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Predictive factors and outcomes of cochlear implantation in patients with connexin 26 mutation: A comparative study☆,☆☆

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ARTICLE INFO

Article history:
Received 27 July 2014

ABSTRACT

Purpose: To compare hearing outcomes in patients with connexin 26 (Cx 26) mutations undergoing cochlear implantation to age matched controls and to examine whether age at implantation, gender and type of mutation were correlated with hearing outcome.
Materials and methods: Retrospective chart review of 21 patients with Cx 26 mutations that underwent cochlear implantation compared to 18 age-matched controls. Patients' characteristics, type of mutation and pre- and postoperative short and long-term hearing thresholds, word and sentence scores were analyzed.
Results: There was no statistically significant difference between the Cx 26 and control group in the mean short term and mean long term post-operative pure tone averages (PTA), speech reception thresholds (SRT), word and sentence scores. Gender, age at implantation and type of connexin 26 mutation did not predict hearing outcomes.
Conclusions: In patients with connexin 26 mutation, cochlear implantation provides an effective mean of auditory habilitation. Mutational status, age and gender do not seem to predict hearing outcomes.

1. Introduction

Congenital hearing loss accounts for 60% of deafness, of which 30% are related to an underlying syndrome while the remaining are non-syndromic. Most genetic causes of hearing loss are inherited in an autosomal recessive manner. Connexin 26 (Cx 26) is the most commonly mutated protein among autosomal recessive prelingual, non-syndromic causes of hearing loss. It is thought that mutations in Cx 26 are responsible for up to 20% of cases of childhood deafness [1,2]. The GJB 2 gene encodes a gap junction protein, Cx 26. Six connexin proteins combine in a circular formation to form a connexon. Connexons from adjacent cells line up forming a gap junction. Gap junctions in the cochlea play an important role in maintaining the transmembrane potassium electrochemical gradient [3]. Cx 26 is found in the non-neural

☆ The authors have no financial relationships, or conflicts of interest to disclose.
☆☆ Clinical and Translational Science Collaborative (CTSC) grant support (UL1TR000439).

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http://dx.doi.org/10.1016/j.amjoto.2014.08.010
0196-0709/

support epithelium of the cochlea including the stria vascularis, basement membrane, and the spiral limbus of the cochlea [4].

Cochlear implantation (CI) is a reliable auditory restorative option for patients with severe and profound sensorineural hearing loss. Factors that influence the hearing outcomes of implantee vary. Studies have demonstrated that age at implantation, amount of residual hearing and mode of communication can influence outcomes [5,6]. The etiology of the hearing loss additionally plays a role in outcomes. In diseases known to impact the central nervous system and the auditory system such as infection with cytomegalovirus (CMV) and meningitis, the outcomes have been shown to be worse than diseases that exclusively affect the hair cells and cochlea [2,7]. The association between Cx26 mutation and CI outcomes has been studied with conflicting results. A recent study analyzing speech outcomes in 11 patients with Cx 26 mutations following cochlear implant found that they had equal or better outcomes compared to a group of prelingually deafened patients of unknown etiology [8]. Bauer et al. [9] also found that patients with Cx 26 mutations had significantly better reading performance. Nonetheless, other studies have demonstrated no short term or long term differences in auditory outcomes between the two patient groups [10,11].

Pathological analysis of temporal bones from patients with the GJB2 mutation has demonstrated that Cx 26 pathology does not affect the spiral ganglion cells [12]. The spiral ganglion cells are stimulated by the cochlear implant; hence patient post-operative outcomes may be expected to depend on their function. Moreover, mutations in Cx 26 do not appear to impact the central nervous system potentially contributing to improved outcomes [7].

We hypothesize that patients with profound sensorineural hearing loss and Cx 26 mutation have better outcomes following cochlear implantation compared to their age matched controls.

Short term (less than 12 months following initial implantation), intermediate term (12–24 months following initial implantation) and long term outcomes (greater than 24 months following initial implantation) were studied; as the full benefits of cochlear implants take 3–4 years to be realized [13]. Moreover, linear regression model analysis was performed to determine the impact of patient factors such as age at implantation, gender and type of mutation on outcomes. This information could be useful to patients in their future visits when their prognosis and expected outcomes following CI are discussed.

2. Materials and methods

Following departmental and institutional review board approval, a retrospective chart review of the cochlear implant database was conducted. The charts of all patients who received a cochlear implant under age 18 at University Hospitals Case Medical Hospital, a tertiary care center, between January 2002 and December 2012 were reviewed. Patient charts, operative reports and laboratory testing were thoroughly reviewed for etiology of hearing loss. Charts were reviewed for demographic information and audiometric outcomes. Patients who had genetic testing that demonstrated homozygous mutations of the GJB2 gene, absence of other radiographically or clinically identifiable causes of hearing loss were included in the Cx 26 study group. A matched group of control subjects for age at first implantation (0–≤24 months, 25–<48 months and ≥48 months) was identified from the same cochlear implant database. All patients in the control group had an identifiable etiology of hearing loss unrelated to Cx 26 mutation or genetic analysis without evidence of mutation in the GJB2 gene. Patients who did not have an identifiable cause of hearing loss had negative connexin 26 genetic testing.

2.1. *Outcome assessment*

Demographic parameters were recorded including age at implantation and gender. Clinical parameters surveyed included results of newborn hearing screen, family history of hearing loss. Radiographic studies were reviewed to exclude alternative causes of hearing loss. Operative reports were reviewed with emphasis on complications and number of electrodes inserted. Audiometric data was collected including pure tone averages (PTA) at 0.5, 1, 2, 4 kHz, speech reception thresholds, word and sentence discrimination scores were recorded for the best aided condition. When no response was detected on the audiometer the threshold was set at 110 decibels. Audiometric data were collected preoperatively, and postoperatively. Data collected less than 12 months following initial implantation were reported as short term (ST), between 12 and 24 months was intermediate term (IT) and long-term (LT) was classified as greater 24 months following initial implantation. IT and LT word and sentence scores will be used to compare outcomes. Preoperative and ST word and sentence scores were not analyzed due to absence of adequate verbal language development. PTA and SRT will be used to compare outcomes for those time periods. The tests given to each child were based on developmental and cognitive abilities. The word scores were recorded according to the NU-6 (Northwestern University words score chip) or PBK-50 (Phonetically Balanced Kindergarten). Sentence scores were recorded according to Hearing in noise test (HINT) or the minimum speech test battery (MSTB).

2.2. *Statistical analysis*

Data from the chart review were collected and entered into Redcap secure data storage software [14]. Collected data were then exported in a de-identified format to an excel file for statistical analysis. The 2-sample T test was used to compare independent means. Paired T tests were used to analyze dependent outcomes. Multivariate analysis was performed using minitab 16. The variables studied were gender, age at implantation and type of mutation in relationship to the outcomes of word and sentence scores, and speech reception thresholds.

3. Results

Twenty one patients of whom eighteen received bilateral sequential cochlear implantation were included in the Cx 26 group (Table 1). Eighteen patients were included in the