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Mitochondrial Hearing Loss

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Introduction

Mitochondria are subcellular organelles arranged in a dynamic reticular network inside eukaryotic cells [1]. Although typified by their role in the generation of cellular energy, throughout their evolutionary history mitochondria have accumulated numerous ancillary cellular functions [2]. Mitochondrial dysfunction therefore compromises a number of aspects of cellular physiology and can lead to a range of human diseases, including hearing loss.

Hearing requires the mechanotransduction of sound pressure waves into neural signals by the inner hair cells of the cochlea. These signals are then relayed by auditory neurones to the auditory cortex. Dysfunction in any component of this pathway results in hearing loss, a dynamic, multifactorial condition that is prevalent both in patients with mitochondrial disease and the general population [3]. Mitochondrial mutations are a significant contributor to cases of genetic hearing loss and are estimated to be causative in approximately 5% of non-syndromic post lingual hearing loss in addition to 1% of pre-lingual cases [4,5]. Studies have also indicated that mitochondrial mutations may play a significant role age associated hearing loss [6].

It is well recognized that hearing loss is a feature of mitochondrial disease although ascertaining its true prevalence in patients with confirmed mitochondrial disease is complicated by both clinical and genetic heterogeneity. Moreover, under diagnosis, particularly in patients with complex neuromuscular phenotypes, is common. However, in one study of 23 patients with mitochondrial disease, including 10 with the m.3243A>G variant, that causes mitochondrial encephalopathy lactic acidosis and stroke like episodes (MELAS), 74% were found to have hearing loss [7]. Further studies investigating patients with a range of mitochondrial diseases have confirmed this high rate of hearing impairment in patients with mitochondrial disease [8,9].

Mitochondrial dysfunction is a cause of hearing loss both in isolation (non-syndromic) and as a feature of systemic mitochondrial disease (syndromic). The cells of the auditory sensory axis, including the cochlea hair cells, stria vascularis (that maintain the endocochlear potential) and auditory neurones are metabolically active and therefore are enriched in mitochondria. Studies have implicated the cochlea as the primary origin of disease with a loss of both outer and inner hair cells [7,10]. However, auditory neuropathy (i.e. hearing impairment with maintenance of cochlear function) has also been shown to be an important cause of hearing loss in a subset of mitochondrial diseases [11,12]. The sensitivity of the auditory pathway to mitochondrial dysfunction may result from inadequate mitochondrial oxidative phosphorylation in these metabolically active tissues. Although to date, the underlying molecular mechanisms, including that governing tissue specificity pose a challenging and an as yet unresolved question [13].

The hearing loss of mitochondrial disease is exclusively symmetrical, sensorineural and primarily affects the higher frequencies, although progressive disease can lead to pan-frequency hearing loss. The incidence of conductive hearing loss has been shown to be comparable to the general population [14].

The onset of mitochondrial hearing loss tends to be in infancy or early life with a gradual progression of the hearing loss, although sudden hearing loss has been described in stroke-like episodes in patients carrying the mt.3243A>G variant [15]. However, broad phenotypic variation means there often existing a range of hearing loss onset and severity even in family members carrying the same genetic variants. It has also been shown that hearing thresholds decline at a faster rate in m.3243A>G carriers compared to the general population, meaning it is important that patients have regular audiology follow up [16].

Mitochondria maintain their own genome, the mitochondrial DNA (mtDNA), which remains distinct from the nuclear genome. This means mitochondrial disease can result from mutation in nuclear genes encoding mitochondrial proteins or from mutation of mtDNA. Subsequently, mitochondrial hearing loss can be inherited following either a Mendelian or maternal inheritance pattern.

Mutations causing non-syndromic hearing loss are found in genes encoding components of mitochondrial translation machinery such as MTRNR1, that encodes the mitochondrial 12S ribosomal RNA and the MTTS1 gene encoding the tRNA for $Ser^{(UCN)}$. Whereas the commonest forms of mitochondrial syndromic hearing loss are associated with the complex neuromuscular syndromes Kearns-Sayre syndrome, MELAS and MERRF that are caused by large mtDNA rearrangements and variants in mitochondrial tRNA genes including MT-TL1 ($tRNA^{Leu(UUR)}$), MT-TK ($tRNA^{Lys}$) and MT-TE ($tRNA^{Glu}$) respectively.

There are also a number of nuclear genes that cause hearing loss directly as a feature of syndromic mitochondrial disease by perturbing mtDNA maintenance, the process of mtDNA replication or repair. For example, *OPA1* encodes a dynamin-related GTPase that regulates both mitochondrial fusion and mtDNA maintenance. Mutations in *OPA1* are commonly associated with Dominant Optic Atropy (DOA), a selective degeneration of retinal ganglion cells, however a subset of missense mutations cause a DOA-plus phenotype presenting with optic atrophy in conjunction with myopathic features, progressive external opthalmoplegia and hearing impairment [17]. Intriguingly, different mutations within this gene result in hearing loss through divergent mechanisms with haploinsufficiency mutations causing a cochlear loss whereas missense mutations manifesting primarily with auditory neuropathy [12]. Other mtDNA maintenance genes associated with mitochondrial deafness include *SUCLA2*, *RRM2B* and *C10ORF2*. Similarly, mutations in genes involved in apoptosis (*SMAC/*

Diablo) and oxidative chain complex assembly (*COX10*, *BCS1L*) have also been implicated.

Mitochondria are the primary source of cellular reactive oxygen species (ROS) generated as a by-product of oxidative phosphorylation. Noise exposure is known to drive increased mitochondrial ROS production that may exceed the buffering capacity of cellular antioxidants thereby leading to oxidative stress. The subsequent death of cochlear hair cells is then driven in part by mitochondrial-mediated activation of cellular apoptosis. Recently, there has been some evidence that treatment with antioxidants may attenuate hair cell death and subsequent threshold shifts [18].

Mitochondria play a key role in cellular homeostasis and hence cellular ageing. Due to the vulnerability of the mtDNA to mutation, genetic changes accumulate throughout life. However, deciphering which of these genetic changes is specific to age induced hearing loss is an ongoing challenge. A common deletion (mtDNA 4977bp) has been seen to be over represented in temporal bone material from patients with age onset hearing loss as compared to aged matched controls [6]. Similarly, studies in mouse models of age associated hearing loss suggest the accumulation of mtDNA mutations and increased oxidative stress in the cochlea contribute to age related hearing loss (ARHL). Yet a recent analysis of the mitochondrial genome in 400 individuals (200 with normal hearing and 200 with hearing loss) found no association between mtDNA mutation load and ARHL [19].

Currently, there are no available pharmacological or cellular treatments for sensorineural hearing loss in general or that associated with mitochondrial disease. Sound amplification by hearing aids used with or without hearing assistive technology systems remain the mainstay of treatment. In cases of severe hearing loss cochlear implantation may be indicated and this technology has been used effectively in patients with m.3243A>G, DOA, Kearns-Sayre syndrome and MNGIE syndrome [12,20-22].

It is the hope of researchers and patients that as our understanding of the pathological mechanisms in mitochondrial disease will continue to grow. In time, these advances will inform genetic counselling, improve prognostication and lead to the design of more effective therapies for patients suffering from mitochondrial associated hearing loss.

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