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Association of *GJB2* gene mutation with cochlear implant performance in genetic non-syndromic hearing loss

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ABSTRACT

Objective: To analyze the association of *GJB2* gene mutations with cochlear implant performance in children.
Methods: Sixty-five consecutive children who underwent cochlear implantation due to congenital profound senseurineural hearing between 2006 and 2008 were included in the study. In children, *GJB2* gene mutation analysis was performed. Their auditory performance was assessed using MAIS, MUSS and LittlEARS tests.
Results: Twenty-two of sixty-five patients *GJB2* mutations, and 35delG was the most frequent mutation. No significant difference was found between the auditory performance of mutation positive and negative children after one year follow up ($p > 0.05$).
Conclusion: *GJB2* gene mutations do not impact on the outcome of cochlear implantation.

1. Introduction

Sixty percent of the congenital hearing losses are genetic in origin [1]. In non-syndromic forms, almost 20% of all hearing losses and 50% of the autosomal recessive hearing losses are caused by *GJB2* gene mutations [2,3] *GJB2* gene is located on chromosome 13q12, and its mutation causes abnormal *Connexin 26* protein synthesis [4]. *Connexin 26* protein functions in K^+ ions homeostasis in the cochlea [5]. *Connexin 26* expression has been shown in the stria vascularis, basement membrane, limbus and spiral prominence of the cochlea [1,6,7]. According to the histopatologic evaluations, despite the near total degeneration of hair cells in the organ of Corti, there is no neural degeneration and a good population of spiral ganglion cells exists in *Connexin 26* related deafness [7].

Cochlear implantation has become a common treatment to restore the auditory sensation in profoundly deaf individuals. Outcomes of cochlear implantation are highly variable depending on numerous factors such as age at onset of the hearing loss, implantation age and amount of residual hearing [8,9]. Another probable factor that can affect the outcomes of the cochlear implants is the etiology of hearing loss. Etiologies including neural and/or central damage to the auditory system have poor outcomes after cochlear implantation than those primarily affecting the hair cells like hereditary non-syndromic deafness [5,9,10].

Evaluation of cochlear implant performance can be performed using different tests, one of which is. EARS (Evaluation of Auditory Response to Speech) test battery. This test battery consists of subgroups of tests such as Meaningful Use of Speech Scale (MUSS) and Meaningful Auditory Integration Scale (MAIS). In infants and little children, LittlEARS Auditory Questionnaire (LEAQ) can be used to assess cochlear implant performance.

The association of *GJB2* mutations with cochlear implant performance has been investigated in numerous studies, and the results are conflicting. In this study, using EARS test battery, we aimed to assess the affect of *GJB2* gene mutations on the auditory performance of children who had cochlear implantation due to profound hearing loss.

2. Materials and methods

Sixty-five consecutive children who underwent cochlear implantation due to congenital bilateral profound senseurineural hearing loss between 2006 and 2008 were included in the study. The study protocol was approved by the Ethical Committee of the University. None of the children had a syndromic hearing loss, malformed inner ear or a disorder that could affect the central auditory pathways. There were 36 girls and 29 boys with

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implantation ages ranging from 1 to 14 years with a mean age of 3.8 years.

Preoperative evaluation included the followings; history, physical examination, audiological tests (behavioral audiometry, evoked response auditometry, and otoacoustic emission testing, and pure tone and speech audiometry if applicable), and computed tomography and magnetic resonance imaging of the temporal bone. A standard cochlear implantation was performed (mini incision, posterior tympanotomy, round window insertion) either with Nucleus or Medel implants. A full electrode insertion could be achieved in all surgeries.

MAIS, MUSS and LittlEARS tests were performed to analyze the auditory performance of the patients. MAIS and MUSS questionnaires were performed to all patients preoperatively and at the 1st, 6th and 12th months after the implantation by the educational audiologist. LittlEARS questionnaire (LEAQ) was used for the patients aged less than 2 years.

The patients were also divided into subgroups which could affect the post-implantation performance of the children. The patients who were regularly using a hearing aid for more than 3 months preoperatively were accepted as adequate hearing aid users. The patients who were irregularly using or never used a hearing aid preoperatively were accepted as inadequate hearing aid users.

2.1. Molecular analysis

Venous blood samples were obtained from the patients during the operation for *GJB2* mutation analyses. Genomic DNA was isolated from samples of peripheral blood of the patients. Molecular analysis was performed by the Department of Molecular Biology and Genetics in Gazi University Faculty of Medicine.

2.2. Statistical analysis

SPSS 11.0 (SPSS, Inc., Chicago, IL, U.S.A.) was used. Paired samples *t* test was used to compare the auditory scores of the patients before and after implantation. Independent samples *t*-test was used to compare the results of mutation positive and mutation negative patients.

3. Results

GJB2 mutations were found in 22 of 65 (33%) patients (11 boys and 11 girls). 35delG was the most frequent mutation, and 16 (72%) children were homozygous for this mutation (Table 1). The mean operation ages of the mutation positive (3.9 ± 3.4 years) and mutation negative (3.6 ± 2.7) children were similar ($p = 0.786$).

In mutation negative group, the mean preoperative MAIS score was 7.12. Postoperatively, this score increased to 15.2, 25.7 and 31.8 at 1st, 6th and 12th months, respectively ($p < 0.01$). Preoperatively, the mean MAIS score was 8 for the mutation positive group. Postoperatively, this score increased to 16.1, 27.5 and 35 at 1st, 6th and 12th months, respectively ($p < 0.01$). There was no significant difference between the MAIS scores of the mutation positive and mutation negative patients ($p = 0.326$) (Fig. 1).

Table 1
Genotypes of the cochlear implantees.

Genotype	*N* (%)
35delG homozygote	16 (72)
Val153Ile heterozygote polimorfism (GTC>ATC) c457G>A	2 (9)
Del120e homozygote	1 (4.5)
L90P CTA>CCA homozygote c.269 T>C	1 (4.5)
c.487 A>G, 163 M>V heterozygote	1 (4.5)
c.100A>G M34V heterozygote	1 (4.5)

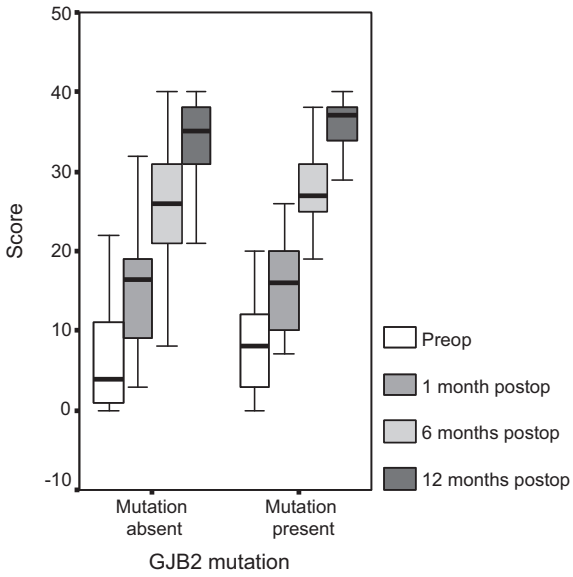

Fig. 1. MAISS scores of *GJB2* mutation positive and negative patients.

In mutation negative group, the mean preoperative MUSS score was 5.7. Postoperatively, this score increased to 7.7, 13.2 and 20 at 1st, 6th and 12th months, respectively ($p < 0.01$). In mutation positive group, the mean preoperative mean MUSS score was 5.6. Postoperatively, this score increased to 8.6, 14.5 and 21.9 at 1st, 6th and 12th months, respectively ($p < 0.01$). There was no significant difference between the MUSS scores of the mutation positive and mutation negative patients ($p = 0.149$) (Fig. 2).

In mutation negative group, the mean preoperative LEAQ score was 0.5. Postoperatively, this score increased to 3, 13, and 21 at 1st, 6th and 12th months, respectively ($p < 0.01$). In mutation positive group, the mean preoperative LEAQ score was 0.3. Postoperatively, this score increased to 2.5, 13.7 and 23.7 at 1st, 6th and 12th months, respectively ($p < 0.01$). There was no significant difference between the LEAQ scores of the mutation positive and mutation negative patients ($p = 0.146$) (Fig. 3).

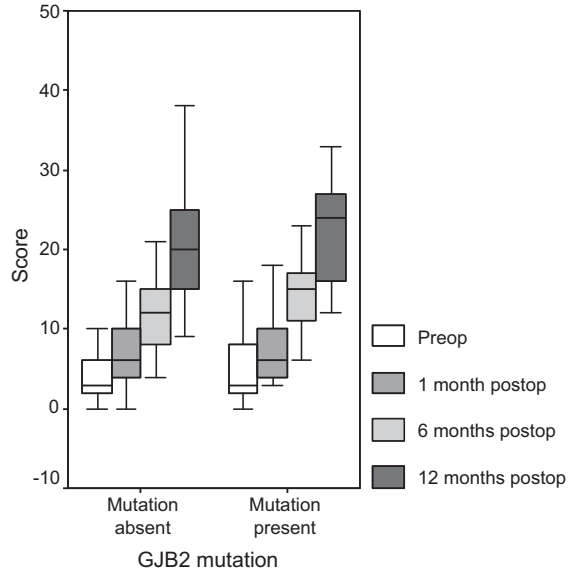

Fig. 2. MUSS scores of *GJB2* mutation positive and negative patients.