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Resolving Auditory Neuropathy Spectrum Disorder in a Case with Leigh's Disease

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Abstract

Leigh's Disease is a rare inherited neuro-metabolic disorder that affects the central nervous system in infants and children. The disorder is characterized by progressive neurologic deterioration. Patients with Leigh syndrome show inconsistent or absent ABR and abnormal interpeak latencies. Auditory neuropathy spectrum disorder has also been reported. Master PM, 2.8 years old, 2nd born to non-consanguineous parents was brought to our department with the complaints of inconsistent response to auditory stimuli and regression of developmental milestones including that of speech-language. MRI brain showed bilateral T2 FLAIR hyper intense signal changes in several sub-cortical regions of the brain including basal ganglia. ABR results showed ringing cochlear microphonics up to 60dB nHL in both the ears. ABR showed presence of 5th peak up to 70dB nHL in the right ear and 60dB nHL in the left ear. Oto-acoustic emissions were present in both the ears. Based on the results of audiological evaluation and improvement shown by PM in speech-language following neurological intervention, it is speculated that PM may have had a transient form of ANSD during his development.

Introduction

Leigh's Disease, named after Archivald Denis Leigh is a rare inherited neuro-metabolic disorder that affects the central nervous system in infants and children. Juvenile or infantile subacute necrotizing encephalomyelopathy and subacute necrotizing encephalomyelopathy are some of the other names for this disorder (Leigh, 1951). Progressive neurologic deterioration and bilateral spongiform lesions with demyelination, neural necrosis, vascular and capillary proliferation, bilateral focal lesions in the brain, brainstem, basal ganglia and spinal cord characterize the disorder. Bilateral involvement of the putamen, medulla, substantia nigra, thalami, globus pallidus, caudate nuclei, basal ganglia, and brain stem is seen on MRI (Ruhoy & Saneto, 2014). Delayed motor and language development, difficulties in feeding and swallowing, hearing impairment and loss of sensation may be seen in persons affected with Leigh's disease (Naviaux & Nguyen 2004; Nesbitt et al., 2013).

Auditory brain stem responses (ABR) are reflections of the electrical activity in the auditory pathway and thus are useful in evaluating the mechanisms of a number of neurological conditions including coma, midbrain and brain stem tumors, demyelination of the brain stem, and the presence of diminished brain stem circulation (Starr & Achor, 1975). Given the neuropathology of Leigh syndrome, ABR abnormalities can be expected in this disorder. Kaga, Naitoh, & Nihei (1987) and Davis, Aminoff, & Berg (1985) reported abnormalities on ABR, though of an inconsistent pattern, in their patients with Leigh's syndrome. Some of the observed deviations in ABRs in persons with Leigh's syndrome include prolonged interpeak latencies (I-V), absent wave V, and completely absent ABRs despite normal otologic examination. However, normal ABRs in these children do not exclude a diagnosis of Leigh syndrome (Taylor & Robinson, 1992) because not all those children with metabolic defects leading to Leigh syndrome showed abnormal ABRs though they manifested neuro-pathologic changes (as observed at autopsy) (Taylor & Robinson, 1992). If ABRs were present in these children, then they appeared to covary with metabolic findings as well as the clinical course of the disease. In addition, no specific pattern of ABRs can be thought as characteristic of Leigh syndrome.

However, Yoshinaga et al. (2003) reported that abnormal ABR recordings seemed to precede clinical signs of brainstem impairment in Leigh's disease. In addition, they noted, on follow-up evaluation, that improvements in clinical status of the patients were reflected in an improvement in ABR findings. Simon et al. (2015) reported bilateral

auditory neuropathy in a case with Leigh's disease as evident in the absence of ABR and preserved cochlear microphonics. However, OAEs were absent bilaterally. Early developmental milestones were normal. The absence of OAEs in this instance may indicate that the degenerative changes seen in Leigh's disease may also affect the inner ear (Ulualp, Wright, Pawlowski, & Roland, 2004). This brief review indicates that auditory system may be affected in children with Leigh's disease, but there is no uniqueness in the pattern of auditory deviations. The purpose of this study is to present atypical auditory findings seen in a child with Leigh's disease and to draw the attention of the readers to the possibility of transient auditory neuropathy in Leigh's disease.

Case Report

PM, a 2.8 years old child and second born to non-consanguineous parents, was brought with the complaint of regression of motor milestones. The child was born full term, cried immediately after birth and weighed 2.8 kg at birth. According to parents, PM was apparently normal until 1.3 years when there was insidious and progressive onset of tremors of upper and lower limbs. PM was able to walk without support before the onset of tremors, but now needed support. Parents were also concerned about the highly inconsistent response to acoustic stimuli by PM and regression of speech-language after he was 1.3 years. Parents observed occurrence of myoclonic jerks triggered by sound, temper tantrums, easy irritability, stranger anxiety and stubbornness in the child. PM was seen by a neurologist at the age of 1.5 years. An MRI of brain showed bilateral T2 FLAIR hyper intense signal changes in basal ganglia, inferior cerebellar peduncle, substantia nigra, symmetric putamen, central tegmental tract, and olivary nucleus. Neurologist initiated treatment for control of myoclonic jerks and tremors. PM responded well to the treatment and showed improvement in developmental milestones too.

The anxious parents brought PM to the Department of Neurology of NIMHANS for further management where a diagnosis of Leigh's disease was made. Eventually, PM was referred to Department of Speech Pathology & Audiology to address the concerns of the parents on the child's speech-language development and inconsistent responses to acoustic stimuli.

Audiological Evaluation

Distortion product OAEs were recorded (Echoport ILO 292-II) for a pair of tones (L1 and L2) at 65 and 55 dB SPL, respectively. Repeatability was checked through two separate runs for each ear. A separate analysis of each distortion product frequency was carried out to establish the validity and reliability of normal outer hair cell function. A distortion product amplitude (signal to noise ratio) of greater than or equal to 6 dB was considered to reflect a valid OAE response.

ABRs (IHS, Miami, Florida) were recorded between the upper forehead and ipsilateral mastoid, with the opposite mastoid as ground. Bandpass filtering was set between 100 and 3000 Hz, with manual and automatic artifact rejection. Responses were recorded for rarefaction and condensation polarity clicks presented at 90 dB nHL through insert earphones (ER-3A) and at a rate of 11.1 clicks per second. It was ensured that electrode impedance was <5 kOhms. ABRs were recorded three times, twice for rarefaction and once for condensation stimuli. 1200 samples were obtained in each instance. Tube clamping was resorted to determine the nature of response components - whether they are CMs or artifacts (recording or stimulus). If the responses are CMs, then they will disappear with tube clamping but the stimulus artifact will persist.

Two experienced audiologists, each with more than 10 years experience, made a blind and independent review of the recorded ABR waveforms. Reviewer 1 suspected cochlear hearing loss while reviewer 2 suspected auditory neuropathy spectrum disorder. Both of them, however, suggested correlation of ABR waveforms with the clinical information.

Speech and Language Evaluation

Receptive and expressive language acquisition of PM was assessed on the Receptive-Expressive Emergent Language tool (REEL3- Bzoch, League & Brown, 2003). PM was also assessed on 3D-LAT for receptive and expressive language as well as cognition.

Results

Ringing cochlear microphonics was present up to 60dB nHL in both the ears. 5th peak could be traced up to 70dB nHL in the right ear and 60dB nHL in the left ear. No other peaks were clear. Waveforms were characterized by poor signal to noise ratio (Figures 1 and 2). The OAEs were present in the right ear, with lower amplitudes, and present only for 3 frequencies in the left ear (Figures 3 and 4).

Speech-language evaluation at 32 months showed that PM had a receptive as well as expressive language age of 30 to 33 months on REEL. PM had a score of 30-32 months on each of the three dimensions of 3D-LAT.

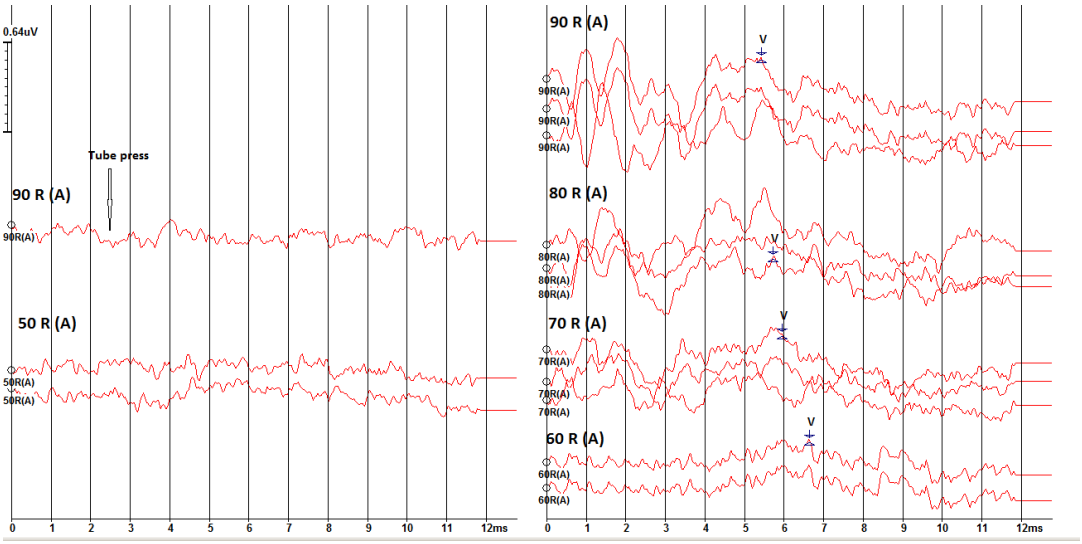

Figure 1: Auditory brainstem responses for the right ear. The four groups of waveforms correspond to 90, 80, 70 and 60 dB nHL.

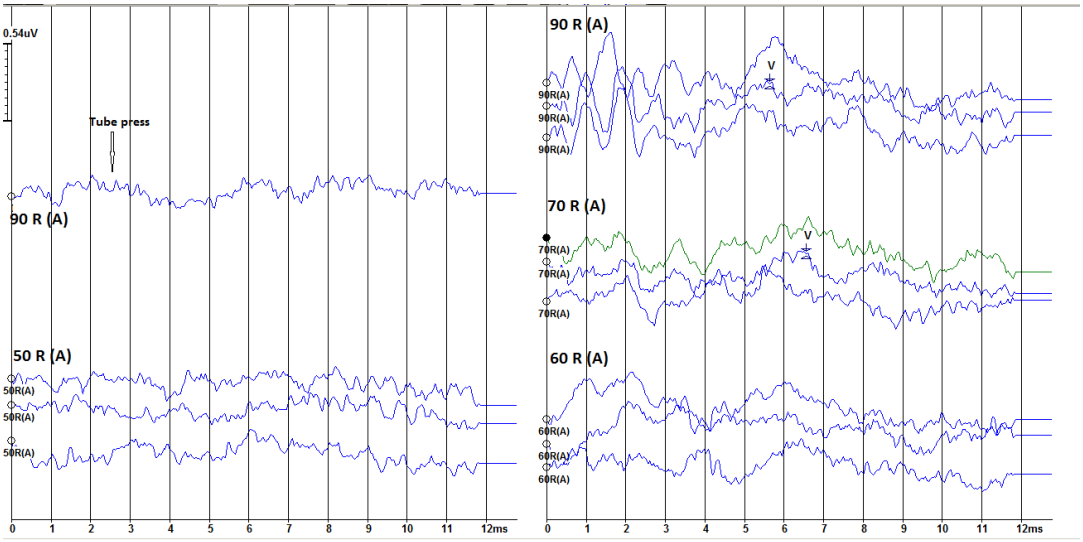

Figure 2: Auditory brainstem responses for the left ear. The four groups of waveforms correspond to 90, 80, 70 and 60 dB nHL.

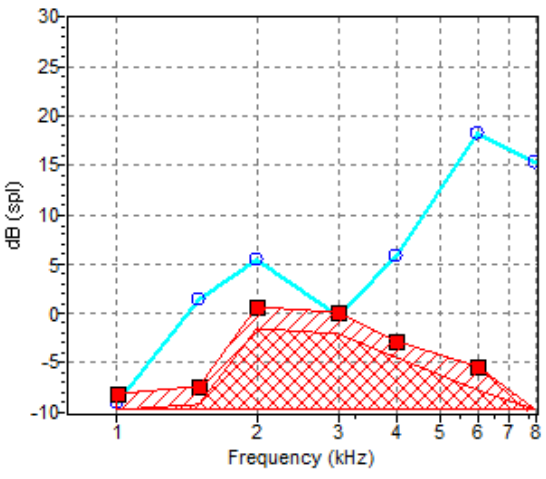

Figure 3: Otoacoustic emissions for the right ear.

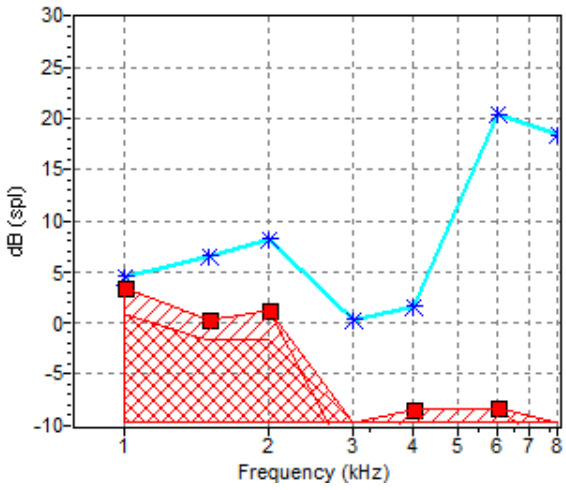

Figure 4: Otoacoustic emissions for the left ear.

Discussion

It is speculated here that audiological results in this child - not so robust OAEs and 5th peak up to 60dB nHL with cochlear microphonics - indicate some variant of ANSD. This assumption is supported by the observation that PM picked up almost normal speech-language after treatment for neurological problems was initiated after 1.5 years (when the child was seen by a neurologist for the first time). This would not have been possible if PM had permanent hearing loss during the crucial period between 1.3 and 2.0 years when the child was showing aberrant auditory behavior. It is true that presence of ABR at 60 dB indicates a 40 dB behavior threshold and a hearing loss of this magnitude may not result in gross speech and language delay. However, these thresholds were observed at 32 months and not in the period between 1.3 and 2 years when the child was showing some hearing related issues. We really do not know about the status of hearing in the child during this period. PM's developmental history as reported by parents (normal speech-language development until 1.3 years, inconsistent response to acoustic stimuli and regression of speech-language between 1.3 years and 2.0 years, and almost normal development of speech-language without any intervention beyond 2 years) support this assumption. Based on ABR, it is further speculated that the aberrant auditory behavior that PM showed earlier may actually be a transient form of ANSD.

Psarommatis et al. (2006) and Eom, Min, Lee, & Lee (2013) have reported cases of transient ANSD though not in children with Leigh's disease. Starr et al. (1998) reported transient deafness due to temperature-sensitive auditory neuropathy in 3 children. They explained that some children may develop a conduction block of the auditory nerve when their core body temperature rises due, most likely, to a demyelinating disorder of the auditory nerve with resultant hearing impairment of a transient nature. The report of Berlin et al. (2010) on 13 of the 260 children with auditory neuropathy who had no problem in language development and ended up needing no treatment can be taken as an instance of transient neuropathy. A suggestion has been made (Uus, 2011) for conceptualizing all observations of ABR recovery as instances of transient ANSD.

It is hoped that a second audiological evaluation will bring clarity on the auditory status of PM. If a second audiological evaluation shows improved ABR recordings compared to the first recording, then it would further substantiate the hypothesis that PM was going through a period of transient ANSD. This case study further confirms that transient ANSD may not be as rare as once believed. It further emphasizes the need to make provision for detecting instances of transient ANSD in all programs of hearing screening and early identification of hearing loss in children and infants.

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