The Otolaryngological Manifestations of Mitochondrial Disease and the Risk of Neurodegeneration With Infection

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Objective: To report the nature and extent of hearing loss and other otolaryngological problems in patients with mitochondrial disease, and to document the risk of neurodegeneration with infection.

Design: Medical chart review and telephone interview of 40 patients with documented mitochondrial disease.

Setting: An international referral center for the diagnosis and management of mitochondrial disorders.

Patients: We describe 40 patients with a definitive diagnosis of mitochondrial disease. Thirty-three (82%) were younger than 15 years.

Results: Hearing loss was the most common clinical finding associated with mitochondrial disease. Twenty-eight (80%) of the 35 patients undergoing testing had hearing loss or significant auditory dysfunction. In 20 (57%) of these, brainstem conduction abnormalities were identified. Eight (30%) of the 27 patients had an abnormal number of recurrent upper respiratory tract infections, and 4 (50%) of these had life-threatening or neurodegenerative sequelae. Mitochondrial disease followed an episodic course, with periods of stasis or slow developmental progress, punctuated by neurodegenerative events in 18 (60%) of 30 patients. Intercurrent infection was recognized as a precipitant of neurodegenerative events in 13 (72%) of 18 patients with a history of episodic degeneration.

Conclusions: Children and adults with mitochondrial disorders are at high risk for hearing loss and life-threatening complications of intercurrent infections. A constellation of audiologic abnormalities, multiorgan system involvement, and history of neuromuscular setbacks with infection strongly suggests mitochondrial disease. Knowledge of these features can lead to more rapid diagnosis and improved medical and surgical management for this special group of patients with fundamental defects in bioenergy metabolism.


MITOCHONDRIAL DISORDERS

More than 400 diseases are grouped under the general heading of mitochondrial disorders. Specific disease entities in the patients studied in this series include Mitochondrial Encephalomyopathy with Lactic acidemia and Strokelike episodes (MELAS); Neuropathy or neurogenic muscular weakness with Ataxia and Retinitis Pigmentosa (NARP); Kearns-Sayre syndrome; Pear-
PATIENTS AND METHODS

PATIENT POPULATION

From June 15, 1994, through December 31, 1999, more than 300 patients underwent evaluation for possible mitochondrial disease. Forty of these patients fulfilled the following 2 requirements for enrollment in this study: (1) lactic acid levels in the blood or cerebrospinal fluid of ≥3 mmol/L, and (2) an objective defect in mtDNA or oxidative phosphorylation. Medical records for these 40 patients were reviewed from The Mitochondrial and Metabolic Disease Center at the University of California–San Diego. Brainstem auditory evoked response (BAER) examinations were performed in 35 of 40 patients as part of an initial multisystem evaluation of those patients with confirmed mitochondrial disease. In addition, careful medical histories were obtained, and physical examinations were performed on all patients. The age and the presentation of each patient were recorded from these initial histories and physical examination findings.

INFORMED CONSENT

All patients or their guardians provided informed consent and underwent evaluation and initial ascertainment under an institutional review board–approved human subjects protocol at the University of California–San Diego School of Medicine for 1994 through 1999.

BRAINSTEM AUDITORY EVOKED RESPONSES

Thirty-five patients of the study group (88%) underwent a diagnostic BAER examination. The BAER data were examined for neuroaudiologic conduction delay (I-V interval), waveform morphology, and auditory threshold. Evaluation of conduction delay was limited to the I-V interval, as this was the most consistently recorded variable on the BAER summary available for review. The I-V interval was converted to a z score to correct for age differences in reference BAER test results. The z score was calculated by taking the recorded interval in milliseconds, subtracting the reference value, then dividing by the SD. An abnormal z score was defined as being more than 2 SDs from the reference value for the patient’s age. The number of patients with at least 1 abnormal z score for the I-V interval is recorded. Asymmetry was determined by subtracting the right from the left z score, with the result being equal to or greater than 2.

HEARING LOSS AND MITOCNDRIAL DISEASE

More than 40 different genetic loci that lead to hearing loss have been identified. These have been traditionally categorized as recessive, dominant, or X-linked disorders. It has become increasingly clear that another group of genetic diseases, mitochondrial diseases, plays a role in the large proportion of previously unexplained, inherited hearing loss. It remains unclear how many of these cases of hearing loss will ultimately be explained by mitochondrial disease. Mitochondrial disorders can be inherited in a traditional mendelian manner, in addition to strict maternal inheritance. Sporadic inheritance patterns are also possible, in which spontaneous mutations in DNA occur during oogenesis or early embryo.

A description of waveform morphology was also consistently present on the BAER report. Waveform morphology was recorded to be normal, normal with conduction delay, unilaterally abnormal, or bilaterally abnormal. In patients undergoing multiple examinations, we noted waveform morphology remaining unchanged, becoming worse, or, in some instances, improving to normal. Threshold data were obtained in 29 (83%) of the 35 patients undergoing BAER examinations. Thresholds were reported to be abnormal if the recorded threshold was greater than 30 dB. The distributions of abnormal brainstem conduction, waveform morphology, and abnormal thresholds were then grouped based on the type of mitochondrial disease.

INFECTIONS

Caregivers were interviewed with attention to the number of URIs and episodes of acute otitis media (OM) in the year preceding this study. The caregivers were also questioned regarding episodes of neurodegeneration and those episodes that were temporally related to an infection. This telephone interview information was combined with information obtained from the hospital medical chart regarding numbers of URIs and episodes of acute OM (as reported in the medical history at initial evaluation). The medical chart reviews and interviews also attempted to collect information regarding surgical procedures performed or other treatments rendered for recurrent OM or URI.

STATISTICAL ANALYSIS

Results were reported and listed descriptively. The incidence of audiologic abnormalities, infection rates, neurodegenerative episodes, and proportion of various presenting symptoms were estimated using 95% confidence intervals. We used a normal approximation to the binomial distribution or simulation (1000 repetitions) to compute the confidence intervals, depending on the magnitude of the number of events. To determine if patients with mitochondrial disease had an abnormal number of infections, we estimated the incidence of infections with a 95% confidence interval. We then compared this interval estimate with the number of infections per year reported for a control population of children and adults. We developed a Venn diagram to reflect the distribution of the numbers of abnormal URIs and neurologic setbacks associated and not associated with infection among the subjects.
Mitochondrial disorders are usually first manifest in tissues with high metabolic demands, such as nerves and muscles. This finding places the complete auditory pathway, peripherally from the cochlea and centrally to the brainstem, at risk in mitochondrial disease and helps to explain the common finding of hearing loss as part of the initial presentation of a mitochondrial disorder.

UPPER RESPIRATORY TRACT INFECTIONS AND MITOCHONDRIAL DISEASE

Because of the relative novelty of mitochondrial disorders, no reports in the literature have quantified the risk for neurodegenerative events triggered by infections in patients with mitochondrial disease. However, a well-known clinical correlation of upper respiratory tract infections (UIRs) and other common infections with neurodegenerative setbacks in mitochondrial disease exists. This association is quantified in this report.

**RESULTS**

**PRESENTING SIGNS AND SYMPTOMS**

No disease-specific presenting signs were present among patients with mitochondrial disease (Table 1 and Table 2). The most common presenting abnormality was motor and/or language developmental delay, which occurred in 16 (40%) of 40 patients. Of the 23 patients who presented at younger than 5 years, 20 (87%) had...
significant developmental delays. The next most common presenting symptom was a stroke-like episode (SLE), which occurred in 10 (25%) of 40 patients, and was not restricted to patients with MELAS. Patients with Pyruvate Dehydrogenase deficiency, Complex I deficiency, Cytochrome-c Oxidase (complex IV) deficiency, and NARP also experienced SLEs at presentation (Tables 1 and 2). Eight patients (20%) had miscellaneous neurologic symptoms, which were initially unexplained. These symptoms included deafness, tongue weakness, swallowing dysfunction, nystagmus, seizures, ophthalmoplegia, hypotonia, and decreased visual acuity. Two neonates received diagnoses of severe lactic acidosis shortly after birth. Two infants had as their initial symptom failure to thrive. One child had dizzi-ness as the initial complaint. The range of ages at presentation was also highly variable, from birth to 53 years (Table 1). The mean age at presentation was 8.4 years. The median age at presentation was 3.3 years (Table 1).

HEARING LOSS

Thirty-five of 40 patients underwent diagnostic BAER examinations (Table 3). The results of the audiologic studies were then summarized according to disease diagnosis (Table 4). Twenty (57%) of 35 patients had central (brainstem) defects, as documented by a significant delay or absence of the I-V interval in at least 1 ear. Fourteen (40%) of 35 patients had a significant delay of the I-V interval in the right and left ears. Five (14%) of 35 patients had significant asymmetry of the I-V interval between the right and left ear. Thirty-three (94%) of these had abnormal waveform morphology. Thirteen (39%) had bilateral abnormalities, and 9 (27%) had a unilateral abnormality. Two (6%) of the 33 had normal waveform morphology with significant conduction delay (Table 3). Nine (27%) of 33 patients had normal waveform morphology and conduction times. Thirty of the 35 patients undergoing a screening BAER underwent testing for hearing sensitivity or hearing threshold. Of these, 23 (77%) had abnormalities in at least 1 ear (Table 4). In the recorded histories, physical examination findings, and subsequent BAER findings, no patients were noted to have OM at the time of threshold evaluation. Overall, audiologic evaluation in patients with mitochondrial disease showed that 28 (80%) of 35 patients had significant hearing dysfunction at the time of first evaluation. Only 7 (20%) of 35 patients had normal hearing.

DISEASE-SPECIFIC AUDILOGIC ABNORMALITIES

Individual disease states were evaluated for differences that might exist between them in the measured hearing or infectious disease variables. The 40 patients in this study were distributed among 9 diagnostic categories (Table 4 and Table 5). No significant differences were detectable with the small numbers of patients within each category. The 10 patients with MELAS tended to be older at diagnosis than other groups, with a mean age at presentation of 22.5 years (Table 5). However, 3 patients with MELAS (30%) presented before age 15 years (Table 1). In all 3 children, the presenting symptom was an SLE, with or without documented antecedent URI.

RISK OF INFECTIONS AND NEURODEGENERATION

Information on infections was available from 27 (68%) of the 40 patients in this study. Four (15%) of 26 patients had abnormally increased rates of recurrent OM. Overall, 94 infections were reported by 27 patients in the year before our survey, leading to an estimate of 3.5 infections per year, with a 95% confidence interval of 2.1 to 4.9 infections per year (Table 5). A Poisson distribution is expected when infections are relatively rare and
We found that a frequency distribution of the hit rate of infections among patients with mitochondrial disease was positively skewed (Figure 1) and suggested a Poisson distribution. Eight (30%) of 27 patients had abnormally frequent (recurrent) URIs, defined as more than 6 per year (Table 5). Mitochondrial disease was episodic, with periods of stasis or slow developmental progress, and punctuated

### Table 3. Auditory Conduction and Threshold Abnormalities in Mitochondrial Disease*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age at BAER, y</th>
<th>Right I-V Interval, ms</th>
<th>Left I-V Interval, ms</th>
<th>Right z Score</th>
<th>Left z Score</th>
<th>Normal†</th>
<th>SD†</th>
<th>Right Threshold</th>
<th>Left Threshold</th>
<th>Waveform Morphology</th>
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<td>CI</td>
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<td>4.86</td>
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<td>1.9</td>
<td>3.1</td>
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<td>CI</td>
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<td>4.8</td>
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<td>85</td>
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<tr>
<td>CI</td>
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<td>1.3</td>
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<td>4.0</td>
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<td>45</td>
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<tr>
<td>CI</td>
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<td>4.44</td>
<td>4.7</td>
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<td>20</td>
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*BAER indicates brainstem auditory evoked response; NV, no wave V; ellipses, not applicable; and AR, absent response. Other abbreviations are given in Table 1.
†Explained in Gorga et al.10
‡Indicates III-V interval.

### Table 4. Audiologic Abnormalities Associated With Mitochondrial Disease*  

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<th>Variable</th>
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<td>Increased I-V interval on right or left</td>
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</tr>
<tr>
<td>Increased I-V interval on right and left</td>
<td>1/1</td>
</tr>
<tr>
<td>I-V asymmetry</td>
<td>1/1</td>
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<tr>
<td>Abnormal waveform morphology</td>
<td>1/1</td>
</tr>
<tr>
<td>Threshold abnormality</td>
<td>1/1</td>
</tr>
<tr>
<td>Threshold asymmetry</td>
<td>1/1</td>
</tr>
</tbody>
</table>

*Denominators reflect the number of patients in each category for whom information was available. Abbreviations are given in Table 1.
†Indicates mean of the summary column, expressed as a fraction.

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by neurodegenerative events in 18 (60%) of 30 patients. Intercurrent infection was recognized as a precipitant of neurodegenerative events in 13 (72%) of 18 patients. Of the 8 patients with a history of recurrent URI, 4 (50%) also had neurodegenerative events associated with infection. These results are summarized in the Venn diagram shown in Figure 2.

The timing of the infection and the neurodegenerative event varied. In a few patients (3/13), the neurologic setback occurred early in the course of infection. In most patients (10/13), the neurologic event occurred 3 to 7 days after the onset of infection and frequently appeared at a time when the infection was resolving. This pattern of delayed neurodegeneration in association with infection is depicted graphically in Figure 3. The pattern was similar to that reported for Reye syndrome, now known to be frequently associated with mitochondrial defects in fatty acid oxidation.12

Several specific mitochondrial diseases with hearing loss as a well-recognized component have been described. Patients with the A1555G mitochondrial DNA mutation exhibit mild high-frequency, progressive hearing loss without aminoglycoside injection and are highly susceptible to profound otologic injury with the administration of aminoglycoside antibiotics.13,14 A study of patients with MELAS reported significant sensorineural hearing loss.15 The loss is sometimes the sole manifestation, but more commonly the hearing loss is asymmetric with an early onset and marked by a stepwise progression and/or partial reversibility. Patients with Kearns-Sayre syndrome were found to have a significantly prolonged I-V interval in 1 study.16 Results of BAER examinations in patients with Leigh disease have shown progressive disturbances of the brainstem wave components.17 Additional BAER data have corroborated abnormalities in the BAER data of patients with Leigh disease, but found the abnormalities to be inconsistent.18,19 Other reports have emphasized the importance of mtDNA mutations in non-syndromic and syndromic deafness20 and have discussed biochemical defects associated with mitochondrial hearing loss.21

The site of the functional lesion leading to hearing loss in mitochondrial disease has been reported to be the cochlea in MELAS.15 The stria vascularis was considered to be the principle site of the defect. However, in our pa-
tients with MELAS, we found that the entire auditory pathway, from cochlea to brainstem, was at risk (Tables 1 and 3). In our study, a 34-year-old patient with MELAS (patient 12) had normal otoacoustic emissions with a grossly abnormal BAER finding (absent waves III and V, with elevated thresholds for 1 ear). These results showed that the cochlear responses in this patient with MELAS were normal, and that the site of the defect was restricted to a central abnormality. Collectively, a central cause was present in 57% of patients with mitochondrial disease, as documented by conduction delay associated with abnormal waveform morphology on the BAER findings (Table 4).

In a seminal report, hearing loss was documented in 19.8% of patients with mitochondrial disease. This finding was necessarily an underestimate, as not all of the patients included in that study underwent formal hearing evaluations. Those patients who had not undergone a hearing evaluation were assumed to have normal hearing. In our population, hearing dysfunction was not recognized before formal testing in 12 (43%) of the 28 patients. In most cases, the reason for this oversight was the young age of the patients, combined with the presence of multorgan system disease that overshadowed the presence of hearing dysfunction.

Among the 40 patients with lactic acidemia and mitochondrial disease in our study, the rate of hearing loss was 80% (Table 4). Our population may represent more severe forms of mitochondrial disease, since all enrolled patients had to meet the requirements of documented respiratory chain disease and baseline lactic acid in blood or cerebral spinal fluid of 30 mg/dL or greater. However, our study confirms and extends the earlier report that hearing loss is common, and may be the presenting symptom in mitochondrial disease.

We found no disease-specific presenting symptoms or characteristic age of presentation of mitochondrial disease (Tables 1 and 2), although developmental delay was observed in 40%, and SLEs occurred in 25%. The broad clinical spectrum is one of the hallmarks of mitochondrial disease. Signs and symptoms that were not present early in the course of disease may appear as the disease progresses. The absence of a specific sign is not evidence of the absence of mitochondrial disease. The pattern of abnormalities should alert the practitioner. Some presentations may cause a patient to undergo evaluation by an otolaryngologist before the diagnosis of mitochondrial disease. Some of these common presenting reasons for otolaryngology referral include swallowing dysfunction, dizziness, tongue weakness, or head and neck infections (URI or OM) complicated with a neurologic event. Patients with mitochondrial disease may also be referred to an otolaryngologist very early in the disease process because of an abnormal BAER finding and the question of hearing loss. This occurrence is probably increasing owing to universal infant screening for hearing loss in the United States.

The overall number of infections per year in our series (mean, 3.5 per year; 95% CI, 2.1-4.9) was not significantly different than the infection rates (4.1 per year) reported in a general population of children and adults. However, in sharp contrast to a general population, 18 (60%) of 30 patients with mitochondrial disease had a history of neurodegenerative events (Table 5). In 13 (72%) of these 18 patients, the neurodegenerative event was associated with infection. The risk of neurodegeneration associated with infection led some parents in the study group to home school their children to avoid exposure to infectious disease. At present, it is unclear if the increased risk of neurodegeneration associated with infection in patients with mitochondrial disease is related to the production of host-defense cytokines and their effects on mitochondria or to a specific cellular, humoral, or mucosal immune defect, or is secondary to impaired mucociliary function related to reduced adenosine triphosphate output from ciliary mitochondria. Regardless of the cause, it is critical to recognize that children with mitochondrial disease are at risk for disease progression with recurrent infection. Acute management should be swift and decisive. The first signs of bacterial infection should be treated with empiric antibiotics and culture of the infection, with a change in antibiotic coverage based on the culture results. Long-term, preemptive otolaryngological management should be considered early in patients who have demonstrated a recurrent risk of infection, because as many as 50% of these will eventually have a neurodegenerative event associated with infection (Figure 2). Bilateral myringotomy and tympanostomy tube placement was effective and safe in 3 of our patients who had recurrent OM. The risk of recurrent infection far exceeds the risks associated with general anesthesia required for tube placement. However, certain precautions are required before subjecting any patient with mitochondrial disease to general anesthesia. In our series, all 3 patients who underwent bilateral myringotomy and tympanostomy tube placement required several surgeries. Therefore, use of long-term myringotomy tubes initially may be warranted in this special group of patients who may retain a lifetime risk for recurrent infections.

**DIAGNOSTIC EVALUATION OF MITOCHONDRIAL DISEASE**

None of the 40 patients with mitochondrial disease we studied had fewer than 3 separate organ systems af-
Effects were noted and not otherwise explained by a patient’s referring diagnosis, the otolaryngologist is justified in raising the question of mitochondrial disease. If neurometabolic consultation is immediately available, then secondary referral is appropriate. If specialty consultation is not immediately available, several baseline studies may be ordered to provide the neurometabolic specialist with useful information that may accelerate the diagnostic process.

A CHECKLIST OF BASIC STUDIES

The following 7 diagnostic studies are considered fundamental in the evaluation of any suspected mitochondrial disease: (1) polymerase chain reaction and Southern blot analyses of blood samples for mitochondrial DNA; (2) testing of blood and cerebrospinal fluid for lactate and pyruvate; (3) gas chromatography–mass spectroscopy analysis of urine for organic acids; (4) testing of plasma and urine for amino acids; (5) testing of blood and urine for carnitine; (6) magnetic resonance imaging of the brain, with or without magnetic resonance spectroscopy; and (7) open muscle biopsy. Open muscle biopsy (with specimens sent for neuropathologic examination, electron microscopy, mitochondrial respiratory chain analysis, fresh mitochondrial polarography, and polymerase chain reaction and Southern blot analyses of muscle mtDNA) is often required for definitive diagnosis, if the mitochondrial DNA studies from blood have proven nondiagnostic. However, a muscle biopsy for mitochondrial disease diagnosis is sufficiently specialized that it is advisable for this last element of the mitochondrial disease workup to be managed in consultation with a neurometabolic specialist.

CONCLUSIONS

Patients with mitochondrial diseases may present with symptoms that result in referral to an otolaryngologist before a definitive diagnosis of respiratory chain disease has been established. The history of neuromuscular setbacks associated with infection and the presence of dysfunctions in 3 or more organ systems are clues that mitochondrial disease may be the cause of the patient’s otolaryngologic symptoms.

Auditory dysfunction was found in 80% of patients with mitochondrial disease and lactic acidemia in this study, whereas only 3 of 40 patients reported hearing loss to be the presenting symptom leading to diagnosis. Objective auditory dysfunction was the single most common clinical abnormality found in this series of patients with mitochondrial disease.

Mitochondrial disease was episodic, with periods of stasis or slow developmental progress, punctuated by neurodegenerative events in 60% of patients. Intercurrent infection was recognized as a precipitant of these neurodegenerative events in 72% of patients. The mechanistic basis of this is not understood at the present time. Intercurrent infections should be managed aggressively in this metabolically fragile group of patients.

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REFERENCES