Otoferlin Gene Mutation
in
Non Syndromic Auditory Neuropathy patients

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In

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By

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I. Introduction and Rationale

Auditory neuropathy (AN) is a hearing disorder characterized by preservation of outer hair cell function as indicated by the presence of oto-acoustic emissions (OAE) and/or cochlear microphonics (CM), with absent auditory brainstem responses (ABRs). Individuals with AN can have various degrees of hearing loss, with generally disproportionately poor speech understanding (Starr et al., 1996& 2000; Berlin et al., 1999, Wang et al., 2003).

Starr et al., (2000) & Varga et al., (2006) pointed out that in auditory neuropathy the lesion lies at the level of the inner hair cells (IHC), the IHC synapse to the afferent nerve fibers, or the auditory nerve itself.

The estimated incidence of auditory neuropathy within at- risk population is 0.23% or 11% of children with sensorineural hearing loss (Rance et al., 1999).

Approximately 50% of AN patients have no defined etiology (Starr et al., 2000). However, a genetic basis for neuropathy had been identified (Varga et al., 2003).

The relation between auditory neuropathy and mutations of OTOF gene were established for the first time in 2003 by Varga et al. who identified four different mutations on such gene to be responsible for auditory neuropathy of recessive heredity in four Spaniard families.

OTOF gene encodes otoferlin, a membrane-anchored calcium-binding protein that plays a role in the exocytosis of synaptic vesicles at the auditory inner hair cell ribbon synapse (Varga et al., 2003).

A multicenter study in 2008 on the prevalence and spectrum of deafness-causing mutations in the OTOF gene revealed that OTOF mutations are a major cause of inherited auditory neuropathy (Rodríguez-Ballesteros et al., 2008).

Morever mutation of the OTOF gene correlates with a phenotype of prelingual, profound non-syndromic recessive auditory neuropathy (NSRAN) without any other detectable peripheral neuropathies (Varga et al., 2003; Rodriguez-Ballesteros et al.; 2003; Tekin et al., 2005).

Identification of the underlying gene(s) for AN is one of the key challenges for understanding the molecular basis of different AN phenotypes. This helps define the mechanism of hearing and the specific role of IHCs and OHCs in this phenomenon. Also it may have important implications for diagnosis, newborn screening and prognosis. It improves our ability to provide appropriate communication skills and tools in a timely manner to those affected.

To date, mutations in OTOF gene among auditory neuropathy Egyptian patients have not been investigated. This work is hoping to explore the role of OTOF gene in auditory neuropathy patients among Egyptian population.

II. Aims of the work

1- To identify the characteristic mutations in the otoferlin gene associated with non syndromic auditory neuropathy in Egyptian population if any.

2- To find the relation between audiological profile and otoferlin gene mutation if found.

Chapter (1)
Auditory Neuropathy

It was almost 30 years ago that audiologists began to hear about patients with absent auditory brain stem responses (ABRs), but normal or near normal audiograms! In the early 1980s, Davis and Hirsh (1979), Worthington and Peters (1980), Lenhardt (1981) and Kraus et al. (1984) were among the first to publish case accounts of people with impaired speech comprehension out of proportion to the pure tone threshold deficits and absent ABR despite of the measurable hearing.

Fortunately, there has been an increasing interest in understanding this pattern of results and discovering underling anatomical and physiological processes. Even though detailed studies of the pathology, etiology even the time course of clinical and auditory test abnormalities in individual patients with this clinical syndrome are still incomplete.

Background of the term "Auditory neuropathy":

The term auditory neuropathy was first used by Starr et al. (1996) they suggested that this type of hearing impairment is due to a disorder of auditory nerve function and may have, as one of its causes, a neuropathy of the auditory nerve, occurring either in isolation or as part of a generalized neuropathic process and thus, coined the term 'auditory neuropathy'

Scientists have described patients with similar clinical findings, but with a wide variety of terms, such as "Low Frequency Sensorineural Hearing Loss Syndrome" (Soliman, 1987), "Neural synchrony disorder" (Starr et al., 1991), "Auditory Nerve Disease" (Kaga et al., 1996) and "Paradoxical hearing loss" (Davis & Hirsh, 1979).

Berlin et al. (2001) suggested the term auditory dys-synchrony instead of auditory neuropathy, as the cochlear nerve was not always injured, and therefore

the old term would be semantically incorrect. Even with this recommendation, however, both terms are still used in papers that describe those patients. As a result, auditory neuropathy/dyssynchrony (AN/AD) has emerged as a new term (Kaga et al., 2002; Santarelli & Arslan, 2002; Berlin et al., 2003a).

Definition of auditory neuropathy/dys-synchrony (AN/AD):

Auditory neuropathy/dys-synchrony (AN/AD) is a hearing disorder affecting auditory nerve function in the presence of preserved cochlear outer hair cell activity (Starr et al. 1996).

Sininger and Oba (2001) proposed that diagnosis of AN/AD ought to be based on all of the following criteria:

(1) Evidence of poor auditory neural function such as: Abnormal auditory brainstem response (ABR) in the form of delayed latencies and/or below normal amplitudes and/or abnormal waveform morphology (Rance, 2005). And elevated or absent other auditory brainstem reflexes such as stapedial reflexes and otoacoustic emissions suppression by noise (which is mediated by the olivocochlear bundle).

(2) Evidence of normal OHC function, such as normal OAE or cochlear microphonics on electrocochleography (ECochG). However, OAEs can disappear over time, whilst cochlear microphonics may remain present (Deltenre et al., 1999).

(3) Evidence of poor hearing with characteristic temporal and speech perception deficits which are disproportionate to the audiometric thresholds (Zeng et al., 2001).

Finally, Sininger and Oba (2001) proposed that exclusion of other potential causes ought to be made by appropriate investigations, such as a brain magnetic resonance imaging (MRI) to establish the structural integrity of the auditory nerve. A recent study identified hypoplastic or absent 8th nerve on brain MRIs in just under 20% of children with clinical characteristics of AN/AD (Buchman et al., 2006). This was more likely to be true if AN/AD was unilateral and/or the associated hearing loss was profound (Bamiou, 2009).

Prevalence of auditory neuropathy/dys-synchrony (AN/AD):

According to Colm et al. (2002) the prevalence of auditory neuropathy among patients with sensorineural hearing loss ranged from 0.5% up to 15% and many investigators lie within such range. Prevalence is estimated to range between 0.23% and 0.94% in infants "at risk" for hearing impairment (Foerst et al., 2006; Rance et al., 1999). The prevalence of auditory neuropathy among Egyptian infants and young children diagnosed to have severe to profound hearing loss is 13.4% (Sanyelbhaa et al., 2009).

Pathology of AN/AD:

Although the underlying lesion(s) and the pathophysiologic mechanisms in AN/AD are key-points in understanding and treating the disease, the related evidence is still unclear and, in some cases confusing (Vlastarakos et al., 2008).

The pathology of AN has not yet been defined but is likely to be similar to temporal bone studies of individuals with a 'sensorineural deafness' and hereditary peripheral neuropathy published about 30 years ago (Spoendlin, 1974; Hallpike et al., 1980). Those studies showed selective loss of auditory nerve and ganglion cells in the presence of preserved inner and outer hair cells. The authors noted their