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Hearing loss molecular analysis

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ABSTRACT

In the past it was difficult to identify children with hearing loss, and many newborns remained undiagnosed, but since early 2000, when Universal Newborn Hearing Screening (UNHS) came into place and made successful strides in hearing loss research and have been able to provide screening of hearing loss at an early age of one month, hence they have been able to receive comprehensive treatment. UNHS also tracks infants for further follow up and wherever necessary. The two main methods used in newborn screening are otoacoustic emission and automated auditory brain stem response. Medical evaluation should begin as soon as possible when hearing loss is suspected, so as to complete prenatal, medical, and family history. Demands have been made to use DNA testing in detecting the molecular basis of hereditary hearing loss. The identification of genes and gene defects faces a lot of challenges due to the fact, there is tremendous genetic heterogeneity, but despite that, there has been successful genetic studies of hearing loss in isolated populations and consanguineous families. Hearing loss is common in patients with mitochondrial disorders, affecting over half of all cases at some time in the course of the disease. Hearing loss has seen some research undertaken to the point now that deafness can be treated and this is through cochlea implantation.

Keywords: Genetic test, Hearing loss, Molecular analysis, Sensorineural

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INTRODUCTION

Hearing loss that is manifested as the single phenotype in deaf patients is classified as a non-syndromic deafness and accounts for 70% of the total cases, whereas in 30% of the cases, deafness occurs as one of multiple phenotypic syndromic manifestations [1]. Hearing loss has a genetic etiology in the majority of cases and is very common. The universal newborn hearing screening program, together with remarkable recent progress in the characterization of genes associated function of hearing, have resulted in increased demand and exciting possibilities of detecting the molecular basis of hereditary hearing loss through DNA testing [2, 3].

In the past, a screening approach with inclusion of only high risk infants failed to identify at least 50% of children with hearing loss, and many newborns without risk factors remained undiagnosed until after 18 months of age, if diagnosis and intervention take place before 6 months of age, however, an almost age appropriate level of language skills can be accomplished [2]. In 2000, the

joint committee on Infant hearing has endorsed Universal Newborn Hearing Screening (UNHS). The aim is to provide hearing screening to all newborns before the age of 1 month, with confirmation of hearing loss in infants who do not pass the initial, or a subsequent screening, through an audio logic evaluation by the age of three months. Comprehensive treatment can then be initiated before the age of 8 months. Most children identified this program have parents with normal hearing [4].

Hearing loss can be identified by several different complementary methods. Following the guidelines from the National Institutes of Health, all United States have adopted UNHS, but testing algorithms and requirements vary.

The two main methods used in newborn screening are optoacoustic emission and automated auditory brain stem response [5]. Despite the fact that UNHS has its own limitations, it is the first step towards a successful and cost-effective program. The main goal for UNHS is the diagnosis and management, normal language development and long term success after intervention. There are developments for data management and tracking of infants for follow up.

As soon as hearing loss is suspected, medical evaluation should begin as soon as possible so to complete prenatal, medical, and family history. Some of the risk factors that should be checked during this time include low birth weight, difficulties in breathing and chromosome abnormalities [6]. Laboratory testing should be individualized and directed toward the suspected diagnosis [7]. Identification of the cause of hearing loss is the highest priority of parents who learn that their child is hearing impaired [8].

Molecular diagnostics

As mentioned earlier that the characterization of genes associated with function of hearing, have resulted in increased demand and exciting possibilities of detecting the molecular basis of hereditary hearing loss through DNA testing [8]. Tremendous progress has been made in our understanding of the molecular basis of hearing and hearing loss. New molecular mechanisms of hearing impairment have been unveiled through recent that have been made in trying to understand the fascinating biology of the auditory system. Diagnostic impact of genetic testing has seen some changes take place, as well as exciting developments in therapeutic options.

It is estimated that in the near future, Molecular diagnosis, which is already a reality for several hearing-associated genes, will doubtlessly continue to increase, both in terms of the number of mutations tested and the spectrum of genes [9].

Genetic analysis for hearing loss is mostly used for diagnosis and treatment, and relatively rare for reproductive decisions, in contrast to other inherited disorders. Impressive genetic heterogeneity is what characterizes Inherited hearing loss. An abundance of genes carries a large number of mutations [10–12], but specific mutations in a single gene may lead to syndromic or non-syndromic hearing loss.

Hearing loss is a major public health concern, because it is common to all ages and affects 6 to 8% of the population in developed nations when all causes are combined and it is the most common birth defect [13, 14]. Following the implementation of the UNHS the incidence was found to be even higher than previously thought. With the vast research that been going on for a while, it has been found that 1 in 1000 newborn are deaf, one in 300 children are affected with congenital hearing loss of a lesser degree, and an additional one in 1000 become profoundly hearing impaired before adulthood [15]. Before the implementation of early hearing detection and intervention programs, the average age at diagnosis was 1.5 to 3 years, which is well beyond the beginning of the critical interval for speech and language acquisition [16]. Undiagnosed hearing loss and diagnostic delay have a profound impact on linguistic and communicative competence, as cognitive psychosocial development. Delayed recognition may lead to isolation later in life.

There are several factors that can lead to hearing loss in one way or the other, the factors may be, environmental factors, genetic defects, or a combination thereof [16]. The best scenario we are going to use is the U.S, whereby hearing loss, is commonly caused by environmental factors such as prematurity, infections, exposure to ototoxic medications, and trauma. It is estimated that at least 50% prelingual hear loss is caused by genetic changes [17], whereas the etiology remains obscure in the remaining 25%. Most of these cases, however, are assumed to be of genetic origin. Hence the largest proportion of hearing loss causes is accounted genetically [18].

Genetic testing for hearing loss

Hearing loss can follow a pattern of autosomal recessive, autosomal dominant, X-linked, and mitochondrial inheritance. The genetic basis is highly complex. Recessive and dominant hearing loss can be caused by Allelic mutations in some genes. Mutations in the same genes can cause syndromic and non-syndromic hearing loss [19], and recessive hearing loss may be caused by a combination of two mutations in different genes from the same functional group.

The identification of genes and gene defects faces a lot of challenges due to the fact; there is tremendous genetic heterogeneity [19, 20]. Considering the complexity of the auditory system, which requires interaction of a diversity of proteins including ion channels, extracellular matrix, cytoskeletal proteins, and transcription factors, this is not surprising. However, it hampers gene identification by traditional genetic methods such as he grouping of multiple families for linkage analysis [21].

Genetic studies of hearing loss have been successful in isolated populations and consanguineous families. Even after the gene has been localized to a region on a chromosome, however, the process of positional cloning

via a physical map followed by transcript identification can be arduous. Some identified loci, including DFNB1, DFNA2, and DFNA3, have been found to harbor multiple genes [22]. Recent advances in genomics has greatly facilitated the identification of genes. In the field of non-syndromic hearing loss, 21 genes associated with autosomal recessive inheritance, 20 associated with autosomal dominant inheritance, and one with X-linked recessive transmission have been identified and characterized [22, 23].

Genetic factors play a major role in up to two thirds of all childhood hearing impairment. Molecular genetic testing assists otologists by providing insight into the etiology of hearing impairment in children. 50 to 100 genes are estimated to be involved in the functioning of the ear. Mutations in any of those genes may cause hearing loss [24].

Mitochondrial hearing loss

Hearing loss can be of two types, either it is sensorineural or conductive. But in this article will shall be majoring mostly on sensorineural hearing loss [17]. Dr. Peter Kullar, Clinical Research Fellow at the Wellcome Trust Research Centre for Mitochondrial Disease at Newcastle University (UK), defines sensorineural hearing loss as the changes within the cochlea or within the nerves that lead to the brain [18].

Mitochondrial diseases are disorders caused by impairment of the mitochondrial respiratory chain. The genetic error can affect both mitochondrial DNA (mtDNA) and nuclear DNA (nDNA) [2]. MtDNA mutations are classified as either large scale rearrangements (duplications) which are usually sporadic or point mutations, which are usually maternally inherited, and concern genes responsible for protein synthesis (rRNAs or tRNAs) [8, 9, 19, 25], or genes encoding subunits of the electron transport chain (ETC) [20]. The phenotypic reaction of mtDNA mutations depends on the affected gene, its tissue distribution, and the different dependency of different organs and tissues on the mitochondrial energy supply. Visual and auditory pathways, heart, central nervous system (CNS), and skeletal muscle are the tissues mostly involved, because of their dependence on aerobic energy production.

Hearing loss is common in patients with mitochondrial disorders, affecting over half of all cases at some time in the course of the disease. Although the final common pathway for the hearing loss is thought to involve ATP deficiency secondary to a biochemical defect of the respiratory chain, the clinical presentation of mitochondrial deafness varies considerably, both in terms of associated clinical features and of natural history [21]. In some patients' deafness is only part of a multisystem disorder, often involving the central nervous system, neuromuscular system, or endocrine organs in other cases, deafness may represent a feature of an oligo syndromic disease.

By contrast, there are also a number of mitochondrial "pure" deafness disorders; maternally inherited deafness is the most common due to the A1555G mutation in the 12 s rRNA gene, MTRNR1 [26]. The use of streptomycin and a lesser extent other aminoglycoside antibiotics can cause hearing loss genetically susceptible individuals. These drugs are known to exert their antibacterial effects at the level of the decoding site of the small ribosomal subunit, causing miscoding or premature termination of protein synthesis. The hearing loss is primarily high frequency and may be unilateral. Risk factors for aminoglycoside ototoxicity include therapy lasting more than seven days, elevated serum levels, prior exposure to aminoglycosides, noise exposure, and high daily dose [22].

Several mutations in the MTRNR1 gene encoding the 12S rRNA (961delT/insC, T1095C, C1494T, A1555G [27–30], and probably A827G, T1005C and A1116G) and possibly also mutations (G7444A) in the COI/MTTS1 gene overlap can contribute to ototoxic hearing loss. The MTRNR1 probably alter the secondary structure of the 12S rRNA molecule, so that it resembles its bacterial counterpart, the 16S rRNA, more closely. Mitochondrial noon syndromic sensory neural hearing loss (SNHL) is also associated with the A7445G, 7472insC, T7510C, and T7511C mutations in the tRNASer (UCN) gene, MTTS1 [24].

The pathological examinations of the inner hear is technically demanding, highly specialized, and only possible postmortem. There have, therefore, only been a few detailed pathological studies of the auditory system in patients with mitochondrial diseases [23]. In the cochlea, the stria vascularis maintains the ionic gradient necessary for sound transduction and the complex interaction between inner and outer hair cells. These relative deficiency of intracellular ATP would impair the function of both the stria and the air cells, ultimately leading to cell death, possibly through apoptosis.

Hearing loss is usually peripheral (due to cochlea or auditory nerve dysfunction), but in patients with a multisystem mitochondrial disorder, the auditory system may be affected at the brain stem, midbrain or at a higher level in the auditory cortex [24]. The peripheral hearing loss typically affects high frequencies first, followed by intermediate frequencies, and finally involving low frequencies and causing the typical "flat" audiogram seen in a severely deaf individual [16]. The preferential involvement of high frequencies [16, 25] may be related to the relatively high energy requirements of the basal cochlea. The vast majority of patients with mitochondrial deafness have absent optoacoustic emission, providing strong evidence that the cochlea is the component most sensitive to mitochondrial dysfunction [26].

The degree of hearing loss correlates well with the mutation load in skeletal muscle, and the progressive nature of the hearing loss may be related to the accumulation of mutated mtDNA within the cochlea [11, 27]. Although this appears to be the general trend, there are clear exceptions to the rule. In one patient with the A323G mutation, severe hearing loss was associated with low levels of mutated mtDNA in skeletal muscle [28,

29]. This may occur because of unequal segregation of mutated mtDNA among different tissues during early development, so that occasionally, by chance high levels are present in the cochlea precursors, and lower levels in skeletal muscle precursor cells [28].

As mentioned earlier that we shall be studying only syndromic form of mitochondrial SNHL, showing that the frequency of hearing loss in our group of patients is the same of the most of studies reported in literature [29].

Treatment

Deafness is the only sensory defect that can be treated successfully even if the deafness is complete. A recent cochlear implant in children of 8 to 9 years of age who received their implants before the age of five, demonstrated that all children benefited from cochlear implantation in the areas of speech production, speech perception and language [2, 17, 30]. There was a significant positive difference in cognitive and reading performance in children with identified GJB2 mutations, which cause an isolated insult to the cochlea without damage to the Vilith nerve or the central auditory system.

Even though the hearing loss in other children may be non-syndromic and isolated in appearance, the underlying etiologies are likely to include asymptomatic congenital cytomegalovirus (CMV) and undiagnosed meningitis. Thus these children are likely to face SNHL with subtle additional disabilities due to central effects. Cochlea implant surgery has also been performed in patients with MELAS, maternally inherited diabetes and deafness. Even though a variety of mutations can cause mitochondrial hearing loss and although variable severity as well as progression after initial onset are characteristic, cochlea surgery has been highly beneficial. This strongly suggests that the pathological changes resulting from the mtDNA mutations primarily affect the cochlea [30].

CONCLUSION

A lot of credit needs to be given to the field of hearing loss and deafness because of the strides they have taken in the areas of research, newborn screening, molecular diagnosis, and treatment. Hearing loss can now be identified early, and early confirmation results in possibility of more inclusive usage of language and speech. In the cases of non-syndromic SNHLGJB2 mutation analysis should always be offered, preferably instep wise combination with GJB6 testing. Mitochondrial inheritance and testing should be considered in any family with multiple affected individuals. When more assays become available, molecular testing could become the first in the casual determination while more invasive testing may be avoided. Once cause is established, treatment such as cochlea implantation can dramatically improve communication and quality of life for many patients.

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Author Contributions

Shuaib Kayode Aremu – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

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Omotosho Wasiu – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

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Data Availability

All relevant data are within the paper and its Supporting Information files.