Audiovestibular Findings in Patients With Deafness Caused by a Mitochondrial Susceptibility Mutation and Precipitated by an Inherited Nuclear Mutation or Aminoglycosides

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**Objective:** To characterize the audiological and vestibular changes associated with a mitochondrial DNA mutation in an Arab-Israeli family and in other families with mitochondrial predisposition to aminoglycoside-induced hearing loss.

**Design:** Evaluation of audiological (pure tone thresholds, speech reception thresholds, speech discrimination, tympanometry, acoustic reflex thresholds, tone decay, and auditory brain-stem evoked response recording) and vestibular (complete history, physical examination, and 2-channel electroneystagmography) systems. In 5 patients, structural evaluation of the inner ear was done by magnetic resonance imaging.

**Patients:** Fifteen members of an Arab-Israeli family, and 1 Chinese woman with the same mitochondrial DNA mutation who experienced hearing loss after short-term exposure to streptomycin.

**Results:** Most of the patients had a profound hearing loss due to cochlear involvement. The hearing loss usually was not accompanied by notable peripheral vestibular dysfunction. In the patient with severe hearing loss after exposure to aminoglycoside, the vestibular function was completely normal.

**Conclusions:** In most of the Arab-Israeli patients with congenital deafness, the vestibular system function was normal, in contrast to the frequency of vestibular abnormality among deaf children, which was described in the literature. This may be related to genetic predisposition to aminoglycoside-induced deafness.


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**HE HUMAN mitochondrial DNA (mtDNA) is a 16,569-nucleotide base pair closed-circular molecule that encodes 13 messenger RNA (mRNA) genes as well as 2 mitochondrial rRNAs and 22 organelle-specific transfer RNA (tRNA) that are required for assembling a functional mitochondrial protein-synthesizing system. The 13 mRNAs are translated on mitochondrial-specific ribosomes, using a mitochondrial-specific genetic code, into 13 proteins. These proteins interact with about 60 nuclear-encoded proteins to form the 5 enzyme complexes required for oxidative phosphorylation.**

Indeed, the mtDNA defect has been identified as an A to G substitution at nucleotide 1555 in the 12S rRNA gene. This mtDNA mutation also was found to predispose to aminoglycoside-induced deafness in Chinese families.

We characterized the audiological and vestibular changes associated with this mutation in the Arab-Israeli family and families with this mitochondrial predisposition to aminoglycoside-induced hearing loss.

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**See Subjects and Methods on next page**
SUBJECTS AND METHODS

SUBJECT CHARACTERISTICS
The subjects tested were 15 hearing-impaired members in the Arab-Israeli family who ranged in age from 19 to 66 years (mean, 31.6 years). Six were men and 9 were women.

In addition, a 24-year-old Chinese woman with bilateral hearing loss after exposure to streptomycin was examined. The patient's grandmother and 8 other maternal relatives also had hearing loss after the use of aminoglycosides. This family was described in detail in a previous publication.

EVALUATION OF THE AUDITORY SYSTEM
Fifteen subjects in the Arab-Israeli pedigree were evaluated. A complete history of the auditory system was obtained and a full otolaryngological examination was performed.

The audiological evaluation included pure-tone thresholds (air and bone). Hearing impairment is defined by the level of hearing loss in the better ear for pure-tone threshold average in the speech frequencies 0.5, 1, 2, and 4 kHz. Hearing loss of 21 to 40 decibels (dB) was considered mild; 41 to 55 dB, moderate; 56 to 70 dB, moderate to severe; 71 to 90 dB, severe; and more than 91 dB, profound.

The audiological evaluation also consisted of speech audiometry, including speech reception threshold or speech detection threshold and, when possible, speech discrimination; tympanometry with an admittance meter (A 720, Amplaid, Milan, Italy) to evaluate the compliance of the tympanic membrane and the status of the middle ear; and acoustic reflex measurements, including acoustic reflex decay, when possible.

In the family members in whom hearing loss was detected, tone-decay tests and auditory brain-stem response were done to locate the precise site of lesion.

The tone-decay test as reported by Carhart was done using 2 kHz or, occasionally, when hearing threshold at 2 kHz was too elevated, a 1- or 0.5-kHz tone. The continuous sound is given to the patient at 10 dB above threshold level for 60 seconds. If the patient does not hear the tone for the full minute, stimulus intensity is elevated in steps of 5 dB until the patient can hear the tone for 60 seconds. Tone-decay results are nonpathological if the patient can follow the tone for a minute at up to 20 dB sensation level (SL). Results are indeterminate at 20 to 30 dB SL, and above 30 dB SL, the results point to possible retrocochlear involvement (positive tone decay).

For the auditory brain-stem response, alternating polarity clicks at a rate of 20 per second were given to the patient at intensities of 135 dB sound pressure level or 120 dB sound pressure level, depending on hearing thresholds.

The electrical activities were recorded as the potential difference between an earlobe clip electrode and a scalp vertex disc electrode and were filtered, amplified, and averaged by a computerized system (Microshev 4000, Efrat, Israel). Evaluation of the results was done according to the absolute latency of the waves and the interpeak latencies. Repeated audiological evaluations were performed twice during the 3-year follow-up period.

Magnetic resonance imaging was done in 5 patients with severe hearing loss to evaluate the structure of the inner ear, cranial nerve VIII, and the brain.

Evaluation of the vestibular system was done in 14 patients. This included a complete and thorough history, physical examination (looking for pathological eye movements, tandem walking, and past pointing tests), and 2-channel electronystagmography. Oculometric tests included measurement of saccadic and pursuit eye movements, gaze nystagmus, and optokinetic nystagmus. Vestibular tests included recording of spontaneous, paroxysmal, and positional nystagmus and the bithermal calorics test of Dix and Hallpike.

In the patient with familial aminoglycoside-induced ototoxicity, audiological testing was performed at the Galaudet Audiology Clinic, Washington, DC, and included pure-tone thresholds, speech audiometry, tympanometry, and acoustic reflex measurements.

Vestibular testing was performed at the Pinehurst (NC) Surgical Clinic, and included 2-channel electronystagmography, including saccades, gaze tests, pendular tracking, optokinetics, the Hallpike maneuver, positional tests, and bithermal calorics tests.

Audiological and vestibular test results were reviewed by one of us (J.E.).

RESULTS

AUDIOLUMINAL EVALUATION IN THE ARAB-ISRAELI FAMILY
Audiological test battery results showed notable sensorineural hearing loss in all 15 patients. In 4 patients, moderate to profound (sloping) hearing loss was seen. The other 11 patients suffered from profound deafness (4 patients had only residual hearing, in the low tones).

In their childhood, hearing aids had been recommended for all patients, but none of them now wear a hearing aid. Audiological evaluation disclosed that 7 patients had good residual hearing and were referred for hearing-aid fittings. Three patients were advised to use a hearing aid for a trial period, because they suffered from severe hearing loss and were not young (older than 15 years). Five other patients with profound hearing loss (mostly "corner" audiograms) and older than 15 years were not referred for hearing aids. At the 3-year follow-up, none of these patients had acted on the recommendations for hearing-aid fitting.

Speech reception threshold could be determined in only 6 patients and was obtained between 65 and 85 dB hearing level (HL). In the other 8 patients, the speech detection threshold level was between 75 and 100 dB HL. In 1 patient, no response was received.

Auditory evoked response was recorded in all 15 patients, and in 12 of them, no response could be detected bilaterally, even with maximal intensity of 135 dB sound pressure level. In 2 patients, normal brain-stem trans-
mission time was measured; in 1 patient, only wave V was identified on 1 side at normal latency.

Tymanometry was found to be of type A bilaterally in all patients.

Acoustic reflexes were recorded successfully in 10 patients at low sensation levels, showing recruitment typical of cochlear lesions. In 6 patients, acoustic reflex decay testing was possible. None of them showed acoustic reflex decay.

In 11 patients, tone decay could be tested. In 9 patients, the test results were negative, and in 2 patients, indeterminate findings (between 20 and 25 dB) were obtained in 1 ear only.

Repeated hearing tests during 3 consecutive years of follow-up did not show deterioration of hearing. Some improvement was seen in 4 patients (Table). Four patients were unavailable for follow-up.

VESTIBULAR EVALUATION IN THE ARAB-ISRAELI FAMILY

Electronystagmography was performed in 14 patients. In 8 of them, the results of electronystagmography were normal with good caloric responses. In 4 others, the caloric responses were normal bilaterally, but mild spontaneous nystagmus (maximal slow-phase velocity, 1°-4°/s) could be detected.

In 1 patient, decreased caloric response was found bilaterally (slow-phase velocity, 3.9°, 3.3°, 3.0°, and 4.8°/s).

In 1 patient, unilateral canal paresis was found (defined in our laboratory as a difference of >22% asymmetry between left- and right-sided responses).

MAGNETIC RESONANCE IMAGING IN THE ARAB-ISRAELI FAMILY

Magnetic resonance imaging of the brain and temporal bones was performed in 5 patients. The images of the inner ears, cranial nerves, and brain showed no abnormalities. One patient had some enlargement of the right lateral ventricle.

AUDIOLOGICAL AND VESTIBULAR EVALUATION IN THE CHINESE PATIENT

On audiometry, the Chinese patient had moderate to severe sensorineural hearing loss with bilateral speech awareness threshold of 50 dB. Tymanometry was found to be of type A bilaterally. Acoustic reflexes showed questionable recruitment typical of cochlear lesion.

Electronystagmography, including saccades, gaze tests, pendular tracking, optokinetics, the Hallpike maneuver, positional tests, and bithermal caloric tests, showed no abnormalities. Bithermal caloric test disclosed good responses in both ears.

COMMENT

General physical examination of all the patients had disclosed normal general health. No pathologic lesion of any system usually connected to mitochondrial inheritance (neurological or muscular), or associated with congenital deafness (renal or ophthalmological) was detected. The present study concentrated on a detailed characterization of the audiovestibular system. Most of the patients had a profound hearing loss (average of 0.5-4 kHz, 91 dB HL). The audiological evaluation in the Arab-Israeli family pointed to cochlear rather than retrocochlear hearing loss. This hearing loss usually was not accompanied by notable peripheral vestibular dysfunction. The caloric responses were normal in 12 of 14 patients, and only 1 patient suffered from bilateral caloric hyporeflexia. Similarly, the audiovestibular evaluation of the Chinese patient with the streptomycin-induced deafness showed sensorineural hearing loss with normal vestibular function. Streptomycin usually damages mainly the vestibular end organ.

Review of the literature disclosed several series that described the frequency of vestibular damage among deaf children. Arving6 examined 486 deaf children in whom 128 (26.3%) had genetic deafness. Among them, normal caloric response was found in 66%, normal response in 21%, and no response in 13%. Goldstein et al7 examined 140 deaf children and found normal caloric response in 51%, hyporeflexia in 23%, and no response in 25%. Absence of vestibular response was more frequent among children who had meningitis or infection as a cause. Feinmesser et al8 evaluated 112 deaf children and found normal vestibular response in 50 of them, hyporeflexia in 18, and no response in 44. Sandberg and Terkildsen9 examined 57 deaf children. The vestibular damage correlated with the severity of hearing loss. In patients with hearing threshold below 90 dB, the caloric response was normal in 80%. When the hearing threshold was between 91 and 97 dB, normal caloric response was found in 50% of the children, and when hearing threshold was above 98 dB, normal caloric response was found in 19%. In another study,10 75 deaf children were evaluated, and among them, absent caloric response was found in 44% to 50% (depending on the cause of deafness).

What is the explanation for the discrepancy between these findings in the literature and the lack of vestibular abnormalities in most of the patients in our series? The basic process that induces the damage to the inner ear probably is completely different and exhibits a specific affinity to the cochlear hair cells, with relative sparing of the vestibular hair cells. Similarly, a dramatic
finding in our study was the complete absence of a vestibular abnormality in a patient with severe hearing loss after a short exposure to streptomycin. Typical streptomycin ototoxicity is characterized by more severe and earlier-onset vestibular damage than cochlear damage. Aminoglycoside ototoxicity is one of the more common causes of acquired deafness. In general, although vestibulocochlear damage is almost universal when high drug levels are present for prolonged periods, at lower drug levels a notable genetic component seems to influence susceptibility to aminoglycoside ototoxicity.13,14 We analyzed 3 families in which several persons became deaf after the use of aminoglycosides.7 The pattern of maternal inheritance in these pedigrees, the known effect of aminoglycosides on ribosomal translation ability, and the presence of aminoglycoside-resistant mutations in a range of prokaryotic and eukaryotic organisms implicated the mitochondrial ribosomes, especially the mitochondrial encoded 12S ribosomal RNA gene, as the most likely locus of predisposition to toxic effects. We identified in all 3 families a mutation in the 12S mitochondrial ribosomal RNA gene that affected a site known to be important in the binding to aminoglycosides and in resistance to the antibiotic.7 In addition, a small proportion of "sporadic" patients, without a positive family history for aminoglycoside ototoxicity, exhibit this mutation.15 The findings were confirmed in 2 Japanese families and sporadic cases in Chinese families.16 We described subsequently an additional heteroplasmic nucleotide deletion/insertion mutation around nucleotide 961 in the 12S rRNA gene, and 2 potential homoplasmic mutations in the same gene, which also seem to predispose to aminoglycoside ototoxicity.17 However, the reason the vestibular function is less affected in these patients is unclear. The vestibular hair cells in the inner ear of adult guinea pigs and humans can regenerate after severe damage from aminoglycosides.18 Whether this also occurs in the organ of corti is unknown. Thus, whether the difference between auditory and vestibular involvement in our patients is related to a difference in regeneration capabilities of the 2 populations of hair cells is yet to be investigated.

We propose, based on the finding in this study, that vestibular testing of persons who became deaf after aminoglycoside administration may lead to the identification of those with a genetic predisposition and separate them from those with a dose-dependent loss of cochlear function. However, additional vestibular testing in other patients with the mitochondrial mutation and aminoglycoside-induced ototoxicity is required. Counting of family members with aminoglycoside-induced ototoxicity due to a genetic predisposing factor is important to prevent more hearing loss in such families.

Accepted for publication May 16, 1996.
This work was supported by grant DC01402 from the National Institute of Deafness and Other Communication Diseases, National Institutes of Health, Bethesda, Md.
We thank the families for participating in this study.
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