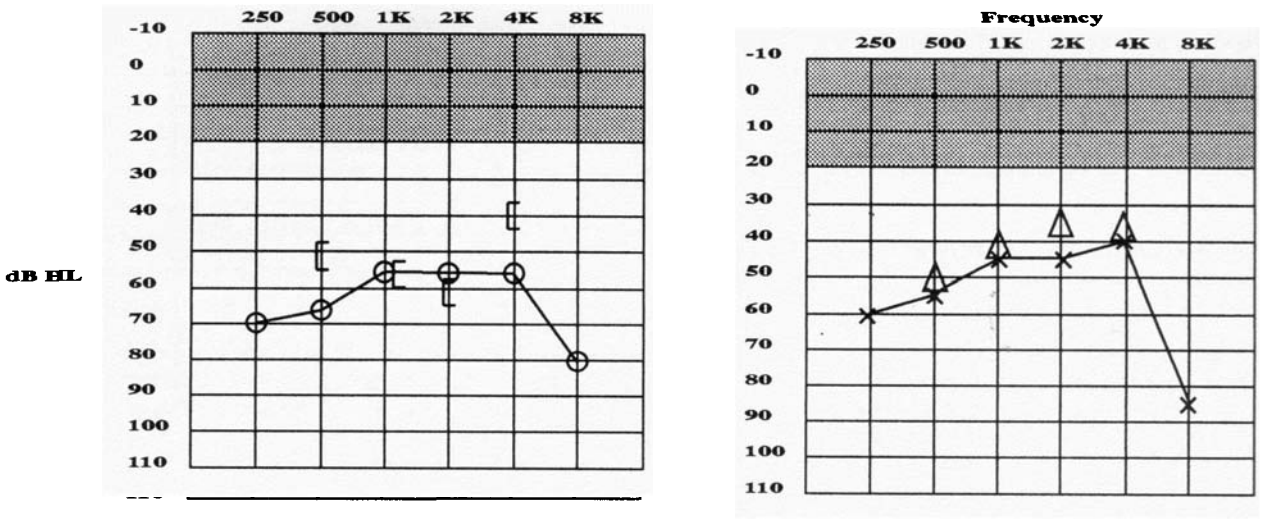


FIG. 1
Pure-tone audiogram of a 39-year-old woman diagnosed one year previously with SNHL resulting from mitochondrial cytopathy.

(Swift and Singh, 1988); Vernham *et al.*, 1994). A left AM520 hearing aid was fitted.

One year later the patient complained of deterioration of her hearing but pure-tone audiometry was essentially unchanged (Figure 2). Because of the slight asymmetry, an ABR test was arranged. Repeatable and symmetrical responses were obtained. In view of her greater difficulty with hearing, the AM520 hearing aid was changed to an AM260PP. Speech audiometry confirmed impaired discrimination. Optimum discrimination scores R–73 per cent and L–97 per cent. Half peak level elevation (threshold) was R–60 dB and L–35 dB.

## Discussion

This woman manifests many of the typical signs of MELAS syndrome: weakness, ptosis, ophthalmoplegia, SNHL, diabetes mellitus, multiple miscarriages, and short stature, as well as the characteristic ragged-red fibres and point mutation. However, she lacked a history of many classical symptoms such as stroke-like episodes of childhood onset (consisting of migrainous headache, vomiting and visual disturbances with progressive neurological deficit), lactic acidosis, peripheral neuropathy or ataxia. Additionally, she demonstrated retinal pigmentation, which is more often associated with the Kearns-Sayre variety of mitochondrial cytopathy.

Symptomatic overlap in this patient underlines the somewhat academic nature of her diagnosis with MELAS. Mitochondrial cytopathies, at present, are difficult to categorize, owing to limited knowledge of their aetiologies. Until a better understanding is achieved, diagnoses based solely on clinical, biochemical or genetic data should be regarded as inadequate, and a combination of all three sources should be sought (Bindoff *et al.*, 1994).

Vernham *et al.*, described a large maternal lineage with a specific mitochondrial DNA point mutation associated with hearing loss but no other features of mitochondrial disease. They found that the amount of mutant DNA bore no relationship to the severity of the hearing loss.

Of the 27 cases of MELAS in the review of Gold and Rapin (1994), 19 (70 per cent) had SNHL. Since this disease frequently begins in childhood (Harding, 1996), otolaryngologists can play an important role in rehabilitating these patients, thereby preventing developmental delay.

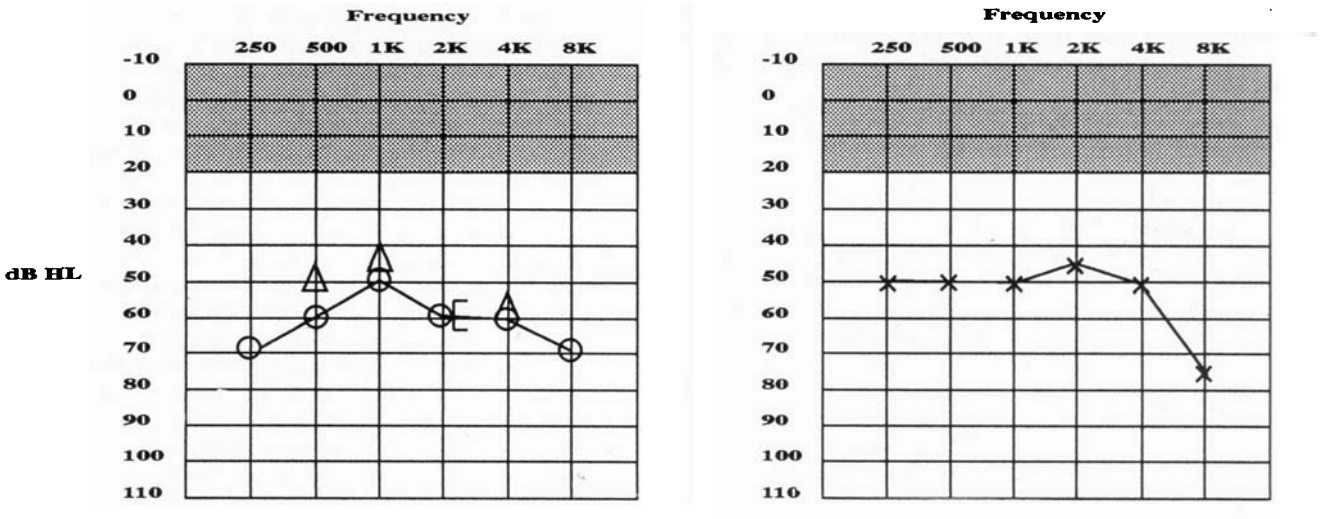


FIG. 2
Pure-tone audiogram of same patient at one-year follow-up (age 40).

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When SNHL is the presenting complaint, otolaryngologists can facilitate early diagnosis and referral to the neurologist, diabetologist or genetic counsellor.

Mitochondrial cytopathy has limited scope for treatment at present. Therapies such as enzyme replacement (eg. ubiquinone) and electron acceptors (eg. vitamin C) await formal evaluation. Gene therapy may offer hope for these patients.

## Conclusion

A case of SNHL associated with the MELAS variety of mitochondrial cytopathy is presented. To our knowledge, this is the first such case in the otolaryngology literature to include sequential audiograms. Although mitochondrial cytopathies are presently regarded to be rare, ongoing advances in identifying genetic defects associated with these disorders may reveal a higher prevalence. In any case, mitochondrial cytopathies need to be considered by the otologist in forming a diagnosis of sensorineural hearing loss, particularly in cases which present before 50 years of age.

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