

Connexin-Associated Deafness and Speech Perception Outcome of Cochlear Implantation

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Objective: To compare performance after cochlear implantation in children with mutations in connexin (Cx) 26 (*GJB2*) or Cx30 (*GJB6*) and children with deafness of unknown etiology.

Design: Genetic analysis and speech perception evaluation was performed in the children with and without Cx mutations who had undergone cochlear implantation. Speech perception performance was retrospectively analyzed 6, 12, 24, 36, and 48 months after implantation. Test material was selected according to the child's age and cognitive and language abilities.

Setting: The study took place at speech and hearing and genetic centers of a hospital in the central part of Israel and the genetics departments of 3 additional centrally located hospitals.

Patients: A total of 30 children who had undergone cochlear implantation were selected for the study, with control patients matched according to age at implantation, duration of implant use, and mode of communication.

There was no evidence for additional disabilities or handicaps in either group.

Main Outcome Measures: Speech perception measurements included a questionnaire, as well as closed and open-set tests.

Results: Overall, the 2 groups showed significant improvement in speech perception results after implantation. Four years after implantation, both groups achieved mean open-set speech perception scores of approximately 60%, 75%, and 90% for monosyllabic, 2 syllables, and words in sentences tests, respectively.

Conclusions: There were no apparent differences in speech perception performance after implantation between the children with Cx mutations and children with deafness of unknown etiology. These data have important implications as a prognostic indicator when counseling candidates for cochlear implantation.

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HEARING IMPAIRMENT AFFECTS approximately 1 in 1000 newborns and 4% of individuals younger than 45 years.¹ Inherited hearing loss (HL) accounts for at least 60% of patients with deafness, of whom HL is syndromic in 30% and nonsyndromic in 70%. The most common form of nonsyndromic HL is autosomal recessive, which accounts for about 80% of cases.² More than 100 genes are thought to be involved in HL. Thus far, 96 loci have been mapped and 43 cloned.³ The genes known to date to be involved in human hereditary nonsyndromic HL encode a large variety of proteins, including transcription factors, ion channels, molecular motors, gap junctions, and proteins that form the extracellular matrix of the inner ear.

The first discovery of an autosomal recessive gene, *GJB2*, was reported in 1997.⁴

GJB2 encodes the gap-junction protein connexin (Cx) 26, which belongs to a family of more than 20 members who share a common structure of 4 transmembrane segments. Most cell types express more than 1 Cx species, which can form homomeric or heteromeric connexons. Inter-cellular channels in the auditory system are formed predominantly by Cx26 but also by Cx30 and Cx31.⁵ Connexin 26 appears to play a role in maintaining a high extracellular electrical potential in the cochlea by facilitating the circulation of K⁺ ions.⁶ A surprising finding was that despite the extreme genetic heterogeneity of deafness, this gene is responsible for a high proportion of nonsyndromic HL cases. Mutations in *GJB2* are responsible for up to 50% of cases of severe to profound pre-lingual recessive deafness in several worldwide populations.⁷ In Israel they account for 38.7% of such cases in the general deaf

Table 1. Description of Groups

Variable	Cx Group (n = 17)	Non-Cx Group (n = 13)
M/F	12/5	10/3
Age at implantation, mean ± SD (range), mo	46 ± 26 (12-89)	44 ± 20 (13-79)
Type of implant		
Nucleus 24*	11	8
Nucleus 22*	5	1
Clarion†	1	3
Med-EL‡	0	1
Mode of communication		
Oral communication	16	12
Total communication	1	1
Pure tone average before implantation	109 dB HL	105 dB HL

Abbreviations: Cx, connexin; HL, hearing loss.

*Cochlear Corp, Englewood, Colo.

†Advanced Bionics Corp, Sylmar, Calif.

‡MED-EL, Innsbruck, Austria.

population⁸ and for 70.4% of cases among Ashkenazi Jews.⁹ In the latter population, a mutation has also been described in the *GJB6* gene encoding the protein Cx30, which is coexpressed with Cx26 in the inner ear. *GJB6* is located on chromosome 13, within 50 kb of *GJB2*. A mutation encountered in the Israeli population, del(*GJB6*-D13S1830), leaves the *GJB2* coding region intact but deletes a large region close to *GJB2* and truncates *GJB6*. This deletion is frequently found in double heterozygosity with a *GJB2* mutation, and the associated HL is assumed to be caused either by the deletion of a putative *GJB2* regulatory element or by digenic inheritance.¹⁰ Pure digenic inheritance seems unlikely, however, because double heterozygosity with a *GJB2* mutation has not been detected with other *GJB6* mutations. Double heterozygotes for Cx26 and Cx30 mutations are associated with profound HL and manifest the same phenotypes as homozygotes for Cx26 and for Cx30.¹⁰⁻¹²

Cochlear implantation is a common rehabilitation option for the population with severe to profound HL. Performance with cochlear implants is highly variable and depends on many factors, such as age of implantation, amount of residual hearing, and mode of communication. The contribution of these factors to speech perception abilities has been documented and was found to explain less than 50% of the variance in the results.¹³ The remaining variability, therefore, is clearly attributable to additional factors.

One factor likely to affect the results of cochlear implantation is the underlying cause of deafness. It is generally assumed that speech perception performance after cochlear implantation might be poorer in underlying causes known to include neural and/or central damage to the auditory system (eg, cytomegalovirus, meningitis, and/or auditory neuropathy)^{14,15} than in those primarily affecting the hair cells (eg, hereditary nonsyndromic deafness). One such cause, which is known to affect the cochlea, is genetic mutations in *GJB2* or *GJB6* genes, leading to nonsyndromic HL.

In several studies the postimplantation speech perception in children with *GJB2* mutations has been compared with that of a control group, but the overall results have been inconclusive. In a study using the Infant-Toddler–Meaningful Auditory Integration Scale (IT-MAIS) questionnaire, 6 months after implantation the results in the Cx26 group were significantly better compared with those of children without Cx mutations.¹⁶ In another study there was a tendency toward better results in the Cx26 group than in the control group, but this was not significant.¹⁷ Sinnathury et al recently reported better speech intelligibility¹⁸ and better auditory perception results¹⁹ in the Cx26 group, whereas other authors have obtained similar speech perception results in the 2 groups.^{20,21} Two studies found higher reading comprehension scores in the Cx26 group compared with the non-Cx26 group.^{21,22} The large variability in the collected data can be attributed to several factors, including the small number of participants, non-identical criteria for selection of the control group, and other confounding factors such as matching of age at implantation and the duration of deafness.

The purpose of this study was to compare the postimplantation performance of a relatively large group of children with *GJB2* or *GJB6* mutations with those of a control group with deafness of unknown etiology. The control group was carefully matched with the experimental group with respect to the factors known to confound the results of previous investigations. Our results demonstrate that there is no inherent advantage in harboring Cx mutations on speech perception outcome.

METHODS

SUBJECTS

A total of 250 (between 1993-2004) children underwent cochlear implantation at the Sheba Medical Center, Tel-Hashomer, Israel. Of these, 49 children with congenital HL and cochlear implants underwent genetic analysis in one of the centers: the Genetic Counseling Center of the Chaim Sheba Medical Center (Tel-Hashomer) and the Genetic Departments of the Rabin Medical Center (Petach Tikva), Sourasky Medical Center (Tel Aviv), and the Wolfson Medical Center (Holon) in Israel. A complete clinical history of each affected individual was collected to ensure that no environmental factors were involved. From the 49 children, only those whose native language was Hebrew and had no suspicion of additional problems were included in the present study. After this screening, 30 subjects participated in the study. Of these subjects, 17 had *GJB2* and/or *GJB6* mutations and 13 were in the non-Cx group. Of this control group, 7 cases were sporadic and 6 were familial (more than 1 subject in the family with HL). The children in the 2 groups were carefully matched according to age at implantation, duration of implant use, mode of communication, and hearing thresholds preimplantation. **Table 1** illustrates the background data of the 2 groups (Cx group and the control group).

The project was approved by the institutional review board committees at Tel Aviv University, Chaim Sheba Medical Center, Rabin Medical Center, Sourasky Medical Center, and the Wolfson Medical Center. Blood samples were obtained following informed consent from the parents of each individual, since they are all younger than 18 years.

MUTATION ANALYSIS OF Cx26 (*GJB2*) AND Cx30 (*GJB6*) GENES

The open reading frame of *GJB2* was examined for mutations as described previously.⁸ Briefly, primers GJB2-1F, 5'-TCT TTT CCA GAG CAA ACC GC-3', and GJB2-2R, 5'-GGG CAA TGC GTT AAA CTG GC-3', amplified a 722-base pair (bp) fragment that was sequenced and checked for mutations. In addition, the noncoding exon 1 of *GJB2* was screened for the splice site mutation IVS1 + 1(G→A). Primers Cx26-Exon1F 5'-GGCGA-CACCACAAACCTC-3' and Cx26-Exon1R 5'-CCTCCGTAACCTTCCAGTC-3' amplified a 540-bp fragment. The polymerase chain reaction product was digested with *Bsp*MI (37°C for 10 hours) and separated by electrophoresis on a 2% gel. The *Bsp*MI restriction enzyme cuts the wild-type fragment into 2 fragments of 309 bp and 231 bp. A mutation eliminates the *Bsp*MI site, and thus the expected band size is 540 bp for the mutant allele.

For *GJB6*, the deletion Δ (*GJB6*-D13S1830) identified in Jewish Ashkenazi and Spanish hearing-impaired individuals^{10,11} was investigated in our DNA samples. Primers *GJB6*-1R, 5'-TTT AGG GCA TGA TTG GGG TGA TTT-3', designed 244 bp upstream of the proximal breakpoint of the deletion and *GJB6*-BKR-1, 5'-CAC CAT GCG TAG CCT TAA CCA TTT T-3', localized 216 bp downstream of the distal breakpoint of the deletion, amplified a 460-bp fragment encompassing the breakpoint deletion if it was present. To obtain a fragment in the event no deletion occurred, we designed a third primer localized 681 bp downstream of the *GJB6*-1R primer, to be included in the same reaction, *GJB6*-RVS2, 5'-TCA TCG GGG GTG TCA ACA AAC A-3'. Wild-type DNA yielded a 681-bp band.

SPEECH PERCEPTION EVALUATION

The tests administered to each child were determined based on age and cognitive and language abilities. We used a questionnaire for the infants as well as closed- and open-set tests for the older children. The questionnaire included the Hebrew Infant Toddler Meaningful Auditory Integration Scale (HIT-MAIS).²³ The Phonological Contrasts test included the Hebrew Picture Speech Pattern Contrast test (HePiSPAC).²⁴ Three subtests included vowel height and place and initial manner. All stimuli are consonant-vocal-consonant (CVC) meaningful words. The open-set tests included 1-syllable CVC isophonemic meaningful word list tests, which are scored by words and phonemes. Open-set 2-syllable word test included lists of 2 syllable isophonemic meaningful word lists. Open-set words in the sentences test included lists of common sentences.

PROCEDURE

The results of the speech perception tests were collected retrospectively. Speech perception abilities were measured at 6, 12, 24, 36, and 48 months after implantation. Note that not all subjects were available at all times. Infants younger than 2.5 years were usually evaluated with the HIT-MAIS. Children 2.5 years or older, who were able

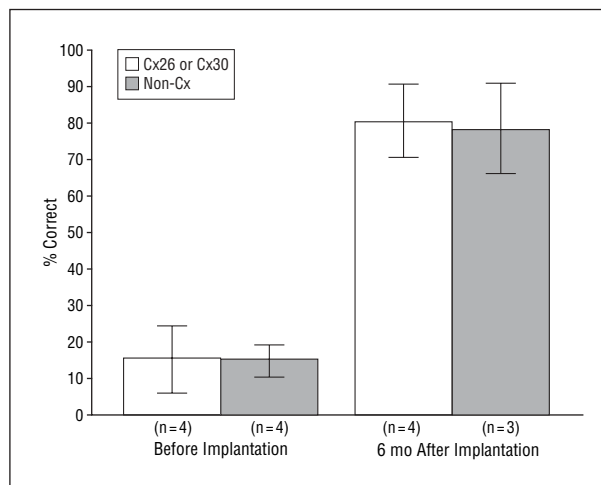


Figure 1. Mean Hebrew Infant-Toddler Meaningful Integration scale of the connexin (Cx) and the non-Cx groups before implantation and 6 months after implantation. Error bars indicate standard deviation.

to respond via the auditory channel alone, were tested with the open-set tests. Children 2.5 years or older were also evaluated by the HePiSPAC closed-set test. All speech perception tests were presented at 70-dB sound pressure level via live voice, with a distance of 1 meter between the loudspeaker and listener.

RESULTS

GENETIC RESULTS

Biallelic Cx mutations were detected in the *GJB2* and/or the *GJB6* genes in 17 children. Five children were homozygous for the 167delT mutation, which is common among the Ashkenazi population in Israel,⁹ 2 were homozygous for the 35delG mutation, 7 had compound 35delG/167delT mutations, and 3 were double heterozygous for both *GJB2* and *GJB6* 35delG/del(*GJB6*-D13S1830) mutations.

SPEECH PERCEPTION RESULTS

Mean HIT-MAIS results of the 2 groups before implantation and 6 months after implantation are illustrated in **Figure 1**. Both groups showed improvement in the scores of the questionnaire 6 months after implantation. The 2 groups showed similar mean scores of approximately 80%. Statistical analysis using the nonparametric Mann-Whitney test revealed no significant differences ($P > .05$) between the groups. Only small groups ($n = 7$) of children who had undergone cochlear implantation were evaluated by the HIT-MAIS questionnaire. Infants who cannot be evaluated by other direct speech perception tests are tested with this questionnaire.

Mean HePiSPAC scores of 3 phonological contrasts (vowel height, vowel place, and initial manner) in experienced children with cochlear implants (implant use of 2-3 years) from the 2 groups are shown in **Figure 2**. Statistical analysis using the nonparametric Mann-Whitney test revealed no significant differences ($P > .05$) between the groups in initial manner and vowel height.

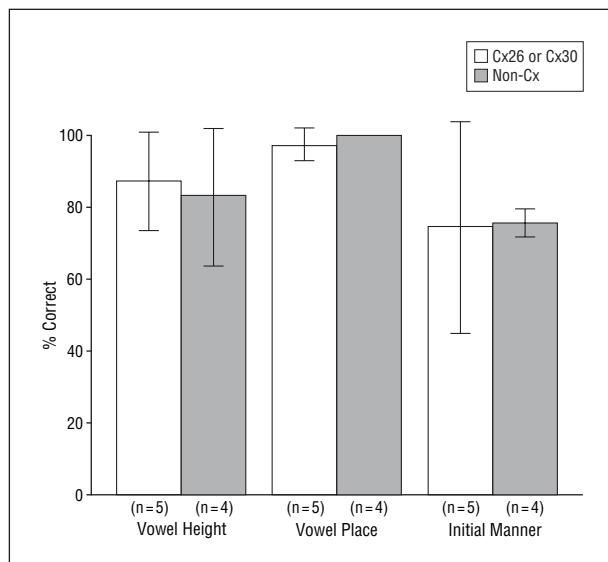


Figure 2. Mean Hebrew Picture Speech Pattern Contrast scores for vowel height, vowel place, and initial manner for the connexin (Cx) and non-Cx groups with duration of implant use between 2 and 3 years. Error bars indicate standard deviation.

Vowel place scores were higher in the non-Cx group. These results were with P values close to statistical significance ($P = .06$). Furthermore, the same hierarchy in speech contrasts can be observed for the 2 groups. Vowel place was the easiest contrast to perceive, while initial manner was the most difficult from the 3 contrasts we evaluated.

Mean open-set speech perception results and standard deviations of the 2 groups 1, 2, 3, and 4 years after implantation are summarized in **Table 2**. Two analyses of variance, one by group (Cx and non-Cx) and one by duration of implant use (1, 2, 3, and 4 years), were conducted with a mixed model. There were no statistical differences between groups in either of the tests, as shown in Table 2. In most of the speech perception tests, there was longitudinal improvement in the results after implantation. The statistical analyses revealed a near-significant effect of duration of implant use in Hebrew AB phonemes ($F_{3,15} = 2.92$, $P = .06$) and a significant effect of time since implantation in word scores ($F_{3,15} = 3.08$, $P = .05$) and words in sentences scores ($F_{2,6} = 6.66$, $P = .03$).

COMMENT

The main purpose of the present study was to retrospectively compare speech perception results of children with and without Cx mutations who had undergone cochlear implantation. The results indicate that when these 2 groups of children are carefully matched by many variables, there are no apparent differences in speech perception scores between the 2 groups. Both groups show improvement in speech perception abilities after implantation. This was found for all speech perception measures, for the questionnaire in the very young children, as well as for the closed-set and the open-set tests in the older children. Our results in the present study support the findings obtained in earlier Cx studies.^{20,25} How-

ever, these results differ from those obtained in other studies,¹⁶⁻¹⁹ which found better results in the Cx group. These differences can be attributed to confounding factors such as the small number of subjects and criteria for selecting the control group.

Specifically, results of the HIT-MAIS questionnaire showed that infants in both groups reached an average score of approximately 80% within 6 months after implantation. On the other hand, the study by Matsushiro et al¹⁶ obtained mean results of approximately 70% in the Cx group 6 months after implantation when using the IT-MAIS but found significantly lower results (mean of 44%) in the non-Cx group. These differences in results can be partly attributed to the older age at implantation in the study by Matsushiro et al,¹⁶ particularly in the non-Cx group. Most of our subjects in the subgroups who were evaluated by the IT-MAIS underwent implantation at an age younger than 2 years, compared with a mean age of 45.3 months in the study by Matsushiro et al¹⁶; this may explain our better results at 6 months after implantation. Our findings are consistent with the published data of McConkey Robbins et al,²³ who found, using the IT-MAIS questionnaire, that infants and toddlers who had undergone cochlear implantation showed rapid improvement in auditory skills during the first year of device use and that younger infants achieve higher scores.

The perception of phonological contrasts of the 2 groups was approximately 100%, 85%, and 75% for vowel place, vowel height, and initial manner, respectively. The highest score for vowel place is similar to the results of Kishon-Rabin et al,²⁴ who found that vowel place is the best contrast to produce and perceive by Hebrew cochlear implants users.

The results from the open-set battery of tests for the older children who had undergone cochlear implantation showed improvement in the 2 groups after implantation. Our mean results in the Cx group 4 years after implantation was 66%, 83%, and 85% for monosyllabic word score, phoneme score, and words in sentences, respectively. These results are similar to the results obtained in the literature of children with Cx mutations who had undergone implantation. In the study by Fukushima et al,¹⁷ the mean monosyllabic words score in the Cx26 group (3 subjects) was approximately 66%. The mean result in the non-Cx26 group (4 subjects) was lower. This can be attributed to the results of 2 of 4 patients who received low scores, but their cause of deafness was low birth weight, which may be associated with other deficits.

These differences in the results strengthened our conviction that when such studies are designed, the control group (the group with non-Cx mutations) should be as similar as possible to the group with Cx mutations. Otherwise, the results can be slanting by confounding factors. In the Chaim Sheba Medical Center, there are more than 250 children who had undergone cochlear implantation, but only a part of them have a "pure" HL without any other difficulties, including learning disabilities, dyspraxia, and motor delay. Thus, the findings of the present study provide evidence that when we carefully select "clean" groups that differ only in the cause of deafness,

Table 2. Mean Speech Perception Open-Set Results

Test/Duration of Implant Use, y	Cx Group		Non-Cx Group		Statistical Analyses Between Groups
	No. of Patients	Results, % Correct, Mean (SD)	No. of Patients	Results, % Correct, Mean (SD)	
Hebrew AB (words)					
1	6	49 (12)	5	49 (26)	$F_{1,23} = 0.1, P = .59$
2	10	46 (12)	6	40 (12)	
3	5	58 (26)	5	53 (22)	
4	5	66 (14)	4	59 (13)	
Hebrew AB (phonemes)					
1	6	74 (6)	5	73 (14)	$F_{1,23} = 0.29, P = .75$
2	10	73 (6)	6	72 (8)	
3	5	79 (17)	5	74 (18)	
4	5	83 (10)	4	80 (5)	
2-Syllable (words)					
1	7	76 (9)	7	64 (23)	$F_{1,23} = 0.06, P = .81$
2	11	71 (15)	6	79 (13)	
3	5	80 (19)	5	73 (22)	
4	5	73 (22)	4	78 (6)	
Words in sentences					
2	6	70 (17)	4	79 (7)	$F_{1,16} = 0.77, P = .39$
3	5	86 (16)	4	86 (14)	
4	5	85 (12)	4	95 (4)	

Abbreviation: Cx, connexin.

the performance with the implant is similar. In our control group, although the cause of deafness is unknown, it is likely that many of these cases have a genetic cause, particularly in those cases in which more than 1 individual in the family has HL. At this time, the cost-benefit of screening for mutations in genes other than *GJB2* and *GJB6* is low owing to the large size of most known genes and the lack of known frequencies in a given population for most of the known genes. Most important, the responsible gene for almost 50 mapped loci has yet to be identified, and there are undoubtedly more loci to be discovered. Furthermore, we would expect cochlear implantation outcome to be similar for deafness due to a nongenetic cause that involves sensory HL but not central auditory pathways.

These results have implications and prognostic value regarding counseling for cochlear implant candidates with Cx mutations, as well as for other nonsyndromic HL cases with no additional complications. Overall, the results were the same in both our study groups and were found to be above average in performance.

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