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REVIEW

The MELAS syndrome. Review of the literature: the role of the otologist

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The MELAS syndrome. Review of the literature: the role of the otologist

The mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome is a rare congenital disorder of mitochondrial DNA (mt-DNA). Patients with this syndrome may present to the otolaryngologist with sensorineural hearing loss (SNHL), which is genetic in origin. A high index of suspicion is required because this hearing loss is part of a syndrome for which early diagnosis and intervention is required.

Keywords *MELAS syndrome* *sensorineural hearing loss* *mitochondrial cytopathy*

There are hundreds or, some say, up to a thousand genes that are involved in the development of the inner ear.[1] Hearing loss is one of the most common disabilities in man. At least a third of late onset hearing loss is believed to be genetic in origin.[2] Of the hundreds of different genetic conditions causing sensorineural hearing loss (SNHL), at least 30% are syndromic.[3] Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS)[4] syndrome is one of the few syndromes described which include mitochondrial cytopathy and hereditary deafness; others are Kearns–Sayre syndrome,[5] myoclonus epilepsy with ragged red fibres (MERRF)[6] and maternally inherited diabetes and deafness (MIDD) syndrome,[7] which is almost always because of MELAS mutation.

Pathophysiology

Mitochondria have their own DNA (mt-DNA). This is mainly maternally inherited, because sperm does not usually contain mitochondria in their heads. The sperm head does carry mitochondria, but paternal transmission, although recently reported, is probably very rare.[8] Therefore, children of either sex can inherit the disease, but children of an affected mother are always affected. Mitochondrial cytopathies can be caused by several mt-DNA mutations in transfer RNA (t-RNA) genes.[9] MELAS is caused by a relatively common point mutation in the leucine (UUR) t-RNA gene at locus 3243 of the mt-DNA L-strand.[10] It was first described by Pavlakis *et al*. in 1984 followed by Goto *et al*. in 1990, and is regarded as the most frequent point mutation. In a Finnish study, the prevalence is greater than 16 in 100 000.[11]

Bilateral hearing loss is a well-recognized feature of mt-DNA disease.[12] The common histopathological finding is atrophy of the stria vascularis.[2] Normal hearing is dependent upon the stria vascularis, which is responsible for providing the ionic environment necessary for sound signal transduction.[13] In 1998, Sue *et al*. studied 18 patients with the MELAS A3243G point mutation from four different kindreds and agreed that strial degeneration is a common finding. Stria vascularis has a high metabolic rate and its cells do not divide.[14] Therefore, when abnormal mitochondria accumulate in the stria, they cause dysfunction and eventually cell death.[15]

Clinical features of hearing loss and predisposing factors

Mitochondria are responsible for the energy-producing process of oxidative phosphorylation. Cells may contain both mutant and normal copies of mt-DNA.[9] If the normal cells can provide adequate energy, normal function is preserved.[9] If they cannot provide energy, especially for high energy-demanding organs like skeletal muscles, heart and brain, then symptoms of dysfunction occur. The clinical features of mt-DNA disease

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can range from asymptomatic or oligosymptomatic individuals to severely affected patients with central neurological complications at a young age.[16] Hirano and Pavlakis divided clinical characteristics into three categories: cardinal (more than 90% of patients), frequent (≈ 90%) and other manifestations (less than 45%).[17] Hearing loss (together with short stature, headaches, nausea or vomiting, hemiparesis or hemianopsia and elevated cerebrospinal fluid protein) was classified as one of the frequent manifestations. In their study of 110 MELAS patients, hearing loss was present in 75% of the cases.

Mitochondrial disorders usually first manifest in tissues with high metabolic demands, such as nerves and muscles. This places the complete auditory pathway at risk and explains why hearing loss is a common finding in mitochondrial disease.[18] Deschauer *et al*. studied 52 patients with mitochondrial encephalomyopathies, from which the A3243G mutation was identified in 16 patients. The most frequent symptom in the last group was hearing loss, found in 11 of the 16 patients on clinical examination. In all five patients with normal hearing on clinical examination, audiometry revealed subclinical hearing loss. In four of these patients, hearing loss was more pronounced than the expected mean hearing impairment of that age group.[19] Chinnery *et al*., in a meta-analysis, found deafness as a clinical feature in 44% of patients with A3243G mutation.[20] The spectrum of hearing loss because of mitochondrial defects has been recently studied by the same team, with otoacoustic emissions, auditory brainstem responses (ABR) and magnetic resonance imaging (MRI) in 23 patients. Hearing loss was present in 8 out of 10 patients. The findings were consistent with a predominantly cochlear origin for the hearing deficit.[21]

In the majority of MELAS patients, an abrupt, stepwise loss of hearing occurs usually in association with stroke-like episodes.[15,21] MELAS patients will present to the otolaryngologist with SNHL. This is usually gradual in onset and can affect the higher frequencies.[22,23] In some cases, the history of a young age at presentation, stepwise progression and partial recovery can distinguish this genetic SNHL from presbycusis.[24] What is of particular interest is that the hearing loss is often very prominent in many oligosymptomatic patients with MELAS or other mt-DNA defects.

Exacerbating factors for MELAS and almost all mitochondrial cytopathies are unusual physical exertion, extremes of temperature, hypoglycaemia, stress and infection with fever, probably because of increased metabolic demands.[15] The correlation of upper respiratory tract infections including recurrent otitis media with effusion (OME) and other common infections as trigger factors for neurodegenerative events is well known.[25,26] In a study of 40 patients with definite mitochondrial disease, Edmonds *et al*. found that intercurrent infection was a precipitant of neurodegenerative events in 72% of the patients.[18]

Diagnosis and investigations

Diagnosis is based on a high index of suspicion, especially for the non-specialist, together with a combination of clinical, biochemical, radiological and genetic tests.[27] Although beyond the specialist interest of otolaryngology, we strongly believe that otolaryngologists should be able to recognize or at least suspect the symptoms associated with 'mitochondrial deafness', and refer to the appropriate specialists.

Hirano *et al*. proposed three diagnostic criteria for MELAS: (i) stroke before the age of 40, (ii) an encephalopathy characterized by seizures, dementia or both and (iii) a blood lactic acidosis or ragged red fibres in skeletal muscle or both.[25] They also suggested that normal early development, recurrent headaches or recurrent vomiting added further weight to the clinical diagnosis. Unfortunately, many MELAS and other 'mitochondrial' patients do not always present in the same way, and therefore, a high index of suspicion is required. Certain clinical features, especially when combined, are strongly suggestive of mitochondrial disease. The combination of myopathy and CNS involvement, such as deafness, is highly suggestive of a metabolic defect. Birth and development may be normal before the onset of recurrent metabolic crises, which are often associated with viral illnesses.[16]

If the clinical picture is suggestive of MELAS, blood should be sent for molecular genetic analysis. This should reveal the characteristic for the MELAS syndrome, A3243G point mutation. If this proves non-diagnostic, then a definitive diagnosis can be made by fresh muscle biopsy with specimens examined for histochemical evidence of a mitochondrial defect. This demonstrates the so-called 'ragged-red fibres', a subsarcolemmal accumulation of mitochondria, giving it a ragged edge that stains red with the Gomori trichrome method.[27,28] Other diagnostic studies are testing blood and cerebrospinal fluid for lactate and pyruvate; these patients often suffer from lactic acidosis, and therefore, the serum lactic acid level will often be increased and so will the lactate-to-pyruvate ratio. However, many neurological events like strokes and seizures may increase lactate concentrations, and these results should be interpreted with caution and in conjunction with the clinical suspicion.[16]

Several audiological and neuro-otological tests are available to the otolaryngologist: pure tone audiometry, speech discrimination testing, acoustic reflexes, tympanometry, auditory brain stem responses, electrocochleography and otoacoustic emissions to assess cochlear involvement. MRI and computerized tomography (CT) of the brain can also be used to assess the possibility of retrocochlear disease.[24] Sue *et al*. showed that the late loss of acoustic reflexes and the preservation of speech discrimination suggest that the MELAS SNHL is of cochlear rather than neural origin. This is confirmed in a more recent study by Chinnery *et al*. In this study, the vast majority of patients noted symptoms before the age of

45 years, and the severity of the hearing loss correlated with the percentage of mutated DNA.[21]

Management

Management is multidisciplinary, and according to Chinnery and Turnbull, falls into four groups: (i) guidance about the future, the prognosis and the chance of transmitting the genetic defect; (ii) regular follow-up over many years may prevent the known complications of MELAS; (iii) intervention, either surgical or along with practical assistance, with mechanical aids and social support and (iv) 'anecdotal' treatments, e.g. vitamins, may be of some benefit.[29] Avoidance of all the exacerbating factors, especially infection, is crucial because, even when minor, infection can trigger a new attack of symptoms.[18] Unfortunately, in the real world, it is virtually impossible to prevent infection. The first signs of infection should be treated aggressively and without any delay with empirical antibiotics and change to appropriate antibiotics based on culture and sensitivity results. Recurrent OME should be treated with insertion of long-term ventilation tubes.

There are certain anaesthetic considerations that need to be addressed prior to an operation on a MELAS patient.[30] The elevated serum lactate levels often found in these patients can lead to acidosis and anaerobic glucose metabolism. Adequate oxygenation and gas exchange with careful monitoring of glucose levels are essential to avoid acidosis. Malignant hyperthermia is associated with muscle abnormalities, and although not described so far in the literature, it is a potential anaesthetic complication of MELAS patients, and therefore, any known triggering drugs should be avoided. Cardiomyopathies and conduction defects can be found in MELAS patients, this is why a preoperative electrocardiogram and intraoperative electrocardiographic monitoring is necessary. Careful titration of opioids and sedatives is essential to avoid further decrease in ventilatory response.[31] Supportive treatment with vitamins and corticosteroids maybe of benefit.[32,33]

The role of the otologist and audiologist falls mainly in the third treatment group. Intervention in the form of cochlear implantation or a hearing aid can provide great comfort for the MELAS patient, can improve the quality of life and aid the rehabilitation process. Cochlear implantation can also give excellent results, provided there are intact neural components to function. Over the recent years, there have been a few cases reported in the literature of successful cochlear implantation in patients with MELAS syndrome.[24,34,35] Cochlear implantation is considered for profoundly deaf patients. This implies hearing thresholds of 100 dB hearing loss (HL) or worse for frequency range of 125–8000 Hz, with aided hearing thresholds worse than 60 dB for frequency range of 250–4000 Hz and scoring less than 30% in a test of sentence discrimination, using their hearing aids and without lip reading.[34]

Conclusion

Sensorineural hearing loss is a common presentation in an otolaryngology clinic. MELAS syndrome and the rest of the mitochondrial cytopathies can present with a variety of symptoms, but they occasionally present with SNHL as their first manifestation. The history of neuromuscular setbacks associated with infection and the presence of multiorgan dysfunction are clues that mitochondrial cytopathies may be the cause of the hearing loss. It is important for the otolaryngologist to maintain an awareness of MELAS syndrome and other mitochondrial cytopathies in the differential diagnosis of SNHL. This way he can play an important role in the successful rehabilitation of these patients.

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