Auditory Neuropathy and a Mitochondrial Disorder in a Child: Case Study

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Abstract

A child was referred for an audiologic evaluation, to include auditory brainstem evoked response testing, due to inconsistent responses to sound and delayed speech and language development. Results were characteristic of auditory neuropathy. In view of subsequent decline in motor function, a genetics evaluation was conducted, revealing a mitochondrial disorder. A brief overview of mitochondrial genetics in association with hearing loss is presented. The patient's audiologic profile is described and the implications for management are discussed.

Key Words: Auditory neuropathy, maternal inheritance, mitochondrial disorder, oxidative phosphorylation

Abbreviations: ABR = auditory brainstem evoked response, ATP = adenosine triphosphate, DPOAE = distortion-product otoacoustic emissions, MRI = magnetic resonance imaging, mtDNA = mitochondrial deoxyribonucleic acid, nDNA = nuclear deoxyribonucleic acid, OAE = otoacoustic emissions, OXPHOR = oxidative phosphorylation

It is only since 1988 that the role of mitochondrial DNA (mtDNA) in hearing loss and in several severe degenerative diseases has been described (Reardon and Harding, 1995). Hearing loss associated with mitochondrial defects can be divided into three major categories: systemic diseases that include hearing loss as part of the clinical presentation, tissue-specific mitochondrial disease where hearing loss is the major or only symptom, and hearing loss associated with aging. It is generally described as a progressive sensorineural hearing loss starting in the high frequencies. This paper describes a child with a major systemic disease caused by a mitochondrial defect and her clinical presentation of auditory neuropathy.

MITOCHONDRIAL DISEASE

Mitochondria are the intracellular organelles that control the synthesis of adenosine triphosphate (ATP) by oxidative phosphorylation (OXPHOR). OXPHOR is the major pathway involved in the production of ATP (Shoffner and Wallace, 1995). ATP is a compound that stores energy that can then be released in controlled and discrete amounts in a cell and is required for normal cell function. Mitochondria are not found in the nucleus but distributed in the cytoplasm of a cell. The number and position vary with the cell type. There are hundreds per cell and several molecules of mitochondrial deoxyribonucleic acid (mtDNA) per mitochondrion (Wallace, 1993; Gold and Rapin, 1994). In humans, the mtDNA is a molecule with 16,569 base pairs in a closed circular double strand rather than the double helical structure of nuclear DNA (nDNA). The mtDNA with its comparatively small number of base pairs has been mapped and abnormalities in the mitochondrial genetic code can be identified to the level of changes in individual base pairs. The DNA in the mitochondria encodes 13 proteins of the OXPHOR system (Vernham et al, 1994). These interact with at least 60 proteins encoded by the nDNA to form the five enzyme complexes required for ATP production (Fischel-Ghodsian et al, 1993; Vernham et al, 1994). The production of ATP is thus under both nuclear and mitochondrial control.
There are several major characteristics of mtDNA that make it distinct from the genetics of nDNA. Primarily, mtDNA has a pattern of maternal inheritance. At fertilization, the mitochondria from the ovum are incorporated into the embryo whereas those from the spermatozoa are lost. The mitochondria replicate independently within the cell and separately from the nucleus (Gold and Rapin, 1994). Mutations that occur in the germ line may result in maternally transmitted disease, whereas those that occur during development will give a spontaneous expression of disease. When a mutation of mtDNA arises, a mixture of normal and mutant mtDNA is created within a cell. The term for this mixture is heteroplasmy. Homoplasmy refers to an intracellular content of either all mutant mtDNA or all normal mtDNA. Heteroplasmy is unstable and tends to move toward homoplasmy (Bu et al, 1993). If heteroplasmy is present, the mitochondria will be randomly distributed between the daughter cells during cell division. Therefore, the proportions of heteroplasmic mtDNA can be different in separate cell lines (Reardon and Harding, 1995). Mutations in somatic tissues may produce heteroplasmy leading to age-related decline in OXPHOR and its consequences (Wallace, 1993). Rapid mtDNA replication occurs during the blastocyst (early embryonic) stage of development and can result in major shifts in the proportions of abnormal to normal mitochondria. So within a family with an inherited defect in mtDNA, there can be a wide variety in the presentation of the disease. If the cell has a percentage of mutant mtDNA such that it cannot produce enough ATP for the energy needs of the cell, then disease develops. Different tissues have different energy requirements. Those with high energy requirements are more susceptible to mitochondrial defects. Therefore, the central nervous system, heart, muscle, kidney, and endocrine organs are most likely to show the effects of mitochondrial transmitted diseases (Wallace, 1992). It has been suggested that sensorineural hearing loss is the presenting symptom in the onset of some mitochondrial inherited disease because of the high energy requirements of the cochlea, in particular, the stria vascularis.

Hearing loss is reported to be common in patients with mitochondrial disease (Matthijs et al, 1996). A review of the literature by Gold and Rapin (1994) found that about two of three individuals with mitochondrial disease have progressive sensorineural hearing loss. However, the hearing losses have not been described extensively, so it is unknown whether auditory neuropathy is a component. Neuropathies are commonly observed in patients with mitochondrial disease (Reardon and Harding, 1995) and so auditory neuropathy would not be an inconsistent finding.

**AUDITORY NEUROPATHY**

In the last few years, auditory neuropathy has become a recognized auditory pathology. Patients with auditory neuropathy complain of poor understanding of speech and have word recognition scores that are lower than expected relative to the measured hearing loss (Sininger et al, 1997). They generally show elevated and inconsistent responses to sound. Masking level differences are reported to be absent (Sininger et al, 1995). Acoustic reflexes are absent for both ipsilateral and contralateral stimulation. Otoacoustic emissions (OAEs) are of normal or greater than normal amplitude with no suppression of OAEs with contralateral stimulation (Berlin et al, 1993; Sinner et al, 1995). Auditory brainstem evoked response (ABR) testing shows reduced or absent neural synchrony, although a cochlear microphonic may be present (Sininger et al, 1995). Harrison (1998) describes these symptoms induced in chinchillas by carboplatin toxicity. The carboplatin selectively destroyed the inner hair cells while the outer hair cells remained relatively intact.

Auditory neuropathy has been associated with several genetic diseases including Charcot-Marie-Tooth (Berlin et al, 1994; Sininger et al, 1995; Starr et al, 1996), Fredrich's ataxia (Berlin et al, 1994), and mitochondrial disease (Deltenre et al, 1997).

**CASE REPORT**

A 2-year, 5-month-old girl was referred for ABR testing following inconsistent results with conventional audiometric soundfield testing and absent acoustic reflexes in the right ear with normal tympanometry. The ipsilateral reflexes in her left ear were present at 1000 and 2000 Hz. Her responses to speech were normal or near normal on two occasions, but responses to tonal stimuli were elevated. By parental report, her early developmental milestones were normal. She was sitting at 5 to 6
months and crawling at 5 to 7 months. She developed a 20- to 40-word expressive vocabulary. However, she failed to progress to walking independently or to combining words to form sentences. Before the age of 2 years, she underwent a neurologic evaluation. The assessment included magnetic resonance imaging (MRI), which was interpreted as normal. At 2 years, 5 months, she presented with speech delays, developmental delays, and possible cerebral palsy. Prior to ABR testing, distortion-product otoacoustic emissions (DPOAEs) of normal amplitude were elicited in the right ear (Fig. 1) (testing in the left ear was postponed due to reduced middle ear compliance). Sedation with chloral hydrate was used for ABR testing. The results for the right ear are shown in Figure 2. Early waves could be identified, but there was no latency change with a change in stimulus intensity. Therefore, it was concluded that the response was not neural in origin. Similar results of normal OAEs and absent neural responses on ABR testing were subsequently obtained for the left ear. Testing for contralateral suppression of OAEs was not possible due to equipment constraints. ABR tests were repeated and the polarity of the click stimuli was reversed for different runs. Reversing the click polarity will cause the polarity of non-neural components of the ABR to reverse as well. Summing the runs of opposite polarities will, therefore, cancel these components. The result of this operation is shown in Figure 3. It was thus confirmed that the original waveform of Figure 2 was a cochlear microphonic rather than a neural response.

Developmentally, this patient shows a severe regression in many of her motor and cognitive skills that she had previously mastered. An MRI of the brain done at 3 years of age showed cerebellar atrophy. A referral for a genetics evaluation was made. Multiple metabolic studies were completed and the results were normal. A muscle biopsy confirmed a suspected mitochondrial disorder and revealed abnormalities of the muscle.
fibers consistent with a defect in OXPHOR. Further tests showed significant defects in OXPHOR involving enzyme complexes I, II, and IV.

Since her initial evaluation at this facility at age 2 years and 5 months, the disease has progressed. She is now 4 years and 4 months and no longer uses any expressive speech, with the exception of “no” and some vowel vocalizations. A simple communication board has been tried without success. She is in a wheelchair and has very poor muscle tone to the extent that she needs head support and can no longer sit alone. An audiological evaluation is scheduled every 6 months. The OAEs continue to be of normal amplitude, but acoustic reflexes are absent. The most recent ABR at a slower repetition rate revealed a poorly formed and delayed wave V. The cochlear microphonic is clearly present. However, her general health has deteriorated to the extent that auditory function is no longer a primary concern.

The family history includes insulin-dependent diabetes mellitus of the mother. She is also reported to have a cardiac arrhythmia of a type commonly found in families with mitochondrial disease. Other significant family history includes a daughter of the maternal aunt who received a cochlear implant for hearing loss several years ago. Tests to distinguish between hearing and auditory neuropathy were not widely available until the mid 1990s. As this child is not available for testing, it is not known whether her OAEs are present in the nonimplanted ear.

**DISCUSSION**

This child has DPOAEs of normal amplitude, inconsistent responses to sound, abnormal ABR, and poor speech and language development. It is not known if this child has two independent rare pathologies of a mitochondrial disorder and auditory neuropathy or if the cause of the defect in oxidative phosphorylation is also the agent in the auditory neuropathy. However, neuropathies are often seen with mitochondrial disease and, if so, the site of dysfunction would probably be neural rather than cochlear. The breakdown of the auditory system could either be at the synapses between the inner hair cells and the type I afferent neurons or at the distal portion of those neurons. The normal OAEs and the intact cochlear microphonic indicate that at least the outer hair cells are intact and functioning; therefore, the breakdown of the auditory pathway is medial to the outer hair cells. Another possibility is that the timing of neural discharge is being affected by the slow recovery of individual neurons after an action potential. This could be caused by reduced availability of energy as produced by mitochondria in the form of ATP. This may disrupt the synchrony and reduce the number of individual neurons firing in response to a stimulus yielding abnormal results on ABR.

The finding of mitochondrial disease led to changes in medical, educational, and rehabilitative management of this child and the prognosis is poor. She was placed on coenzyme Q10 to improve oxidative phosphorylation. Education was changed to home bound. Therapy goals became the maintenance of skills already acquired and physical therapy focused more on the use of supports and assistive devices. Visual cuing in the form of visual phonics had been incorporated into speech therapy since the finding of auditory neuropathy, but with only limited success. Visual phonics attempts to provide a concurrent visual representation of speech sounds in a manner similar to cued speech.

This case serves as a reminder of the advantage of using a test battery approach. If OAEs had been used as a screen for normal hearing in this involved child and she had not received ABR testing, then the nature of her auditory deficits may not have been identified. When the etiology of auditory neuropathy is not known, a referral for a genetics evaluation may be a consideration. As mitochondrial disease caused by a mutation of mtDNA will be maternally transmitted, there is a high risk that all of the children of that mother will be affected to a greater or lesser extent and genetic counseling is crucial.

Anyone with known mitochondrial disease should be monitored for developing or progressive hearing loss. Conversely, a mitochondrial disorder should be considered in patients with progressive hearing loss, given the mode of inheritance and the possible expression of the disease in other organ systems.

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**REFERENCES**


