TONAL AUDIOLOGICAL PERFORMANCE EVALUATION AFTER COCHLEAR IMPLANTATION IN CHILDREN WITH GJB2 GENE RELATED HEARING LOSS

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Abstract:
Introduction: Audiological performance in cochlear implanted children may vary depending of the etiology of the deafness, one of which is GJB2 gene mutations.
Aim: In this study we evaluated the auditory performance by pure tone audiogram testing after unilateral cochlear implantation for children with GJB2 related mutations and to compare the results with the ones from children that did not show any mutations in the GJB2 gene.
Material and Methods: We have determined the auditory tonal thresholds in 28 patients and we calculated the average of these thresholds for the frequencies of 500, 1000, 2000 and 4000Hz. We have taken into consideration the first tonal thresholds that averaged at 35dB or better for the given frequencies.
Results and Discussions: Comparison between the average tonal thresholds between the two groups show that even though children from the GJB2 mutation related deafness group need a slightly longer period of time to reach minimal conversational level thresholds, the dB value of these levels is lower than the ones in the second group.
Conclusions: This can prove to be a useful tool for the clinician regarding cochlear implant counselling and for the patient in terms of better speech understanding skills and oral communication with parents and educational staff.

Key words: connexin 26, GJB2 mutation, audiological evaluation, deafness, cochlear implant.

INTRODUCTION

Hearing loss is the most common sensorial deficit of the childhood and the sensorineural hearing loss is the most common of all congenital hearing losses with an incidence in new born of 1 to 1000. Sensorineural hearing loss has a great impact on communication skills due to lack of normal development of verbal abilities and leads to inadequate language acquisition. The children that are affected by this condition will permanently be followed by these disabilities unless optimal treatment is implemented early. The best treatment choice is cochlear implantation at the right moment so that the child can have the best verbal and auditory rehabilitation possibilities[(1)].

At least 50% of all congenital sensorineural hearing loss are considered to be genetic and 2/3 of these are nonsyndromic, where the hearing loss is the only pathologic condition. About 80% of the genetic nonsyndromic forms sensorineural hearing losses are autosomal recessive transmitted [(2,3)].

The sensorineural hearing loss causes are genetic (syndromic and nonsyndromic), viral, bacterial,

immunologic, iatrogenic (ototoxic drugs related) and traumatic.

The evaluation protocol consisted of: medical history of the disease, associated symptoms, past personal and family medical history, complete clinical examination, complete ENT examination, imaging testing – CT and IRM, examination of thyroid, renal, hepatic and immunologic functions, tests for syphilis, toxoplasmosis and cytomegalovirus and also interdisciplinary complex examination (ophthalmologic, paediatric, clinical genetic, psychiatric, neurologic)[4].

The genetic evaluation of a child with sensorineural hearing loss was limited in the past to a dismorphologic evaluation and a detailed family study. The genetic advice offered so little information to the patient that most of them (including some physicians) didn't find it very helpful.

The identification, in the years that passed, of many genes that can cause nonsyndromic or syndromic sensorineural hearing loss brings light upon diagnosing genetic deafness. Data from the literature shows for the nonsyndromic cases the identification of 28 loci for recessive hearing loss, 33 for dominant, 3 for either dominant or recessive inheritance, 5 for X-linked and 2 for mitochondrial[5]. In addition to these loci, 19 genes have been cloned for nonsyndromic deafness. Regarding the syndromic deafness there have been over 400 forms described and the most common are: Waardenburg, Usher, Alport, Jervel and Lange-Nielsen, Norrie, brachio-oto-renal, Stickler, Pendred and Treacher Collins[5].

A big progress was made in 1997 when the first nuclear gene implicated in nonsyndromic sensorineural hearing loss was discovered – the gap-jonction-beta-2 gene (GJB2)[6]. The mutations in the GJB2 gene on the DFNB1 locus on 13q12 are responsible for 50% of the cases of autosomal recessive nonsyndromic sensorineural hearing loss[7].

In the last years there have been more that 70 mutations of the GJB2 gene discovered in patients with nonsyndromic sensorineural hearing loss [8,9]. However these mutations have a wide variation dependant on different types of populations[8,10,11]. The most frequent of these mutation in the European population is the 35delG mutation, having also a frequency of homozygous occurrence of over 60%[8,9].

The GJB2 gene encodes for connexin 26, a protein that forms intercellular gap junctions connecting the supporting cells in the cochleea. The dysfunction of these channels, that have an important role in recycling the K^+ from the extra cellular space to stria vascularis [12], leads to hair cells intoxication and hearing loss.

The hearing loss caused by the 35delG mutation varies from mild to profound and most of the patients with homozygous state have hearing loss ranging from severe to profound[8,13].

AIM: In this study we have tried to evaluate the auditory performance by pure tone audiogram testing after unilateral cochlear implantation for children with GJB2 related mutations and to compare the results with the ones from children that did not show any mutations in the GJB2 gene. Because of the lack of statistic analysis and insufficient numbers in literature the evaluation of the auditory

outcome of unilateral cochlear implanted GJB2 related sensorineural hearing loss represents a very useful tool for the counselling clinician and to help predict the auditory outcome before the cochlear implant surgery.

MATERIALS AND METHODS

Our study consisted of 28 patients and the inclusion criteria were children with prelingual sensorineural hearing loss and unilateral cochlear implantation. These children were randomly selected from a group of 95 patients, cochlear implanted in the ENT Clinic, Clinical Rehabilitation Hospital, "Gr. T. Popa" University of Medicine and Pharmacy in Iasi.

The genetic tests for the GJB2 mutations were carried out in accordance with the protocol, in the Department of Oto-Rhino-Laryngology, Head and Neck Surgery, University Medical Center Freiburg, Albert-Ludwigs University Freiburg, Germany. The study was approved also by the Ethics Committee of the Rehabilitation Hospital Iasi (No. 12511 – 10.07.2009).

Informed consent was obtained from the patients, parents or legal guardians for children before collecting blood for genetic testing.

We have formed 2 groups: group A comprised 14 children with GJB2 related sensorineural hearing loss and group B comprised 14 children with sensorineural hearing loss without any mutations in the GJB2 gene. These two groups are comparable by sex, age and age of implantation.

The tonal auditory performance with the cochlear implant was evaluated by free field pure tone audiogram. The tests were carried out with the AA222 AudioTraveler audiometer and calibrated speaker system with Interacoustics preamplifier.

Audiometric testing was carried out after the implant activation on account of the visits to the hospital for periodic fitment in the Audiometry Compartment of the Clinical Rehabilitation Hospital, without any knowledge regarding the genetic test results.

RESULTS AND DISCUSSIONS

In this study we intended to research whether there is any difference regarding post-implantation auditory performances of the children from the two groups: group A with GJB2 related sensorineural hearing loss and group B with non-GJB2 related sensorineural hearing loss.

The auditory outcome in children after cochlear implantation can be influenced by early age of implantation[14], socioeconomic status[15] and etiology of hearing loss[16].

The cochlear implant works by directly stimulating the auditory nerve cells and the spiral ganglion cells [17] with electric impulses.

According to previous experimental studies conducted on man and mouse, the GJB2 mutation related sensorineural hearing loss does not affect the spiral ganglion cells, all lesions being limited to the cilia cells. Furthermore patients with GJB2 related deafness do not exhibit any other neurological problems except from the sensorineural hearing loss, although GJB2 expression is absent in their brain.

Studies on patients with GJB2 unrelated deafness have showed a smaller

cellular population in the spiral ganglion [11]. These patients can have other mutations in nonsyndromic deafness genes such as OTOF [18], GJB3 (connexin 31) [19], KCNQ [20] associated with pathologic changes in the auditory nerve of central auditory pathway.

We have determined the auditory tonal thresholds and we calculated the average of these thresholds for the frequencies of 500, 1000, 2000 and 4000Hz. We have taken into consideration the first tonal thresholds that averaged at 35dB or better for the given frequencies. The testing method was adapted according to the age of the cochlear implanted child and we used the subjective audiometric method as well as the visual reinforcement audiometry.

The auditory rehabilitation protocol used by our clinic offers successive fitting sessions after activation at one month, 3 months, 6 months, 9 months, 12 months, 18 months, 24 months and then yearly. There are however cases that require reconfiguration of this protocol according to personal needs.

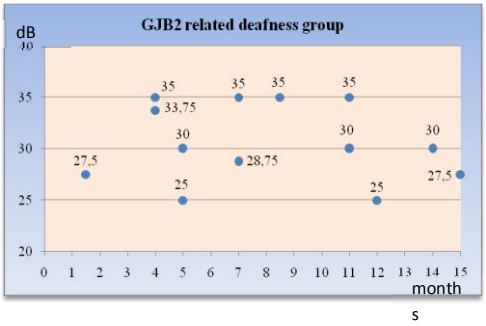

Figure 1. Average tonal threshold values distribution in time

Although we want to evaluate the free field auditory performance with the cochlear implant after every fitment session, it is not always possible to carry out this test because of several issues: the age of the child, the child may become tired or develop lack of collaboration.

After analyzing the data provided by the audiologic testing we have found out that the group A – GJB2 related sensorineural hearing loss had reached the first average tonal threshold of 35dB or better in a greater period of time from the implant activation as seen on Fig. 1.

We have discovered a relatively even time distribution to reach the required average after activation, ranging from 1,5 months to 15 months. The average tonal threshold values reached in this period was relatively evenly distributed starting from 25dB up to the limit of 35dB.

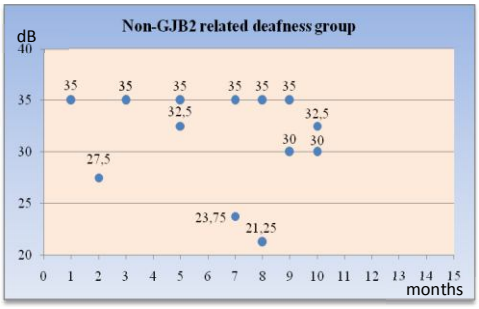

Figure 2. Average tonal threshold values distribution in time

In the second group – non-GJB2 related sensorineural hearing loss we have found a shorter period of time for the patients to reach the average tonal threshold, ranging from 1 month to 10 months after implant activation (Fig. 2). In contrast to the first group, we can see that most of the patients reach the considered average threshold between months 5 and 10. Furthermore the tonal threshold values are less evenly distributed, few of them averaging less than 30dB.

Fig. 3 shows clearly that the GJB2 related deafness group (shown in red line) has a lower overall average of the tonal thresholds (30.53dB) and thus reaching a conversational tonal thresholds faster than the non-GJB2 related sensorineural hearing loss group (average of 31.60dB).

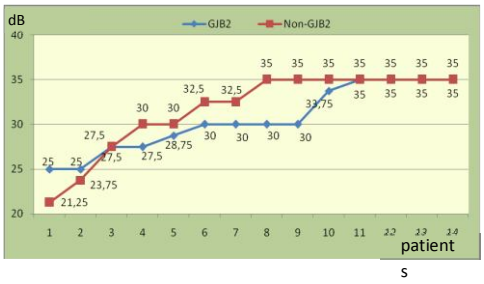

Figure 3. Average tonal threshold values distribution for the two patient groups

The results we found are in accordance with studies that have examined GJB2 related sensorineural hearing loss [21,22,23,24,25]. However some studies found no difference between the two groups [26,27,28,29]. This might arise partially from the fact that some of these studies have small sample size, lack of proper statistically analysis or short follow-up.

CONCLUSIONS

The aim of this study was to analyze if the children with a GJB2 mutation sensorineural hearing loss have better

audiometric outcome than those with other etiologies.

Comparison between the average tonal thresholds between the two groups show that even though children from group A need a slightly longer period of time to reach minimal conversational level thresholds, the dB value of these levels is lower than the ones in the second group. This can prove to be a useful tool for the clinician regarding cochlear implant counselling, as an accurate prediction of the auditory outcome before cochlear implantation is extremely valuable. Results are even more important for the patient who can have an advantage related to better speech understanding skills, thus improving his chances for oral communication with parents and educational staff.

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