OBSERVATION

A Patient With DNMT1 Gene Mutation Presenting With Polyneuropathy, Hearing Loss, and Personality Changes

Hereditary sensorineural hearing loss can be syndromic or non-syndromic. Genetic causes of hearing loss must be distinguished from acquired causes for purposes of genetic counseling. Next-generation sequencing (NGS) panels are now used widely in clinical settings to try to identify genetic causes of hearing loss.

Report of a Case | A woman in her 40s was initially referred to our neuromuscular clinic for polyneuropathy and hearing loss. On examination, she was inappropriately happy and indifferent. Her neurologic examination was notable for clinically significant sensory loss to pinprick, vibration, and position sensation distally in the upper and lower extremities and symmetric hyporeflexia. A nerve conduction study showed severe sensory neuropathy, with absent potentials in upper and lower extremity. Common causes of neuropathy, such as inflammatory, vitamin deficiencies, diabetes mellitus, alcoholism, and paraneoplastic and immune-mediated causes, were considered and excluded by appropriate studies.

An otolaryngology consultation was obtained for her associated hearing loss. She reported a 5-year history of hearing loss and denied having significant noise exposure or family history of hearing loss. A hearing test performed at onset of her hearing loss demonstrated right-ear mid-frequency moderate sensorineural hearing loss between the frequencies of 500 and 2000 Hz. In the left ear there was moderately severe mid- and high-frequency hearing loss. Asymmetry between the ears was noted in the high frequencies between 1500 and 4000 Hz with the left ear having 30-dB HL worse hearing loss. (Figure 1A)

Progressive and asymmetric hearing loss in adulthood led to consideration of autoimmune inner ear disease or a retrocochlear lesion. Results from a workup for autoimmune inner ear disease were negative. Magnetic resonance imaging of the head was negative for a retrocochlear lesion but showed cerebellar atrophy (Figure 2). At the time of her initial hearing test, the audiometric configuration in her right ear demonstrated mid-frequency sensorineural hearing loss or "cookie

Figure 1. Audiograms

A, The audiogram from 2011 demonstrates asymmetric mid- and high-frequency hearing loss in left ear (blue) worse than right ear (yellow). B, The audiogram from 2014 demonstrates worsening of right ear (yellow) hearing loss to match left ear (blue) hearing loss.
HSAN1E is an autosomal dominant disorder characterized by progressive dementia, sensory polyneuropathy, autonomic dysfunction (including sudomotor loss), and sensorineural hearing loss. It is caused by DNMT1 mutation.1,2 DNA methyltransferase 1 (DNMT1) is a molecule needed for DNA methylation, and individuals with pathogenic mutation in HSANIE have been found to have global hypomethylation of DNA.3 Individuals with mutations are typically normal in young age and progress to have severe sensory loss, sensorineural hearing loss, and dementia (similar to frontotemporal dementia) by the fourth decade of life.3,4

Our patient presented initially with a classic mid-frequency hearing loss suggesting a genetic cause of hearing loss.5 This case report highlights the pattern of hearing loss of patients with HSANIE. In a case series by Klein et al,6 11 of 18 patients initially presented with hearing loss alone and subsequently developed other clinical symptoms. Therefore, otolaryngologists and audiologists, when presented with patients with early-onset hearing loss with a genetic pattern, should be vigilant for symptoms that may distinguish patients who could have this rare cause of hearing loss with a poor prognosis.

Treatment of HSAN1E is based on symptoms. Because it is inherited in an autosomal dominant manner, children of affected individuals have a 50% chance of inheriting the pathologic mutation.

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To the Editor

Regarding the recently published, randomized clinical trial by Folmer et al,7 using 1-Hz repetitive transcranial magnetic stimulation (rTMS) applied to the temporal cortex in patients with tinnitus for 10 days compared with placebo, the authors7 reported a significant reduction in tinnitus symptoms, the primary outcome measure. However, rTMS for tinnitus is still not significantly beneficial, so we have some considerations to share:

1. Most of the randomized, sham controlled studies on rTMS for chronic tinnitus used similar, short protocols: low-frequency stimulation to the temporal cortex for 10 days or less (5 days), with some benefit in tinnitus severity and an-