Auditory Brainstem Response and Hearing Loss in MELAS: Post Mortem Analysis of Temporal Bone to Explain Abnormal ABR

Keywords: Auditory brainstem response; microRNAs; SGs

Abbreviations: ABR: Auditory Brainstem Response; SNHL: SensoriNeural Hearing Loss; PTA: Pure Tone Audiometry; SV: Stria Vascularis; ROS: Redox Oxidative Species; MELAS: Myopathy, Encephalopathy, Lactic Acidosis and Stroke-Like Episodes

Editorial

We would like to bring to the readers’ attention a specific aspect of Auditory Brainstem Response (ABR) in patients with Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis and Stroke-Like Episodes (MELAS). In the literature, it is often reported that the outcome of ABR testing is normal in these patients, even when they suffer from severe to profound SensoriNeural Hearing Loss (SNHL); however, some authors observed absence of ABR waves in mild forms of SNHL [1-6]. How can this disagreement in observations be explained?

We observed a MELAS patient who came to our Clinical Center for moderate SNHL. The ABR from this patient displayed waves (Figure 1) with amplitude and latency too reduced to be considered within the normal range, but not completely absent as it would be expected considering his auditory threshold in pure tone audiometry (PTA).

In an attempt to explain this observation, we reviewed the literature on the temporal bone aspect of MELAS patients. Loss of Spiral Ganglions (SGs) and atrophy of Stria Vascularis (SV) are typical findings in temporal bone of patients with MELAS even when the Organ of Corti is entirely preserved.

In SGs and SV mitochondria are abundant [7], as they are necessary to support the high metabolic functions of these structures. In MELAS, mitochondria that have been damaged (by deletion/mutation in their DNA) increase the Redox Oxidative Species (ROS) concentration [8] and cell apoptosis [9] which reduce the number of inner ear cells (SG, VS and Hair cells) and, cause a malfunction of the remaining cells.

ABR reflects the way the auditory signal travels from the retrocochlear portion (synapse, SGs, cochlear nerve and cochlear nuclei) (Waves I, III) to the cortex (wave V); if all the structures in the retro-cochlear hearing pathways function correctly, the ABR displays normal amplitude and latency; but damage in even one of the structures causes abnormal ABR latency and/or amplitude, which in turn alter the overall signal shape.

We think that the abnormal ABR of our patient can be explained by the altered functions of residual SGs, which cannot sufficiently amplify the signal to generate an actual ABR wave. The numerous mitochondrial mutations observed in the temporal bone of patients with MELAS [10-11] support the idea that the residual SGs do not function well enough to allow a correct transmission of the impulse, which in turn leads to an abnormal ABR. Arguably, the high ABR variability in MELAS patients reported in the literature [2,3,4,6] is due to the stochastic segregation of mitochondria during embryogenesis; the concentration of damaged mitochondria could differ among patients just due to...
“chance”. In a mitochondrial disease the cellular metabolism is altered (i.e., the ATP is reduced and the concentration of ROS is increased); this could lead to cell death and/or malfunctioning of residual cells.

Unfortunately, mitochondria are segregated in the cells in a random manner so an electrophysiological test such as ABR may not be sensitive enough to measure the inner ear damage. We are in the process of exploring the viability of using different techniques based on microRNAs specific for hair cells and SGs [12,13] for monitoring hearing loss progression. Due to their high sensitivity to detect cells death [9] and altered function [8], microRNAs may provide a valid alternative to traditional ABR test.

Acknowledgement
None.

Conflict of Interest
None.

References
1. Zwirner P, Wilczowski E (2001) Progressive sensorineural hearing loss in children with mitochondrial encephalomyopathies. Laryngoscope 111(3): 515-521.
2. Kullar PJ, Quail J, Lindsey P, Wilson JA, Horvath R, et al. (2016) Both mitochondrial DNA and mitonuclear gene mutations can cause hearing loss through cochlear dysfunction. Brain 139(Pt 6): e33.
3. Santarelli RM, Cama E, Scimeni P, La Morgia C, Caporali L (2016) Both mitochondrial DNA and mitonuclear gene mutations can cause hearing loss through cochlear dysfunction. Brain 140: 1-5.e1.
4. Sue CM, Lipsett LJ, Crimmins DS, Tsang CS, Boyages SC, et al. (1998) Cochlear origin of hearing loss in MELAS syndrome. Ann Neurol 43(3): 350-359.
5. Chen JN, Ho KY, Juan KH (1998) Sensorineural hearing loss in MELAS syndrome--case report. Kaohsiung J Med Sci 14(8): 519-523.
6. Vandanikk P, Binda PS, Sonam K, Govindaraj P, Taly AB, et al. (2016) Audiology manifestations in mitochondrial encephalomyopathy. J Laryngol Otol 130(3): m334-m3350.
7. Chiutsu I, Tatsuya Y (2014) Oxidative Stresses and Mitochondrial Dysfunction in Age-Related Hearing Loss. Oxidative Medicine and Cellular Longevity, 2014(2014): 6.
8. Xue T, Wei L, Zha DJ, Qiu JH, Chen FQ, et al. (2016) miR-29b overexpression induces cochlear hair cell apoptosis through the regulation of SIRT1/PGC-1α signaling: Implications for age-related hearing loss. Int J Mol Med 38(5): 1387-1394.
9. Someya S, Xu J, Kondo K, Ding D, Salvi RJ, et al. (2009) Age-related hearing loss in C57BL/6J mice is mediated by Bak-dependent mitochondrial apoptosis. Proc Natl Acad Sci U S A 106(46): 19432-34.
10. Takahashi K, Merchant SN, Miyazawa T, Yamaguchi T, McKenna MJ, et al. (2003) Temporal bone histopathological and quantitative analysis of mitochondrial DNA in MELAS. Laryngoscope 113(8): 1362-1368.
11. Koda H, Kimura Y, Ishige I, Iishi Y, Iino Y, et al. (2010) Quantitative cellular level analysis of mitochondrial DNA 3243A > G mutations in individual tissues from the archival temporal bones of a MELAS patient. Acta Otolaryngol 130(3): m344-m350.
12. Pang J, Xiong H, Yang H, Ou Y, Xu Y, et al. (2016) Circulating miR-34a levels correlate with age-related hearing loss in mice and humans. Exp Gerontol 76: 58-67.
13. Di Stadio A, Pegoraro V, Dipietro L, Giaretta L, Marozzo R, (2010) Hearing Impairment in MELAS: new prospective in clinical use of microRNA, a systematic review. Orphanet Journal of Rare Diseases publication in progress. UK.