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Hearing Loss and M.1555a>G Mitochondrial Mutation

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Abstract- *Introduction:* Hearing loss (HL), one of the commonest sensory disorders, can be caused by a variety of environmental and genetic factors 1. Genetic HL of nonsyndromic form can be caused by mutations in both nuclear and mitochondrial genes 3. Mitochondrial mutation (m.1555A>G) in the MTRNR1 gene is related to HL. The aim of this study is to describe the m.1555A>G genetic mutation in the MTRNR1 gene and its relationship with hearing loss plus medical literature review.

Methods: A retrospective study of medical records of a patient who was diagnosed with profound hearing loss and m.1555A>G mutation. The medical literature review was performed using the MeshTerms: genetic hearing loss; non-syndromic hearing loss and m.1555A>G.

Keywords: *genetic deafness; A155G; hearing loss.*

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Hearing Loss and M.1555a>G Mitochondrial Mutation

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Abstract- *Introduction:* Hearing loss (HL), one of the commonest sensory disorders, can be caused by a variety of environmental and genetic factors [1]. Genetic HL of nonsyndromic form can be caused by mutations in both nuclear and mitochondrial genes [3]. Mitochondrial mutation (m.1555A>G) in the MTRNR1 gene is related to HL. The aim of this study is to describe the m.1555A>G genetic mutation in the MTRNR1 gene and its relationship with hearing loss plus medical literature review.

Methods: A retrospective study of medical records of a patient who was diagnosed with profound hearing loss and m.1555A>G mutation. The medical literature review was performed using the MeshTerms: genetic hearing loss; non-syndromic hearing loss and m.1555A>G.

Results: Female, 16 years-old, hearing loss since birth, whith a sister and niece profoundly deaf since birth too, no change in the physical examination. Imaging studies without anatomical alterations. Auditory evoked potential in 90 dB HL bilaterally. Genetic study identified the presence of m.1555A>G mutation in the MTRNR1 gene without aminoglycoside exposure. Discussion: The m.1555A>G mutation is a common cause of genetic HL in Brazil. Genetic counseling regarding maternal inheritance, and assist pharmacological strategies for the prevention or diminution of HL progression.

Conclusions: Early treatment can allow many infants to develop normal language skills, using hearing aids, cochlear implants, audiologic rehabilitation, speech-language therapy and pharmacological therapy. Gene transfer by viral vectors or nanoparticles represents a promising approach for delivering therapeutic genes into the inner ear[18]. Stem cells have been the subject of intense speculation as they open radically new therapeutic possibilities[18].

Keywords: *genetic deafness; A155G; hearing loss.*

I. Introduction

Hearing loss (HL) is one of the commonest sensory disorders and can be caused by a variety of environmental and genetic factors [1]. More than 70% of hereditary HL is non-syndromic, while the remaining cases are accompanied by other clinical features and categorized as syndromic ones [2].

Genetic HL of non-syndromic form can be caused by mutations in both nuclear and mitochondrial genes [3]. It is estimated that the inheritance of non-syndromic HL is autosomal recessive in 80% of cases, autosomal dominant in 20%, X-linked in 1% and mitochondrial in 1% of cases [2].

In 1993, Prezant et al. first reported the association of HL with a mitochondrial mutation, the m.1555A>G in the *MTRNR1* gene. It has been found that this mutation is related to aminoglycoside-induced HL, since it alters 12S rRNA subunit, making it more similar to the bacterial ribosomal 16S rRNA and thereby enhancing aminoglycoside binding and its toxic effects on the ear [4].

An overview of reported mitochondrial mutations can be found in the Human Mitochondrial Genome Database – MITOMAP (http://www.mitomap.org) [5].

The aim of this study is to describe the m.1555A>G genetic mutation in the *MTRNR1* gene and its relationship with hearing loss plus medical literature review of this topic.

II. Materials and Methods

A retrospective study of medical records of a patient who was diagnosed with profound hearing loss and m.1555A>G mutation.

The medical literature review was performed using the MeshTerms: *genetic hearing loss; non-syndromic hearing loss and* m.1555A>G.

a) Audiometric Testing

The subject had unaided pure tone audiometry tests at 250, 500, 1000, 2000, 3000, 4000, 6000, and 8000Hz. We used an AC30-SD25 audiometer, calibrated according to ISO389/64. The same audiologist conducted all the pre- and postoperative tests.

b) Molecular study

Genomic DNA was extracted from the peripheral venous blood of patients, according to standard protocols.

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Genetic testing for mutations in the *GJB2* gene, as well as the del (*GJB6*- D13S1830) and del (*GJB6*-D13S1854) mutations in the *GJB6* gene, and the m.1555A>G mutation in the *MTRNR1* gene was performed. *GJB2* mutations were screened by direct sequencing of the gene coding region [6,7].

A multiplex PCR methodology was used to detect del (*GJB6*-D13S1830) and del (*GJB6*-D13S1854), according to the procedures reported previously [8,9].

Analysis of m.1555A>G was performed by PCR amplification followed by digestion with the *Bsm*AI restriction endonuclease, as described by Prezant et al.[4].

c) Ethics

The institutional review board approved this study and all subjects gave written
informed consent.

Recognizes only loud noises and alert sounds. Denies tinnitus, dizziness or otorrhea. Do not have gestational or perinatal history.

Sister and niece (sister's daughter) has profoundly deaf since birth, with the use of hearing aids.

Patient oral language, is literate, but have poorly developed speech.

No change in the physical examination.

The imaging studies (CT and MRI) do not reveal anatomical alterations of the peripheral and central auditory system of the patient.

Audiological evaluation showed remnants hearing in the low frequencies bilaterally, as shown in Table 1. Tympanometry is normal bilaterally, with the acoustic reflections.

The auditory evoked potential (ABR) showed electrophysiological hearing threshold 90 dB HL bilaterally.

III. Results

Female, 16 years-old, complaints of hearing loss since birth.

Tabela 1 : Audiometric pure tone thresholds.

kHz/dB	0,25	0,5	1	2	3	4	6	8	SD
Right Ear	75	85	95	105	115	120	Aus	110	80
Left ear	85	95	100	105	120	Aus	Aus	110	85

Legend: SD: detection threshold speaks in monosyllables.

Genetic study identified the presence of m.1555A>G mutation in the *MTRNR1* gene in a homoplasmic state. The patient with the m.1555A>G mutation had not aminoglycoside exposure. A family history of HL was also noted, with a strong matrilineal inheritance.

IV. Discussion

According to previous studies, this is a common cause of genetic HL in Brazil. It was found in approximately 2% of unselected subjects with HL, and was recommended for inclusion in molecular diagnostic testing for HL [10, 11]. Additonally, mutation screening is especially important in countries where aminoglycosides are widely used, as in Brazil.

Early identification of patients with SNHL due to mutations in mitochondrial DNA can influence genetic counseling regarding maternal inheritance, enable avoidance of known risk factors, and assist pharmacological strategies for the prevention or diminution of HL progression [12]. Of the children who develop childhood-onset HL with a genetic basis, the majority (around 70%) are non-syndromic, and arise predominantly from mutations inherited in an autosomal recessive pattern. In less than 1% of cases, inheritance is either X-linked, or mitochondrial13. The most frequent causative genes that have been identified in autosomal recessive non-syndromic HL, in ordem of frequency are GJB2, SLC26A4, MYO15A, OTOF, CDH23, and TMC1[13].

Maternally-inherited hearing impairment due to mutations in the mitochondrial genome appears to be a rare cause of prelingual HL, but the most commom mitochondrial mutation, m.1555A>G, can predispose to irreversible HL resulting from aminoglycoside exposure[13].

A recent study from China analyzed 658 unrelated patients with NSHL and 462 normal-hearing individuals for a mutational screening including GJB2 and mtDNA 12S rRNA genes using PCR and DNA sequencing technology. There were 7 pathogenic mutations in the 12S rRNA gene and 39 subjects harbored the m.1555A>G mutation
(5,93%) in mtDNA 12S rRNA[14].

A Taiwanese study was performed to explore the factors that might contribute to the differences in the phenotypes, including aminoglycoside exposure, mutation load and mitochondrial DNA background. As

the result it was found that the mitochondrial m.1555A>G mutation accounted for 3,2% of the Taiwanese families with sensorineural hearing impairment of unknown etiology[15].

Another study was performed in China to make a clinical, molecular, and genetic characterization of maternal hereditary pedigree in a Province from that country. The G7598A mutation was absent in 100 unrelated healthy controls in that region. Therefore, it may have a modifying role, enhancing its penetrance and severity, in the aminoglycoside antibiotic-induced deafness associated with the 12S rRNA A1555G mutation in the Han Chinese pedigree[16].

A previous Spanish study found a prevalence of the A1555G mutation of 25,8% among patients with family history of HL, of 75% in patients with cochlear ototoxicity and family history of HL and 100% in patients with cochlear ototoxicity and family history of aminoglycoside cochlear ototoxicity via maternal transmission[17]. In general, the prevalence of the A1555G mutation has been shown to be between 20-30% in deaf individuals in Spain and Asia, of which 15% had a history of aminoglycoside ototoxicity.

In Italy, the A1555G mutation is responsible for 5,4% of cases affected with isolated idiopathic sensorineural hearing impairment[18]. Genetic screening for the A1555G mutation is still laborious, and no cost-effective has been demonstrated; thus,
the use of aminoglycosides should be limited to very severe infections[18].

Early treatment of HL can allow many infants to develop normal language skills. Current approaches of SNHL are represented by hearing aids and cochlear implants, although recent advances in human genomics and molecular biology have led to the identification of mechanisms and defective genes causing deafness, which represent novel putative therapeutic targets[18].

a) Conventional hearing aids

Conventional hearing aids are indicated in children with moderate to severe hearing loss inducting delayed speech or articulation disorders. Indication for hearing aids in children with bilateral severe SNHL is also discussed in relation to the cochlear implant and depends on the benefits of amplification[18].

b) Bone-anchored hearing device (BAHD)

The principle of a bone-anchored hearing aid (BAHA) is based on sound conduction through bone via a percutaneous osseointegrated implant. In the pediatric population, the indications for BAHA include congenital aural atresia and microtia, and unilateral profound and mixed HL.

BAHA has also been used in children with chronic suppurative otitis media, chronic otitis externa and traumatic ossicular chain disruption after failure with conventional aids[18]. Marsella et al. described that the main indications for BAHA are a minimum age of three years at the time of implantation and/or cortical bone thickness ≥ 3mm as documented by CT[19].

c) Implantable middle-ear devices

These devices stimulate the ossicles and improve comfort by allowing the ear canal to remain open and not occluded. Currently, implantable middle-ear devices are indicated for patients aged 18 years or older, as an alternative to conventional hearing aids for individuals who are either unable to wear hearing aids or reject them for a variety of reasons[20].

d) Cochlear implants

Indications for cochlear implantation are constantly changing and are influenced by developments in technology, disease knowledge and experience of the physicians involved. The guidelines adopted by most European centres are those issued by the National Institute for Health and Clinical Excellence (NICE, UK, 2009). The timing for surgery is still controversial: in the US, the FDA requires waiting until the child is one year of age, while NICE does not establish a lower limit of age. According to the literature, the age limit below which the cochlear implant guarantees the development of languages skills and understanding closer to those of normal hearing subjects is around 18 months of age[18].

e) Auditory brainstem implant (ABI)

The auditory brainstem implant (ABI) is similar in terms of design and function to a CI except that the electrode is placed in the cochlear nucleus in the brainstem. ABI is designed for individuals with HL due a non-functional auditory nerve such as those affected by VIII nerve aplasia, temporal bone fractures, bilateral vestibular schwannomas (from neurofibromatosis type 2; NF2) or severe ossification of the cochlea and modiolus.

Limitations for good performance of ABI are represented by the lower stimulation selectivity due to the positioning of the electrode on the surface of the
brainstem that allows large electric field interactions between electrodes[18].

f) Audiologic rehabilitation and speech-language therapy

Audiologic rehabilitation is the process of providing training and treatment to improve hearing for children who are hearing impaired. The services provided will depend on each individual´s needs and are based on the following factors: age, age of onset of the HL, age when HL was discovered, degree of HL, type of HL and age when hearing aids were first used[21].

g) Pharmacological therapy

Several experimental drugs have been proposed for treatment of SNHL, although few clinical trails have been conducted. Clinically, antioxidant strategies can be used as add-on neuroprotective

therapy after perinatal oxidative stress, but they are not studied in preventing deafness.

Corticosteroids have been proposed for the treatment of the trauma after the insertion of a cochlear implant electrode and in preventing sequelae of meningitis.

Antiviral therapy has been proposed in the treatment of CMV: ganciclovir, valganciclovir, foscarnet, cidofovir and CMV hyperimmune globulin.

V. Final Comments

Finally, knowledge of molecular mechanisms of developmental process (i.e. Sox 2, Atoh1 and Notch signaling pathways) or genes involved in differentiation (i.e. espin, myosin VII, whirlin) offers hope for the treatment of inner ear diseases.

Gene therapy involves the up-regulation or down-regulation of specific genes in order to treat human disease[22]. Genes can be inserted in to cells using electric pulses, encasement in lipid-like spheres, or by packaging into viruses[22]. Gene transfer by viral vectors or nanoparticles represents a promising and novel approach for delivering therapeutic genes or molecules into the inner ear[18].

Stem cells have been the subject of intense speculation and controversy for many years as they open radically new therapeutic possibilities[18].

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