Rapidly Progressive Bilateral Sensory Neural Hearing Loss as a Presentation of Mitochondrial Neurogastrointestinal Encephalomyopathy

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A 23-year-old woman presented to the department of Otolaryngology–Head and Neck Surgery at Rambam Medical Center because of a rapidly progressive bilateral sensory neural hearing loss (SNHL) that worsened 3 days before presentation.

The patient had been hospitalized and treated a month before, at another institution, because of sudden onset bilateral SNHL (right > left), which developed after an acute upper respiratory infection.

At that time, she was treated with oral steroids and carbogen inhalations and discharged 5 days later with no improvement. Her audiogram at that time showed bilateral SNHL (left ear: average loss at speech frequencies of 27 dB; right ear: average loss at speech frequencies of 70 dB).

At presentation to our department, a detailed history revealed no previous exposure to loud noise, no prior ear infections or surgery, and no history of chronic diseases, tinnitus, or vertigo; she was not being treated with any known ototoxic medications.

Family history revealed that her parents were first cousins and that her brother died at the age of 17 because of pancreatitis and an obscure neurologic disease. There was no family history of hearing loss.

On physical examination, mild hirsutism and bilateral ptosis were noted. Her intellect was normal. All deep tendon reflexes were absent; there was mild general muscle wasting and polyneuropathy. Otoscopy was normal; cranial nerve function was preserved. There were no vestibular or cerebellar deficits or nystagmus.

By this time, the audiogram showed an average loss at speech frequencies of 60 dB in the left ear and profound hearing loss (>90 dB) in the right ear. Routine laboratory tests for sudden SNHL were performed and included complete blood count, which was normal except for mild macrocytosis.

Erythrocyte sedimentation rate, thyroid function tests, electrolytes, glucose, and coagulation profiles were all normal. Lactate dehydrogenase, γ-glutamyl transpeptidase, and alanine amino transferase were all slightly elevated. A chest radiograph and echocardiogram were both normal.

Despite the elapsed time interval from onset treatment for sudden SNHL, treatment was attempted and included carbogen inhalations, intravenous magnesium sulfate, and oral steroids. Despite this treatment, her condition worsened, and serial audiograms showed a rapid progressive deterioration over 3 days time. She progressed to a bilateral profound SNHL.

A brain stem–evoked response threshold was performed and showed an absence of waves I, III, and V and a hearing threshold of more than 95 dB on the right and an absence of waves I and III and a hearing threshold of 95 dB on the left.

A magnetic resonance imaging (MRI) of the brain was performed (Fig 1). The MRI shows diffuse plaques seen as high signal intensity areas within the white matter of the brain, particularly in the periventricular area. These imaging findings raised the possibility of multiple sclerosis (MS) or a metabolic disorder including a mitochondrial disorder. The patient was referred for a neurologic and a genetic consultation. Repeated detailed history and physical ex-
amination were performed. New information about the patient’s deceased brother revealed that he had been repeatedly hospitalized for pancreatitis, recurrent intestinal obstruction, and progressive polyneuropathy. The actual cause of his death is unknown. Laboratory screening of the patient’s serum and cerebrospinal fluid (CSF) for oligomeric antibodies was performed, and the findings were not consistent with the diagnosis of MS. There were, however, mildly elevated levels of lactate and protein in the CSF. These findings together with the clinical and radiologic picture as well as the consanguineous relationship of the patient’s parents were suggestive of a mitochondrial disorder, and therefore a muscle biopsy and leukocyte thymidine phosphorylase assay were performed. The muscle biopsy was normal with no ragged red fibers. However, a severe reduction of thymidine phosphorylase (TP) activity in leukocytes was found. This finding is diagnostic of mitochondrial neurogastrointestinal encephalopathy (MNGIE).3

**DISCUSSION**

Demyelinating diseases such as MS or mitochondrial cytopathies have both been described as possible causes of SNHL.1,2 On MRI, the symmetrical homogenous pattern within the white matter is not typical for demyelinating diseases. The absence of individual linear or ovoid lesions of various sizes and locations often seen in demyelinating diseases should raise the suspicion of a metabolic disorder, such as a mitochondrial disease. In the presented case, the MRI showed no plaques in the auditory cortex (temporal lobe). There were, however, diffuse symmetrical plaques in the periventricular area that raised the suspicion of a mitochondrial disorder, and a genetic consult was requested.

Mitochondrial disorders are responsible for a variety of neurologic syndromes. They are a group of rare congenital disorders of mitochondrial DNA (deletion, point mutation, or duplication). They particularly affect tissues with high-energy demand such as the nervous system, muscle, retina, ear, kidney, and liver.4 Hearing loss has long been recognized as an important feature in mitochondrial cytopathies. In some studies, up to 60% of patients with mitochondrial disorders exhibited SNHL.5 As a characteristic pattern of the hearing loss in mitochondrial disease, initially the higher frequencies are affected and then the hearing loss progresses to involve all of the frequencies. There is no definitive treatment, and the prognosis is uniformly poor.6

MNGIE is a rare autosomal recessive disorder, which is caused by a mutation in the TP gene. The clinical findings are severe gastrointestinal dysmotility, cachexia, ptosis and ophthalmoparesis, peripheral neuropathy, leukoencephalopathy, and mitochondrial abnormalities. Many of these findings were found in the patient described in the case described.

The study of CSF specimen revealed slightly elevated protein level (80 mg/dL) and elevated lactate level (3.8; normal 1-1.7 mmol/L) but no abnormal oligomoniclonal antibodies combined. The findings of persistent moderate hyperlacticemia provided an additional clue to the possible diagnosis of a mitochondrial disorder (MD).3

Although the term MD is very broad, it usually refers to diseases that are caused by disturbances in the mitochondrial oxidative phosphorylation (ie, adenosine triphosphate synthesis by the respiratory chain [RC], which
supplies most organs and tissues with energy). Consequently, RC deficiency can theoretically give rise to any symptom, in any organ or tissue, at any age, with any mode of inheritance, because of the 2-fold genetic origin of RC components (nuclear DNA and mitochondrial DNA). In the past few years, it has become increasingly clear that defects of oxidative phosphorylation account for a large variety of clinical symptoms in both childhood and adulthood.3,4

Hearing loss has long been recognized as a frequent presentation of MD (45%-60% of reported cases)3,5-7; however, this group of disorders received relatively scant attention in the otolaryngology literature. As a characteristic pattern of the hearing loss in mitochondrial disease, initially the higher frequencies are affected and then the hearing loss progresses to involve all of the frequencies. There is no definitive treatment, and the prognosis is uniformly poor.7

The present patient’s clinical symptoms including ptosis, peripheral neuropathy, cachexia, rapidly progressive SNHL, and the leukodystrophy, combined with her history of consanguineous parents and another sibling with fatal progressive multisystem organ disease (gastrointestinal and central nervous system raised the possibility of the recently described MNGIE disease.8

MNGIE is an autosomal recessive disorder with mitochondrial DNA alterations (deletion and/or depletion).8,9 The disease is clinically characterized by onset between the first to fifth decades, ptosis, progressive external ophthalmoparesis, abdominal pain, gastrointestinal dysmotility, cachexia, peripheral neuropathy, and leukodystrophy. Hearing loss has been described in 45% of MNGIE patients.8 To date, there is no effective treatment for MNGIE. Recently the disease locus has been mapped to chromosome 22q13.32-qter. The gene-encoding TP was identified as the MNGIE gene.9 TP catalyzes the phosphorolysis of thymidine to thymine. In agreement with this notion, plasma thymidine levels is increased more than 20-fold in MNGIE patients compared with controls. The study of plasma thymidine level constitutes a screening assay for the diagnosis of MNGIE. The supply of thymidine and other nucleotides is essential for the maintenance of the mitochondrial genome. It is hypothesized that the imbalance of nucleotide pools caused by elevated thymidine levels probably affects mitochondrial DNA resulting in mitochondrial DNA deletion and mitochondrial DNA depletions.8,9 The identification of the MNGIE gene allows to classify MNGIE as a disease of nucleoside dysmetabolism.8

The diagnosis of MNGIE in the present patient was confirmed by the finding of elevated blood concentration of thymidine (14 μmol/L vs controls <0.05 μmol/L).

CONCLUSION

We present a patient with SNHL associated with MNGIE disorder. Among the different groups of inborn errors of metabolism, mitochondrial disorders are the most frequent, with an estimated incidence of at least 1 in 10,000.

Ongoing advances in identifying additional genetic defects associated with these disorders may reveal a higher prevalence. MD although rare should be considered by the otolaryngologist in forming a diagnosis of the “atypical” sudden onset and rapidly progressive sensorineural hearing loss.

REFERENCES
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