Speech Recognition Scores Related to Age and Degree of Hearing Impairment in DFNA2/KCNQ4 and DFNA9/COCH

Steven J. H. Bom, MD; Els M. R. De Leenheer, MD; François X. Lemaire, MD; Martijn H. Kemperman, MD; Wim I. M. Verhagen, PhD; Henri A. M. Marres, PhD; Henricus P. M. Kunst, PhD; Robert J. H. Ensink, PhD; Arjan J. Bosman, PhD; Guy Van Camp, PhD; Frans P. M. Cremers, PhD; Patrick L. M. Huygen, PhD; Cor W. R. J. Cremers, PhD

Objective: To analyze the relationship between pure-tone hearing threshold and speech recognition performance in DFNA2/KCNQ4 and DFNA9/COCH, 2 types of high-frequency nonsyndromic hearing impairment.

Design: Case series with cross-sectional analysis of phoneme recognition scores related to age and hearing level.

Setting: University hospital.

Patients: Forty-five members of 4 separate families, all carrying 1 of 3 different mutations in the KCNQ4 gene at the DFNA2 locus (1p34); 42 members of 7 separate families, all carrying the same Pro51Ser mutation in the COCH gene at the DFNA9 locus (14q12-q13).

Results: The deterioration of speech recognition dropped to a 90% score at a higher level of hearing impairment (pure-tone-average at 1, 2, and 4 kHz) in DFNA2-affected patients (65 dB) than in DFNA9-affected patients (46 dB).

Conclusion: At similar levels of hearing impairment, DFNA2/KCNQ4-affected patients showed better speech recognition performance than DFNA9/COCH-affected patients.


A UTOSOMAL dominant non-syndromic types of hereditary sensorineural hearing impairment can be identified by genetic linkage and mutation analysis. The corresponding chromosomal loci are genetically designated DFNA, followed by a number in order of discovery (DFN = deafness, A = autosomal dominant inheritance).1 One locus may harbor 1 or more disease-causing genes. The discovery of such genes and their function may enhance our understanding of the pathophysiology of the inner ear. Concurrently, clinical studies are necessary to relate the latter to the resulting phenotype.

Clinical studies on DFNA2/KCNQ4-affected families and DFNA9/COCH-affected families have demonstrated fairly similar high-frequency sensorineural hearing impairment and progression (S.J.H.B., unpublished data, 2000)12-16 In addition to sensorineural hearing loss, DFNA9-affected patients also develop vestibular failure.6-16 The DFNA9-affected families studied in the Netherlands and Flanders all have the same mutation in the COCH gene, corresponding to a P51S substitution in the expressed protein, cochlin.12,17,18 The function of cochlin is still unknown. In the 4 Dutch DFNA2-affected families, 3 different mutations (W276S, G321S, L274W) of the KCNQ4 gene were found.19,20 KCNQ4 encodes a potassium (K+) channel that is predominantly expressed in the basolateral membrane of cochlear hair cells.21,22

The present study focuses on the relationship between speech recognition performance on the one hand and age and pure-tone hearing threshold on the other hand in 2 different types of non-syndromic, autosomal dominant, sensorineural hearing impairment. The 2, DFNA2/KCNQ4 and DFNA9/COCH, are both characterized by progressive, predominantly high-frequency hearing impairment.

RESULTS

In each group, the SRT showed an excellent correlation with the corresponding PTA1,2,4 kHz (n=33-44 after exclusion of 3 outlying values; r=0.8-0.9, residual SD=9-13 dB). This corresponds fairly well with the residual SD found by Bosman and Smoorenburg.24 Mean pure-tone thresholds for a representative, “modal-age” se-
PATIENTS AND METHODS

This study compared speech recognition data between patients with DFNA2/KCNQ4-affected patients and DFNA9/COCH-affected patients. Speech recognition data for patients with DFNA2 were obtained from 45 carriers of a mutation in the KCNQ4 gene. There were 30 patients from 2 families with a W276S mutation (G.V.C., unpublished data, 2000; 2,3,10 10 patients with a G321S mutation,3,18 and 5 patients with a L274W mutation.6,20 Speech recognition data for patients with DFNA9 were obtained from 42 carriers of the P515 mutation in the ALG7 gene, from 6 Dutch families6-11,17 and 1 Flemish family (S.J.H.B., unpublished data, 2000).13,18

Auditory thresholds were performed according to common clinical standards. For speech recognition, standard monosyllabic Dutch word lists were presented at either ear.23 Performance-intensity curves relating to the phoneme recognition score were analyzed for the right ear only. The last-visit speech reception threshold (SRT) (in decibels sound pressure level [dB SPL] for 50% phoneme score) and the maximum phoneme recognition score (percentage correct), at which the pure-tone-threshold at 1, 2, and 4 kHz could be measured, were used.

Plots of SRT vs pure-tone-average at 1, 2, and 4 kHz (PTA1,2,4 kHz) were used with linear regression analysis to check for the reliability of the phoneme recognition scores. The Chauvenet criterion24 and the residual SD were used to identify and exclude outlying values.

Because a comparison of speech recognition scores between the patient groups may be complicated by underlying differences in sensorineural hearing thresholds, the thresholds at each frequency for “modal-age” patients between the groups were compared, using the t test. These patients were selected from each group by requiring their age to be within the limits of the percentiles P17.5 and P0.25 of the corresponding age distribution.

Nonlinear regression analysis of the maximum phoneme recognition score on log(age) and on log(PTA1,2,4 kHz) was performed using the Prism PC version 3.02 program (GraphPad, San Diego, Calif). Cross-sectional and individual longitudinal performance-age (percentage recognition vs age) and performance-impairment plots (percentage recognition vs PTA1,2,4 kHz) were fitted with a sigmoidal dose-response function with a variable slope: \[ Y = \frac{100\%}{1 + 10^{(X_{90} - X_0) \times \text{HillSlope}^{B}}}, \] where Y is the phoneme score, X is either age or PTA1,2,4 kHz, X90 is the value of X where Y = 90%, and HillSlope is the slope factor on a log scale of X. The fitted values of X90 and HillSlope were used to test between curves relating to the patient groups, using the t test (with the Welch correction if the Bartlett test detected unequal variances).

To simplify the results and allow for additional testing, “local average” slope (ie, on a linear scale) for X>X90 was obtained by using a linear regression line as an approximation of the corresponding part of the fitted sigmoidal curve. Slope was the deterioration rate in the performance-age plot, whereas it was the deterioration gradient in the performance-impairment plot X90 was the onset age for the performance-age plot and onset level for the performance-impairment plot. Regression lines were compared between the groups using analysis of covariance (ANCOVA) to find out whether slopes and intercepts were significantly different. Again, Chauvenet’s criterion24 was used in combination with the residual SD to detect outlying values.

Individual longitudinal data were available in 18 DFNA2/KCNQ4-affected patients and 23 DFNA9/COCH-affected patients. Analyses constituted plotting of serial phoneme recognition scores against age and PTA1,2,4 kHz, and comparing these to the curves fitted to the corresponding cross-sectional data. A 5% lower normal limit established at the Nijmegen Otorhinolaryngology department (P.L.M.H., unpublished data, 2000) was used to see whether there were scores that raised suspicion of retrocochlear dysfunction.

The phenotype of the DFNA2/KCNQ4-affected patients may be influenced by the nature of the mutation that is present in the family. In addition, even for patients carrying the same mutation, differences in other genes (genetic background) may also influence the phenotype. It was, therefore, checked whether there were significant differences in score behavior between either the different DFNA2/KCNQ4-affected families or the different DFNA9/COCH-affected families.

The Figure shows cross-sectional performance vs age plots (A-B) and combined performance-impairment plots (C). Onset age was 34 years in DFNA2/KCNQ4-affected patients and 43 years in DFNA9/COCH-affected patients. The local average deterioration rate in DFNA2-affected patients was 0.3% per year, while in DFNA9-affected patients, it was 1.8% per year (Figure A-B). There was no significant difference in HillSlope between the plotted curves in Figure C. However, the local average deterioration gradients were significantly different (0.5% per decibel vs 1.2% per decibel). The latter finding is related to the significant difference in onset level that can be detected (65 vs 46 dB), as well as the observation that there is a clear separation between the data points (Figure C). In other words, at a given level of impairment, DFNA2/KCNQ4-affected patients showed higher scores than DFNA9/COCH-affected patients.

Individual longitudinal analyses produced fairly similar results to the cross-sectional analysis (data not shown). Four of the DFNA9/COCH-affected patients had scores below the normal limit that would have been suggestive of retrocochlear dysfunction. Some of these scores renormalized during follow-up. None of the DFNA2/KCNQ4-affected patients had any scores suggestive of retrocochlear dysfunction. No significant differences in score behavior between either the different DFNA2/KCNQ4-affected families or the different DFNA9/COCH-affected families were found (data not shown).

The marked difference in speech recognition performance as related to sensorineural hearing level between
DFNA2/KCNQ4 and DFNA9/COCH, both characterized by predominantly high-frequency sensorineural hearing impairment, is an appealing finding in this study. Better recognition scores in the DFNA2-affected patients are remarkable, especially in light of recent findings that the mouse homologue of KCNQ4 is abundantly expressed in the central auditory pathways. KCNQ4 is thought to play a role in the K+ recycling pathway of the inner ear. Three of the 4 studied families with DFNA2/KCNQ4-affected patients had different mutations, but fairly similar speech recognition. The L274W and W276S mutations produce changes in the pore region of the expressed K+ channel protein, whereas the G321S mutation exerts an effect just outside the pore region, however, apparently to a similar phenotypic effect.

On the other hand, the DFNA9/COCH-affected patients had poorer speech recognition scores compared with age and sensorineural hearing level (Figure C). The American DFNA9-affected patients, with a V66G mutation within the COCH gene, however, showed an even greater drop in recognition scores. The latter had earlier onset (at age 20 years) and anacusis at around age 45 years. Combined speech performance-impairment plots of the recognition scores (not shown) are suggestive of poorer scores in the American V66G carriers. However, our longitudinal analyses also disclosed the existence of temporarily poor scores in some of our DFNA9/COCH-affected patients. Such poor scores may have been related to Ménière-like paroxysms.

Histopathologic findings reported for 1 American COCH/V66G–mutation carrier comprised general destruction of the cochlear and vestibular sensory elements, including hair cells and dendrites (cochlea, crista, and macula), as well as accumulation of an acellular substance (glycosaminoglycan) throughout the labyrinth. These findings were similar to those reported previously in DFNA9/COCH-affected patients. In chicken, COCH expression was found in fairly similar places where the deposits were found in human patients. It has been postulated that “strangulation” of cochlear and vestibular nerve endings occurs. Alternatively, the possibility was suggested that normal fibrillogenesis is disrupted by an excess in microfibrillar substance, which results in degradation of collagens and extracellular matrix components. It is also possible that cochlin, which is expressed in the stroma underlying the sensory structures of the inner ear, has a role in ion homeostasis, for example, recycling of K+ ions from the hair cells to the endolymph.

In the present study, DFNA2/KCNQ4-affected patients seemed to have better speech recognition scores than DFNA9/COCH-affected patients (Figure C); the difference could not be explained by underlying differences in pure-tone thresholds. Cochlear KCNQ4 expression was initially thought to be confined to the outer hair cells. However, recent findings in the rat have shown that it is also expressed in inner hair cells and the spiral ganglion. The strongest KCNQ4 expression, that is, in normally hearing animals, was found in inner hair cells in the lower cochlear turns and in outer hair cells in the upper turns. Thus DFNA2/KCNQ4-related high-frequency sensorineural hearing impairment, which is associated with primary dysfunction of the lower cochlear turns, might be attributed to a lack of expression of K+ channels, especially in inner hair cells. Relative sparing of function of outer hair cells in the lower turns, thus preserving their function as “cochlear preamplifier” in fine tuning mechanisms, might account for the better
speech recognition in DFNA2/KCNQ4-affected patients. On the other hand, the poor recognition scores in DFNA9/COCH-affected patients might be explained by the generalized, histopathologic, vestibulocochlear changes,\textsuperscript{15,16,28,29} already mentioned earlier, and, in part, by its Méniéreiform features.\textsuperscript{11,12}

Accepted for publication February 7, 2001.

This study was supported in part by the Heinsius Houbolt Foundation, Wassenaar, the Netherlands, and the Nijmegen KNO-Research Foundation (Dr Cor Cremers). We thank the family members who participated in this study.

Drs Bom and De Leenheer contributed equally to this work.

Corresponding author: Steven J. H. Bom, MD, Department of Otorhinolaryngology, University Medical Centre St Radboud, PO Box 9101, 6500 HB Nijmegen, the Netherlands (e-mail: S.Bom@kno.azn.nl).

REFERENCES


