# MITOCHONDRIAL ENCEPHALOMYOPATHY: A RARE GENETIC CAUSE OF SENSORINEURAL HEARING LOSS

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A 44-year-old man with a documented 12-year history of progressive sensorineural hearing loss developed a generalized tonic-clonic seizure followed by a visual field deficit and apraxia. Six months later he developed a peripheral neuropathy and muscle fatigue followed by a slowly progressive aphasia and cortical blindness as well as increased seizure activity. A computed tomography scan showed bilateral basal ganglion calcification. The serum lactate level was elevated at 3.4 mEq/dL. A muscle biopsy enabled the diagnosis of mitochondrial myopathy. This disorder is presented as an unusual cause of progressive sensorineural hearing loss in adults.

KEY WORDS --- genetics, MELAS syndrome (mitochondrial encephalomyopathy with lactic acidosis and stroke), mitochondrial encephalomyopathy, sensorineural hearing loss.

#### CASE REPORT

A 44-year-old right-handed pathologist with neurologic disease had presented 12 years earlier with a slowly progressive bilateral sensorineural hearing loss. His first audiogram showed a left mild sensorineural hearing loss, dropping to moderate in the high frequencies, with excellent speech discrimination. His right ear showed a moderate flat sensorineural hearing loss, also with excellent speech discrimination (Fig 1A). A neurotologic evaluation at that time yielded unremarkable findings. The family history was also unremarkable. In 1984 he showed a threshold shift in his left ear only. Over the next year he showed a progressive drop in auditory thresholds in both ears, with a marked discrimination change in his right ear. His discrimination at that time was 48%. An auditory brain stem response test was performed and the findings were normal in both ears. Laboratory tests, including complete blood count, urinalysis, blood urea nitrogen testing, and serologic tests, showed normal results. There was no clinical evidence of thyroid disease.

In 1985, because of the fairly rapid progression of the sensorineural hearing loss, he was treated with high-dose steroids for the possibility of an autoimmune sensorineural hearing loss. He showed no response to steroids and did not wish to be placed on Cytoxan. He continued to show a progressive sensorineural hearing loss, mainly in his right ear, and by 1987 had an auditory discrimination of 28% (Fig 1B,C).

In 1991, when he presented with seizures, he had a severe sensorineural hearing loss in the right ear and a moderate to severe loss in the left ear. His auditory discrimination was 12% in the right ear and 20% in the left (Fig 1D). On May 24, 1991, he presented with an acute tonic-clonic seizure. A computed tomography scan was normal except for calcification of the basal ganglion bilaterally. On this admission he had a normal complete blood count, and a sedimentation rate of 5 mm/h. Results of chemistry studies were normal, with the exception of slightly elevated triglycerides, lactate dehydrogenase, creatine phosphokinase, and serum glutamate-pyruvate transaminase. Levels of thyroxine, thyroid-stimulating hormone, and parathyroid hormone and partial thromboplastin time were normal. Testing for antinuclear antibodies was negative. Complements C3 and C4 and total serum hemolytic complement levels were normal. Human immunodeficiency virus testing was negative. The cerebrospinal fluid (CSF) was clear and no significant cells were found. The CSF protein level was elevated at 90 mg/dL and the glucose level was normal. Routine viral, fungal, and acid-fast bacillus cultures of the CSF were normal. Testing for cryptococcal antigen was negative. Serum and CSF tests for syphilis (VDRL) were negative. The herpes simplex virus 1 CSF-serum ratio was normal. Serum toxoplasma, IgM, and IgG titers for cytomegalovirus and Epstein-Barr virus were negative.

Magnetic resonance imaging (MRI) showed an area of increased proton density in the right temporal and parietal lobes. There was decreased signal intensity in the basal ganglion consistent with heavy calcification (Fig 2A). There were punctate areas of increased T2 signal intensity in the white matter of both hemispheres (Fig 2B). A selective right carotid arteriogram was normal, an echocardiogram was normal, and electroencephalography showed focal

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Fig 1. Pure tone audiograms. A) November 15, 1979. B) Left ear 1979-1991. C) Right ear 1979-1991. D) June 18, 1991.

slowing with periodic spikes in the right posterior quadrant. Acyclovir was prescribed for the possibility of herpes encephalitis,<sup>1</sup> and at the time of discharge the patient had minimal apraxia, receptive aphasia, and homonymous hemianopsia. He was placed on a regimen of Dilantin and was discharged from the hospital.

Over the next few months the patient complained of generalized myalgia associated with mild proximal muscle weakness. His creatine phosphokinase level was persistently elevated, but his tests for sedimentation rate, antinuclear antibodies, anticardiolipin antibodies, and rheumatoid factor were negative. Lupus anticoagulant assay and Lyme disease enzyme immunoassay were negative. Complement levels were again normal. Hepatitis A, B, and C serology was negative. Repeat Epstein-Barr virus titers were negative. A repeat MRI scan showed a resolving inflammatory process in the right side of the brain, with some brain loss in the temporal, parietal, and inferior occipital lobes.

In January 1992 the patient showed deterioration in mental status, with progressive expressive and receptive aphasia, dyspraxia, and the development of cortical blindness. A repeat MRI showed a new abnormal focus in the inferior aspect of the left temporal lobe, with meningeal and parenchymal contrast enhancement. Brain and meningeal biopsy to look for central nervous system vasculitis was refused. Electromyography had shown a polyneuropathy, so muscle and sural nerve biopsies were done to look for vasculitis. The surprising finding in the muscle biopsy was a mitochondrial myopathy, which led to the correct diagnosis of mitochondrial encephalomyopathy by polymerase chain reaction studies of muscle and then urinary sediment and blood. The serum lactic acid level was 3.4 mEq/dL (normal range is 0.7 to 2.5 mEq/dL).

Barbiturates and Dilantin have both been shown to decrease the function of the respiratory chain.<sup>2</sup> As a result, Dilantin and phenobarbital are both contraindicated in patients with the MELAS syndrome



Fig 2. Magnetic resonance images. A) Increased proton density signal in temporal and parietal lobes (open arrow), and decreased signal in basal ganglia due to heavy calcification (closed arrow). B) Increased T2 signal intensity of both hemispheres.

(mitochondrial encephalomyopathy with lactic acidosis and stroke). After the diagnosis was confirmed with muscle biopsy, the patient was given Tegretol and his Dilantin was discontinued. It was felt that his recent exacerbation of symptoms may have been caused by the drug Dilantin. Late in January 1992 the patient developed a progressive cortical blindness and for that reason was given steroids, initially Solu-Medrol, 100 mg every 8 hours, and later prednisone, 60 mg per day. The patient was also started on the MELAS cocktail, which consists of vitamin K4, vitamin C, vitamin E, coenzyme Q10 (ubiquinone), riboflavin, thiamine, vitamin B2 (niacin), and biotin.

The patient's family history showed no evidence of symptoms consistent with the MELAS syndrome. The patient's mother and siblings were evaluated by urinary and blood analysis for polymerase chain reaction studies and their laboratory tests were negative.

The patient has shown gradual improvement of his neurologic status on the MELAS cocktail along with Tegretol for seizure control. The cortical blindness has resolved with minimal visual impairment. His sensorineural hearing loss is unchanged and he persists with a marked loss of auditory discrimination. He still has a very mild apraxia. He is presently on prednisone, 20 mg per day, and Tegretol, 900 mg per day, along with the MELAS cocktail.

### DISCUSSION

Mitochondrial encephalomyopathy has not been recognized by our specialty as a cause of progressive sensorineural hearing loss. While the neurologic literature mentions sensorineural hearing loss as one of the symptoms of mitochondrial encephalopathy, there is no mention in the otolaryngological literature of this entity. In the last decade there has been increasing interest in the multisystem diseases caused by defects of mitochondrial function. These disorders have been referred to as mitochondrial myopathy or mitochondrial encephalomyopathy.<sup>3-5</sup> Three syndromes associated with mitochondrial encephalomyopathy have been described: Kearns-Sayre syndrome,<sup>6</sup> MELAS,<sup>7</sup> and myoclonus epilepsy with ragged red fibers (MERRF).<sup>8</sup>

Myoclonic epilepsy associated with abnormalities of skeletal muscle was first described by Tsairis et al<sup>9</sup> in 1973. The acronym MERRF was suggested by Fukuhara<sup>10</sup> in 1983, when he was reviewing eight additional cases. The MELAS syndrome is considered in the differential diagnosis of encephalopathy and stroke in children and young adults. Although sensorineural hearing loss is reported as a symptom of the MELAS syndrome, the connection is not appreciated by our specialty. In the adult population the hearing loss may be the first presenting symptom of a much more complex disease. Most MELAS patients develop normally until they experience intermittent nausea, vomiting, and headache (migrainous in nature), followed by their first strokelike episode. The episodes most commonly result in transient cortical blindness, hemianopia, focal paresis, paralysis, and/or dysphasia. Initially these patients seem to improve despite the abnormalities seen on computed tomography and MRI scans. Their course is that of an episodic exacerbation of strokelike symptoms followed by partial recovery and eventual deterioration. Angiography has not revealed significant vascular disease in these patients.

The clinical course of the patient described is consistent with the MELAS syndrome. As demon-

TABLE 1. MULTISYSTEM INVOLVEMENT OF MITOCHONDRIAL ENCEPHALOPATHY

 Skeletal
Central nervous system
Muscle
Nerve (peripheral)
Heart
Retina
Kidney
Liver
Intestine
Endocrine and metabolic

strated in this patient, the MELAS syndrome has many overlapping symptoms compatible with herpes simplex encephalopathy. A distinguishing clinical feature is the absence of fever and a normal CSF count.<sup>1</sup> When mitochondrial encephalomyopathy presents in childhood, the patient is of short stature and the course of the disease is typically more severe. Our pediatric neurologic colleagues frequently assay for serum lactic acid to evaluate early-onset and congenital encephalopathy. As otologists, we do not typically investigate serum lactic acid, especially in the adult population.

Mitochondrial encephalomyopathies tend to be exacerbated by extremes of temperature, unusual physical exertion, hypoglycemia, emotional stress, and infection accompanied by fever, most likely because of the increased metabolic demands. The multisystem involvement and associated clinical features reported in mitochondrial encephalomyopathies are summarized in Tables 1 and 2.

At the present time it is not obvious whether these three clinical syndromes (Kearns-Sayre syndrome, MELAS, and MERRF) have distinct biochemical causes. The course of the disease appears to correlate better with the severity of respiratory chain dysfunction rather than with deficiency of a specific enzyme. As the patients progress with their illness, the clinical features may become less characteristic and the syndromes seem to overlap.

Mitochondrial disorders have a wide range of both clinical and imaging findings. Although no one set of findings is diagnostic of these disorders, a combination of deep gray matter involvement and peripheral white matter involvement in young adults and children suggests the diagnosis. Abnormal tissue primarily involves the posterior temporal, parietal, and occipital lobes. Prolonged T2 relaxation and heterogeneous uptake is seen on MRI in the involved regions. Mitochondrial disorders primarily affect the gray matter. When white matter abnormalities are present, they are almost always superimposed on

TABLE 2. CLINICAL FEATURES OF MITOCHONDRIAL ENCEPHALOPATHY

Kearns-Sayre syndrome
Ptosis
Retinopathy
Heart block
Cerebellar syndrome
Endocrinopathies
Elevated cerebrospinal fluid protein
White matter spongiosis
MELAS
Episodic nausea and vomiting
Migrainelike headaches
Strokelike episodes
Seizures
Gray matter spongiosis
MERRF
Myoclonic epilepsy
Cerebellar syndrome
Proximal weakness
Central hypoventilation
White and gray matter spongiosis

## gray matter disease.<sup>11</sup>

There are three other types of mitochondrial dysfunction associated with hearing loss in the literature. The first is out of an Israeli-Arab kindred, <sup>12</sup> including 55 persons identified with a progressive sensorineural hearing loss. The family aggregation is most consistent with a two-locus mode of inheritance. One locus is mitochondrial and the other autosomal. The second mitochondrial disorder is that of individuals identified who have a genetically determined susceptibility to aminoglycoside antibiotic–induced hearing loss.<sup>13</sup> Third, it has been suggested that mitochondrial DNA mutations are important as a contributing factor in aging-related degenerative sensorineural hearing loss, <sup>14</sup> particularly the strial presbycusis type.

In 1992, Jaber et al<sup>12</sup> reported an Israeli-Arab kindred in which 55 deaf subjects were identified who had a progressive sensorineural hearing loss. The genetic mode of transmission seems most consistent with a two-locus mode of inheritance, one mitochondrial and the other autosomal recessive. Audiometric studies confirmed a severe to profound sensorineural hearing loss in all of these individuals. General examination of the deaf subjects showed no abnormalities in general state of health, vestibular function, or other organ systems frequently associated with mitochondrial disorders. This pedigree shows a maternal inheritance by nonmendelian genetic factors and this can be explained either by genetic imprinting or mitochondrial inheritance. The authors felt the transmission was most compatible with mitochondrial inheritance. The authors also studied two other possibilities: a two-locus disease with simultaneous mitochondrial and autosomal genes, and second, a mitochondrial inheritance with various amounts of heteroplasmy. Mitochondrial analysis using various enzymes showed no evidence of deletions, duplications, or heteroplasmy. The authors conclude that the mutated mitochondrial subunit may function normally until it interacts abnormally with a hearing-specific protein encoded by the nuclear locus. They believe that their pedigree presents a unique opportunity to investigate for the first time the molecular basis of a nonsyndrome deafness.

Hu et al<sup>13</sup> describe an analysis of 36 pedigrees with a positive family history of aminoglycoside antibiotic-induced deafness. They studied a Shanghai population of 483,611 people in which there was a subset of patients who had antibiotic-induced ototoxicity transmitted by females exclusively, suggesting mitochondrial inheritance. They performed a reanalysis of 18 other published pedigrees that seemed to confirm that conclusion. Hu et al report familial aggregations of aminoglycoside antibiotic-induced toxicity, indicating that there is a possibility of genetic predetermination of the aminoglycoside susceptibility. Some authors have previously suggested an autosomal dominant inheritance, but Hu et al feel their 36 pedigrees are very suggestive of a mitochondrially transmitted disease. In their study, they demonstrated that the duration of therapy was definitely shorter in the group with a positive family history than in other individuals studied with aminoglycoside-induced ototoxicity. In 2 cases, hearing loss occurred after 1 day of treatment with streptomycin. When they reviewed the other 18 pedigrees that had been reported, they felt that reanalysis of 15 pedigrees showed exclusive female transmission, suggesting that the susceptibility to antibiotic ototoxicity is inherited through the maternal line. Maternal transmission can be explained by mitochondrial inheritance. Given that mitochondrial inheritance is the mode of inheritance of susceptibility to antibiotic ototoxicity, aminoglycoside antibiotic therapy should be avoided in those persons with a family history of ototoxic side effects from the drug.

In 1989, Linnane et al<sup>14</sup> reported the possibility of mitochondrial DNA mutations as an important contributor to aging and degenerative diseases. They proposed that the high rate of somatic gene mutation in the mitochondrial DNA and accumulation during life contributes substantially to aging. Mutations occur at a much higher rate in the mitochondrial DNA than in chromosomal DNA. Linnane et al suggest that tissues consist of a mosaic of cells with different mitochondrial bioenergetic capacities, in which the bioenergetically deficient components increase with age. They further raise the possibility of restoring critical enzyme activities encoded by the mitochondrial DNA with suitable redox substances.

Biochemical Aspects. Mitochondria are the subcellular organelles in which cellular respiration takes place in aerobic tissues. Energy is generated in the mitochondria by oxidative phosphorylation. Respiratory chain dysfunction produces signs and symptoms of disease primarily due to energy insufficiency. The specific clinical picture most likely depends on the degree of the particular enzyme deficiency and the specific tissues affected.

Mitochondrial Genetics. Mitochondria contain their own DNA and a complete system for replication, transcription, and translation. Mitochondrial DNA codes only 10% of total mitochondrial protein. The majority is coded by nuclear DNA, synthesized outside mitochondria, and then translocated across the membranes into the mitochondria. Biosynthesis of a normal respiratory enzyme complex requires the coordinated actions of both the nuclear and mitochondrial genomes. If either is dysfunctional, the system will fail.

Most mitochondria of a zygote are from the ovum. Sperm do not transfer mitochondrial DNA. Mitochondrial DNA is primarily inherited from the mother. Therefore, genetic information is transmitted only from females to both male and female offspring. The degree of involvement of a particular tissue may depend on how the abnormal mitochondrial DNA segregate (what percentage of mitochondria in that tissue is abnormal).

Evaluation of Patient With Mitochondrial Encephalomyopathy. The incidence of mitochondrial encephalomyopathy is probably greater than currently appreciated. Clinical involvement of muscle is usually not obvious in the majority of patients, and most physicians lack familiarity with the disease. It is important, therefore, for clinicians to recognize a pattern of signs and symptoms.

When the diagnosis of mitochondrial encephalomyopathy is suspected, lactic acid and pyruvic acid levels should be measured in both blood and CSF, and the lactate-pyruvate ratio calculated. All levels are usually elevated with respiratory chain dysfunction. Physical stress will cause an abnormal rise in venous lactate levels. If there is no other reason for a secondary elevation of lactate such as seizure, shock, or sepsis, the diagnosis should be considered and can be made with a muscle biopsy. Muscle tissue should be sent for histochemical and electron microscopic studies, and fresh muscle tissue sent to specialized laboratories for assays of mitochondrial function. Ophthalmologic evaluation may reveal signs of retinopathy, most commonly of the salt-and-pepper type. However, 60% of a heterogeneous group of patients with mitochondrial encephalopathy lacked evidence of retinopathy.<sup>15</sup>

*Treatment*. Treatment should consist of avoidance of stress and fever, small, frequent meals, avoidance of dehydration and certain drugs (barbiturates and phenytoin, which decrease the function of the respiratory chain; chloromycetin, which inhibits mitochondrial protein synthesis; and tetracycline, which inhibits mitochondrial protein synthesis), use of artificial electron acceptors, vitamins (K3, C, coenzyme Q, riboflavin, carnitine), and corticosteroids.<sup>16,17</sup>

## CONCLUSIONS

Mitochondrial encephalopathy is a cause of progressive sensorineural hearing loss in children and adults. Children usually present with encephalopathy, and the pediatric neurologist will usually evaluate these children with serum lactate and pyruvate levels. Because our patient presented first with sensorineural hearing loss as an adult, this case illustrates that it is important for otologists to be aware of this disease and evaluate patients with serum lactate and pyruvate levels. Because this disease does respond to therapy, we need to investigate whether or not we can slow the progression if we identify these patients early. There are no good studies to prove whether or not the progression of hearing loss can be prevented by appropriate therapeutic intervention.

Prior to 1992 there were only 10 cases in the world literature of sensorineural hearing loss in mitochondrial encephalomyopathy.<sup>18-24</sup> In 1993, three cases of the MELAS syndrome that were initially treated as herpes simplex encephalitis were presented.<sup>1</sup> None of these cases were presented in the otolaryngological literature. It is hoped that the present case will alert our specialty to the importance of pursuing an unusual cause of progressive sensorineural hearing loss.

Other mitochondrial DNA defects can lead to deafness, as evidenced by the description of the 22 pedigrees with deafness caused by mitochondrially transmitted susceptibility to aminoglycosides.<sup>13</sup> In addition, the Israeli-Arab pedigree<sup>12</sup> that suggests a combined mitochondrial and autosomal recessive disorder suggests yet another mitochondrially transmitted defect responsible for sensorineural hearing loss. As mitochondrial DNA mutations may be an important contributor to aging and degenerative diseases, further research in mitochondrial DNA and mitochondrially transmitted diseases may be very helpful to the identification of and potential therapy for various forms of sensorineural hearing loss.

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