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Auditory Perception and Speech Discrimination After Cochlear Implantation in Patients with Connexin 26 (*GJB2*) Gene-Related Deafness

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Hypothesis: Auditory perception and speech discrimination among pediatric cochlear implantees may vary because of underlying deafness etiology, including connexin 26 (*GJB2*) gene-related deafness.

Background: Preliminary data suggest pathologic changes due to *GJB2* mutations do not affect the spiral ganglion cells, which are stimulated by the cochlear implant. The survival of the spiral ganglion cells is believed to be an important determinant of outcome after surgery. Patients with *GJB2*-related deafness may therefore have enhanced prospects for good speech discrimination after implantation.

Methods: In an observational cohort study, *GJB2* mutation analysis was performed using polymerase chain reaction amplification and direct sequencing on 31 prelingually deaf pediatric cochlear implantees, of which there were 30 with nonsyndromic deafness of unknown etiology, and one with keratitis-ichthyosis-deafness syndrome. Speech discrimination was assessed prospectively when they had reached postoperative year 3 using the IOWA Matrix Level B Sentences test and Glendonald Auditory Screening Procedure (GASP), with both patients and assessors blind to *GJB2* status.

Results: Eleven patients had *GJB2*-related deafness and 20 patients had *GJB2*-unrelated deafness. IOWA Matrix scores were higher in patients with *GJB2*-related deafness but did not reach statistical significance. However, GASP scores were statistically significantly higher in patients with *GJB2*-related deafness (median word score, 92%; median sentence score, 80%), compared with those of patients with *GJB2*-unrelated deafness (median word score, 63%; median sentence score, 45%; word score, $p = 0.037$; sentence score, $p = 0.045$). Ordinal logistic regression analysis on IOWA Matrix and GASP sentence scores found better statistically significant scores in patients with *GJB2*-related deafness ($p < 0.05$) after adjustment for confounding variables.

Conclusion: Pediatric cochlear implantees with *GJB2*-related deafness appear to have equal or better speech discrimination compared with a group of prelingually deaf children with deafness of unknown etiology. **Key Words:** Cochlear implantation—Connexin 26—Deafness—*GJB2*—Speech discrimination.

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We have previously shown that children with *GJB2*-related deafness, the most common known genetic cause of prelingual deafness (1), have significantly better speech intelligibility after cochlear implantation compared with those with deafness of unknown etiology (2). It would be interesting to investigate word recognition and higher levels of speech understanding in these children via outcome measures that require different levels of linguistic competence. Comparing these outcomes in implanted children, segregated according to *GJB2* status,

may reveal where differences in their auditory systems exist and areas to be targeted by therapeutic advances toward improving speech intelligibility. Three small, single-center studies comparing prelingually deaf patients with cochlear implants and having *GJB2*-related deafness and *GJB2*-unrelated deafness have been reported (3–5). One found statistically better results in implanted patients with *GJB2*-related deafness with regard to speech perception (6-mo follow-up, $N = 15$, $p = 0.0001$) (4); however, no significant differences were found in the other two studies. We present a larger cohort study with longer follow-up of implanted patients, comparing auditory perception and speech discrimination in those with *GJB2*-related deafness to those with *GJB2*-unrelated deafness.

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MATERIALS AND METHODS

Recruitment of subjects and segregation into groups based on deafness etiologies

This study considered 30 children with prelingual nonsyndromic deafness of unknown etiology (verified at interviews and ascertained from case notes) and one child with prelingual deafness due to keratitis-ichthyosis-deafness syndrome (6). All were in the Northern Ireland regional cochlear implant program and had undergone unilateral cochlear implantation by the same surgeon (J.G.T.) and had their devices activated for at least 3 years. Parents gave informed consent for genetic testing. The exclusion criteria were additional disorders with the potential to affect speech discrimination, such as developmental verbal dyspraxia (7).

All patients in our cohort were excluded as having had rubella virus embryopathy, cytomegalovirus embryopathy, measles, or mumps as the cause of their deafness, by history taking and by cross-referencing their names against data from the Regional Virology Laboratory. After genetic testing, children were grouped as having *GJB2*-related or *GJB2*-unrelated deafness. The demographic details of the children were evaluated after separation according to *GJB2* status. Ethical approval was obtained from Queen's University Belfast Research Ethics Committee.

GJB2 and *GJB6* 342 kb deletion mutation screening

Methods of sampling, DNA extraction, and mutation screening have been previously described (2).

Outcome measures

Communication skills for the 31 children in this study were assessed at the fixed postoperative time interval of year 3, before genetic testing commenced. Initially, we compared auditory perception using prospectively gathered implant-aided audiograms. These were assessed in the implanted ear and averaged over 500 Hz, 1 kHz, 2 kHz, 3 kHz, and 4 kHz in all 31 cases. Speech discrimination results were gathered prospectively using the IOWA Matrix Level B closed-set sentence test (8,9). Thirty information-carrying, four-word sentences were presented to the children, who responded by pointing to 4 × 4 picture matrices. For each word recognized correctly, each child was given a mark, giving a final score out of 120. Results from prospectively gathered assessments using the Glendonald Auditory Screening Procedure (GASP) (10,11) were also obtained. The GASP is an open-set speech discrimination test with two components of increasing difficulty. The word test, in which 12 words of different syllable number and/or stress pattern were spoken, was administered, and the children scored on how many they orally repeated correctly. The sentence test asked 10 questions with short answers and the children were scored on how many they orally responded to correctly. Raw scores in the IOWA Matrix and GASP tests were converted into percentages for ease of comparison, and both tests were administered in an auditory-only mode via live voice at approximately 70 dB sound pressure level. The tests were administered (usually by the same experienced member of the habilitation team) at the implant center, where the children were regular attendees.

Tests could not be performed by some children of very limited hearing ability; failure in easier tests clearly showed them to be too difficult. These children (four for the IOWA Matrix test, six for the GASP word test, and eight for the GASP sentence test) were accredited scores of 0 to avoid bias through exclusion (see Tables 1 and 2 for details). In an alternate situ-

TABLE 1. Individual scores on the IOWA Matrix Test and GASP word and sentence tests of children with *GJB2*-related deafness at postoperative year 3^a

Subject	Year 3 IOWA Matrix (%)	Year 3 GASP Word (%)	Year 3 GASP Sentence (%)
5	95	92	100
9	95	100	90
14	92	100	90
10 ^b	—	100	80
2	100	92	80
6	75	83	80
8	87	92	60
4	83	75	50
1 ^c	98	0	0
7 ^d	91	—	—
3 ^d	66	—	—
Median (interquartile range)	91 (81–96)	92 (79–100)	80 (55–90)

^aSubject identification numbers are the same as those in our study on speech intelligibility (2).

^bOne child was not tested with IOWA Matrix test and was excluded because they were too tired.

^cOne child was not tested with GASP word and sentence tests but was included and accredited a score of zero (the tests were too difficult).

^dTwo children were not tested with GASP tests and were excluded because they were not cooperative.

ation, the IOWA Matrix test was not performed on two children and the GASP test was not performed on another two children because of tiredness or lack of cooperation; they had to be excluded. Hence, there is follow-up for 29 of 31 patients with regards to the IOWA Matrix test, and follow-up for a different subset of 29 of 31 patients with regards to the GASP word and sentence tests.

As a secondary outcome measure, we assessed at interview the amount of oral-only communication possible between parents and their implanted child at home at year 3 (i.e., without accompanying sign and/or gesture).

Statistical analysis

Demographic details and outcomes were compared as appropriate by the independent samples *t* test, Mann-Whitney *U* test, χ^2 test, or Fisher's exact test. Ordinal logistic regression analyses (12) were performed to compare groups and to adjust for confounding variables. This approach requires categorization of outcome scores and assumes that the odds on a score being above a threshold for a category in one group relative to the other remains constant, irrespective of the choice of threshold in the outcome score, considered as the response variable. Tests of significance were conducted at the 5% level ($p < 0.05$). Statistical analysis was performed using SPSS software version 11.0 (SPSS Inc., Chicago, IL, U.S.A.).

RESULTS

GJB2-related deafness group (N = 11)

Nine children had two pathogenic recessive mutations in *GJB2*: 7 homozygotes for 35delG, and 2 compound heterozygotes for 35delG/169C > T. A tenth patient carried a 35delG mutation in *GJB2* and the 342kb deletion in *GJB6*, a compound heterozygote for *GJB2* and *GJB6*

TABLE 2. Individual scores on the IOWA Matrix Test and GASP word and sentence tests of children with *GJB2*-unrelated deafness at postoperative year 3^a

Subject	Year 3 IOWA Matrix (%)	Year 3 GASP Word (%)	Year 3 GASP Sentence (%)
24	93	100	100
38	82	100	90
36	100	92	90
28	91	83	80
39	79	75	70
16 ^b	—	92	60
26	92	67	60
23	91	67	60
22	95	25	60
21	92	42	50
27	55	33	40
25	74	92	20
18	43	58	10
30 ^{c,d}	0	92	0
29 ^d	49	17	0
20 ^{d,e}	93	0	0
19 ^{d,e}	88	0	0
15 ^{c-e}	0	0	0
17 ^{c-e}	0	0	0
31 ^{c-e}	0	0	0
Median (interquartile range)	82 (43–92)	63 (4–92)	45 (0–68)

^aSubject identification numbers are the same as those in our study on speech intelligibility (2).

^bOne child was not tested with IOWA Matrix test and was excluded because they were not cooperative.

^cFour children were not tested with the IOWA Matrix test, but they were included and accredited a score of 0 since the test was too difficult.

^dSeven children were not tested with GASP sentence tests, but they were included and accredited a score of 0 since the test was too difficult.

^eFive children were not tested with the GASP word test, but they were included and accredited a score of 0 since the test was too difficult.

(13). The only syndromic child in this group had keratitis-ichthyosis-deafness syndrome caused by a de novo heterozygous dominant mutation in *GJB2* (148G > A) that was absent in both parents (6). These 11 children were classified together as having *GJB2*-related deafness.

***GJB2*-unrelated deafness group (N = 20)**

Eighteen children had neither *GJB2* mutations nor *GJB6* 342kb deletions. A single recessive *GJB2* mutation was identified in two children (478G > A and 249C > G). These 20 children were classified together as having *GJB2*-unrelated deafness.

Demographic details

All patients had preoperative, prelingual, profound deafness (preoperative unaided residual hearing thresholds >90 dB hearing level) and received a full insertion of electrodes (all 22 active electrodes inside the cochlea) using the SPEAK coding strategy. In comparing those with *GJB2*-related deafness to those with *GJB2*-unrelated deafness, there were no significant differences in the following variables: socioeconomic status, (manual: nonmanual) 6:5 versus 12:8 ($p = 1.00$); sex, (M:F) 8:3 versus 13:7 ($p = 0.97$); congenital onset of profound deafness, 11 of 11 versus 19 of 20 ($p = 1.00$); preoperative aided auditory perception (mean dB hearing level [SD]) 65.2 [10.2] versus 65.9 [10.1] ($p = 0.85$); contralateral hearing aid usage, 2 of 11 versus 1 of 20 ($p = 0.28$); timing of postoperative speech and language habilitation from start of program (median [range]) 3 years [1–4 yr] versus 3 years [0–5 yr] ($p = 0.64$); nucleus device/processor type, (CI22M/Spectra:CI24M/SPrint), 8:3 versus 16:4 ($p = 0.68$); and implant daily usage amount during waking hours (median [range]) 14 hours [13–15 hr] versus 13 hours [9–16 hr] ($p = 0.32$).

In comparing those with *GJB2*-related deafness to those with *GJB2*-unrelated deafness, the following variables differed significantly: length of profound deafness (mean [SD]), 4.1 years [1.3 yr] versus 6.1 years [2.4 yr] ($p = 0.02$); age at implantation (median [range]) 3.9 years [2.5–6.3 yr] versus 5.8 years [2.8–10.3 yr] ($p = 0.007$); and postoperative complications, 3 of 11 versus 0 of 20 ($p = 0.04$).

Outcomes measures

Children with *GJB2*-related deafness had better postoperative auditory perception (implant-aided thresholds, 500 Hz–4 kHz) than those with *GJB2*-unrelated deafness, but these differences were not statistically significant (Table 3). IOWA Matrix scores were also higher in those with *GJB2*-related deafness (median, 91%) compared with those with *GJB2*-unrelated deafness (median, 82%) ($p = 0.09$). However, GASP word and sentence scores differed significantly between the groups; patients with *GJB2*-related deafness (median word score, 92%; median sentence score, 80%) had statistically significantly higher scores than those with *GJB2*-unrelated deafness (median word score, 63%; median sentence score, 45%; word score, $p = 0.037$; sentence score, $p = 0.045$).

Ordinal logistic regression analysis on categorized raw IOWA Matrix scores (0, 1–100, 101–110, and >110) and

TABLE 3. Comparisons of auditory perception and speech discrimination between patients with *GJB2*-related deafness and *GJB2*-unrelated deafness 3 years postoperatively

	<i>GJB2</i> -Related Deafness	<i>GJB2</i> -Unrelated Deafness	Significance
Year 3 postoperative aided auditory perception, mean dBHL (SD)	39 (3.7)	41 (4.8)	$p = 0.18$
Year 3 IOWA Matrix Level B test, median % (interquartile range)	91 (81–96)	82 (43–92)	$p = 0.09$
Year 3 GASP word test, median % (interquartile range)	92 (79–100)	63 (4–92)	$p = 0.037$
Year 3 GASP sentence test, median % (interquartile range)	80 (55–90)	45 (0–68)	$p = 0.045$

categorized GASP scores (word: 0%, 1–60%, 61–90%, 91–99%, and 100%; sentence: 0%, 1–50%, 51–60%, 61–80%, and 81–100%), considered age at implantation and socioeconomic status as confounders. As shown in Table 4, the unadjusted odds ratio for higher postoperative IOWA Matrix scores in those with *GJB2*-related deafness compared with *GJB2*-unrelated deafness was 2.9 (95% confidence interval [CI], 0.7–12.4; $p = 0.14$). After adjustment for the confounders, the odds ratio attained statistical significance: 6.8 (95% CI, 1.2–38.3; $p = 0.029$). The unadjusted odds ratio for higher postoperative GASP word scores in those with *GJB2*-related deafness compared with *GJB2*-unrelated deafness was 4.8 (95% CI, 1.1–21.8; $p = 0.04$). The same comparison for postoperative GASP sentence scores was 4.2 (95% CI, 1.0–18.4; $p = 0.057$). After adjustment for the confounders, the odds ratio was no longer significant for GASP word scores at 3.4 (95% CI, 0.7–17.0; $p = 0.13$), but attained statistical significance for GASP sentence scores at 7.7 (95% CI, 1.4–42.2; $p = 0.019$).

The amount of oral-only communication possible between parents and their implanted child at home was higher in families with children having *GJB2*-related deafness (100% for all patients) compared with *GJB2*-unrelated deafness (median, 90% [40–100%]; $p = 0.002$).

DISCUSSION

Because of age and language limitations, the IOWA Matrix Level B and GASP tests could usually only be administered from postoperative year 3 onwards. Year 3 also affords a reasonable compromise between availability of sufficient children for study and postoperative time, allowing genuine differences to emerge between the implanted groups with regard to all the outcome measures. The closed-set format in the IOWA Matrix test controls for learning effects associated with successive test presentations, making it a valid outcome measure to assess speech discrimination in young children with poor linguistic skills. Both the IOWA Matrix and GASP tests were assessed prospectively in our study, and are also widely used in other implant programs around the world (8–11). O'Donoghue et al. (9) found that by the third year postoperative interval, the median IOWA Matrix score in a cohort of 32 pediatric cochlear implantees was

99%. The medians of both groups in our study are lower than this, but O'Donoghue et al. had used the IOWA Matrix Level A closed-set sentence test, carried out in a similar format to the Level B test we used, but more appropriate for those with lesser linguistic skills. The GASP test was used by Waltzman et al. (11) to assess a cohort of 38 pediatric implantees preoperatively and postoperatively, revealing significant open-set speech recognition achieved after surgery.

A possible weakness in our study is that there were patients who had not actually performed the GASP or the IOWA Matrix tests and were included in analyses using accredited scores of zero, while others were excluded. Some children had limited abilities based on the results of easier tests, and were not assessed with the GASP or the IOWA Matrix tests because the habilitation team did not wish to have them feel a sense of failure. Accrediting them with scores of zero appropriately avoided bias through exclusion. Interestingly, these cases occurred more often in the *GJB2*-unrelated deafness group. Alternatively, four children who would not perform both tests because of tiredness or lack of cooperation were excluded from analyses of their “nonperformed” test. If these four had also been accredited with scores of zero in their “nonperformed” test, the differences in outcomes between groups may have narrowed, since three of the four were in the *GJB2*-related deafness group. It was, however, felt that accrediting them with a mark of zero may have underestimated their general known abilities, reflected partly by their results in the test they *had* performed (three of them scored at or above the group median score) (Tables 1 and 2).

The hearing advantage of children with *GJB2*-related deafness appears to be related to better speech understanding skills. These children performed better in all hearing outcome measures, although comparisons of postoperative audiograms and IOWA Matrix Level B scores did not reach statistical significance. Univariate analyses on GASP scores at year 3 did, however, reveal that children with *GJB2*-related deafness had significantly higher word and sentence scores than those with *GJB2*-unrelated deafness. There was also a significantly larger amount of oral-only communication possible between parents and their implanted child at home in families having children with *GJB2*-related deafness.

TABLE 4. Results of ordinal logistic regression on year 3 IOWA Matrix and GASP scores with adjustment for confounding variables

Scores adjusted for	Year 3 IOWA Matrix Test			Year 3 GASP Word Test			Year 3 GASP Sentence Test		
	Odds ratio	95% CI	p	Odds ratio	95% CI	p	Odds ratio	95% CI	p
Unadjusted	2.9	(0.7–12.4)	0.14	4.8	(1.1–21.8)	0.04	4.2	(1.0–18.4)	0.057
Age at implantation	7.0	(1.3–39.1)	0.027	3.4	(0.7–17.0)	0.13	7.4	(1.4–40.2)	0.02
Socioeconomic status	2.9	(0.7–12.3)	0.14	4.9	(1.1–22.0)	0.04	4.6	(1.0–20.6)	0.04
Socioeconomic status and age at implantation	6.8	(1.2–38.3)	0.029	3.4	(0.7–17.0)	0.13	7.7	(1.4–42.2)	0.019

The odds ratio estimates the odds of achieving a higher categorized year 3 IOWA Matrix score, year 3 GASP word score, or year 3 GASP sentence score in a patient having *GJB2*-related deafness relative to a patient having *GJB2*-unrelated deafness.

Our numbers were large enough to use regression-based analyses to adjust for potential confounders and to tease out the contribution of deafness etiology on outcome. For these analyses, categorization of IOWA Matrix and GASP scores was required. The resulting categories of IOWA Matrix and GASP scores were defined by ranges of values that allowed similar numbers within each category. Age at implantation and another known confounder, socioeconomic status, were controlled for in the regression analyses. Age at implantation was also one of the variables differing significantly between groups (lower in those with *GJB2*-related deafness).

The other two variables significantly different between groups; length of deafness and postoperative complications were not controlled for, since length of deafness was almost identical to age at implantation and postoperative complications were actually higher in those with *GJB2*-related deafness. In the regression analysis, the best outcomes were observed in those with *GJB2*-related deafness (Table 4). There was also a negative correlation noted between age at implantation and GASP word scores, but a significant positive correlation between age at implantation and IOWA Matrix test scores and between age at implantation and GASP Sentence scores. This could be because the latter two outcomes are more dependent on the linguistic vocabulary abilities of test subjects, which improves with age at testing, and those with later ages at implantation would be older at testing since they were compared at a fixed postoperative time interval of 3 years. Thus, despite longer auditory deprivation, a later age at implantation appeared to be a predictor of better outcome in the IOWA Matrix Level B test and GASP sentence test. Since those with *GJB2*-related deafness had the lowest ages of implantation, the odds ratios increased when adjusted for this in these two tests. This finding has also been shown in another study, where children implanted at an older age performed better at 2 years after implantation; however, the reverse occurred at the 3 and 4 year postoperative intervals (14). The variability of results in our study, depending on the outcome measure used, may reflect lack of sensitivity in these tests and/or may be related to the site(s) of pathologic changes in the auditory pathway of patients.

The findings of this study are that implanted children with *GJB2*-related deafness appear to have equal or bet-

ter speech discrimination compared with a group of prelingually deaf children with deafness of unknown etiology.

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