Hearing Impairment Related to Age in Usher Syndrome Types 1B and 2A

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Objective: To evaluate hearing impairment in 2 common genetic subtypes of Usher syndrome, USH1B and USH2A.

Design: Cross-sectional analysis of hearing threshold related to age in patients with genotypes determined by linkage and mutation analysis.

Setting: Otolaryngology department, university referral center.

Patients: Nineteen patients with USH1B and 27 with USH2A were examined. All participants were living in the Netherlands and Belgium.

Main Outcome Measure: Pure tone audiometry of the best ear at last visit.

Results: The patients with USH1B had residual hearing without age dependence, with minimum thresholds of 80, 95, and 120 dB at 0.25, 0.5, and 1 to 2 kHz, respectively. Mean thresholds of patients with USH2A were about 45 to 55 dB better than these minimum values. Distinctive audiographic features of patients with USH2A were maximum hearing thresholds of 70, 80, and 100 dB at 0.25, 0.5, and 1 kHz, respectively, only at younger than 40 years. Progression of hearing impairment in USH2A was 0.7 dB/y on average for 0.25 to 4 kHz and could not be explained by presbyacusis alone.

Conclusions: The USH1B and USH2A can be easily distinguished by hearing impairment at younger than 40 years at the low frequencies. Hearing impairment in our patients with USH2A could be characterized as progressive.


The Usher syndrome was first described in 1858 and characterized as a disorder with bilateral sensorineural hearing loss and visual impairment caused by tapetoretinal degeneration. Several authors emphasized a high prevalence of this syndrome in certain families, and a hereditary nature was suspected. von Wibout suggested that the syndrome had an autosomal recessive mode of inheritance.

Clinical heterogeneity within the syndrome was first described by Bell. Later, Hallgren pointed out that at least 2 distinct clinical types existed. Extensive clinical studies have been performed to outline the clinical heterogeneity. Three clinical types, Usher types I, II, and III, were distinguished, which was important for counseling purposes and gene linkage studies.

As early as 1959, Hallgren suggested that the different clinical subtypes were related to different genetic subtypes. Since 1990, linkage studies by several groups have demonstrated extensive genetic heterogeneity within Usher syndrome. Usher syndrome type I consists of 6 genetic subtypes (USH1A through F), whereas Usher syndrome type II has 2 genetic subtypes (USH2A and B). Usher syndrome type III has been linked to only 1 locus so far (USH3) and is mainly diagnosed in Finland. In the Netherlands and Belgium, USH1B and USH2A are most frequently encountered.

In 1995, mutations in the human myosin VIIa gene were found to be responsible for USH1B. Recently, Eudy et al reported on a gene encoding a protein with extracellular matrix motifs. Mutations in this gene seem to cause USH2A.

Whereas in the past clinical examination was needed for diagnosing the subtypes of Usher syndrome, such a diagnosis, at present, will be based mainly on either linkage analysis or mutation analysis. This does not disqualify clinical studies on the Usher syndromes. These are still
PATIENTS AND METHODS

In this study, 19 patients (14 men and 5 women; mean age, 27.8 years) with Usher syndrome type I and 27 patients (13 men and 14 women; mean age, 38.2 years) with Usher syndrome type II were examined. All patients, except for 2 isolated cases, either had 1 or more affected siblings or their parents were consanguinely related. The patients and their families were living in the Netherlands or Belgium.

Genetic subtypes of Usher syndrome were determined by linkage analysis or mutation analysis. Two isolated cases of Usher syndrome could be included because their genotype was confirmed by mutation analysis. Pathogenic mutations in the myosin VIIa gene on chromosome 11q13 (USH1B) were detected in 7 type I families (12 patients) and in 1 isolated case. The other 3 type I families (6 patients) showed linkage to 11q13 (USH1B) and are still being analyzed. All 14 type II families, as well as the other isolated case, showed linkage to chromosome 1q32 (USH2A). Linkage to USH3 (chromosome 3q) was excluded in these cases. Eudy et al recently found mutations in a gene encoding a protein with extracellular matrix motifs that seemed to be responsible for USH2A. In 6 type 2A families (10 patients) in this study, as well as in the isolated case, the 2314delG mutation in this gene was demonstrated.

Clinical examination of the affected patients included medical history, audiovestibular testing, and ophthalmologic examination. The latter included external eye examination, corrected visual acuity measurements, slit-lamp microscopy, ophthalmoscopy, Goldmann perimetry, electroretinography, and electro-oculography. The results of ophthalmologic examinations confirmed the diagnosis of tapetoretinal degeneration in all patients with type 1B and 2A (M.W., A.V.A., P.H., W.K., C.C., and Alfred Pinckers, MD, PhD, unpublished data, August 1998). Electronystagmography was performed to evaluate vestibularly evoked and visually guided eye movements; it disclosed vestibular areflexia in all patients with USH1B, whereas vestibular responses could be elicited in all patients with USH2A.

Audiometric evaluation of 26 patients with USH2A was performed at the Department of Otorhinolaryngology, University Hospital Nijmegen, Nijmegen, the Netherlands. It consisted of standard pure-tone audiometry, assessment of speech discrimination scores, and auditory brainstem responses. The audiometric data of 1 patient with USH2A were obtained from elsewhere. In 17 patients with USH1B, pure-tone audiometry was performed at the Department of Otorhinolaryngology in Nijmegen. Hearing impairment in these patients was too severe to yield any meaningful speech discrimination scores or auditory brainstem response data. We obtained pure tone audiograms of 2 patients with USH1B from elsewhere. Pure-tone audiometry of the best ear at the last visit was used for a cross-sectional comparison of hearing impairment in USH1B and USH2A. Pure tone audiograms were measured with a clinical audiometer (AC40; Interacoustics, Assens, Denmark) according to the International Organization for Standardization 8523-1 standard (1989) at 0.25, 0.5, 1, 2, 4, and 8 kHz for air and bone conduction.

Because residual hearing in USH1B is only detectable in the low frequencies and no thresholds could be measured in the high frequencies, it was not possible to determine a pure tone average hearing loss for all frequencies. We therefore evaluated hearing impairment for each frequency separately. Furthermore, a method had to be found to visualize the nonmeasurable thresholds and the observed vibrotactile sensations in audiogram format. Out-of-scale thresholds (>130 dB), or thresholds that could be attributed to vibrotactile stimulation instead of auditory stimulation, were set at the vibrotactile thresholds for 0.25, 0.5, 1.0, and 2.0 kHz (95, 115, 125, and 130 dB, respectively). At 4 and 8 kHz, out-of-scale thresholds were set at 130 dB. Obviously, the distribution of thresholds in USH1B was nongaussian, and further statistical analysis with regard to hearing impairment in this population was not applicable.

Hearing impairment in USH2A was compared with that in USH1B to see whether these genotypes can be distinguished by their hearing impairment. We also looked for progression of hearing impairment in the patients with USH2A. A linear regression analysis was applicable to model hearing impairment related to age in USH2A at each frequency, except for 8 kHz, because data were biased by out-of-scale thresholds. A longitudinal study on individual USH2A data had already proved that USH2A can be progressive in some cases. The USH1B threshold data did not permit a cross-sectional analysis by means of regression analysis. We analyzed the longitudinal data in 7 patients with USH1B. When progression of hearing loss was analyzed, the threshold values were also corrected for presbyacusis. The 50th percentile threshold values for presbyacusis, corrected for age and sex, were calculated according to the International Organization for Standardization 7029 method (1984).

RESULTS

All patients with USH1B had residual hearing only at the lower frequencies, whereas the patients with USH2A generally showed a down-sloping audiogram. Figure 1 shows the audiogram data of all cases. The asterisk indicates a 56-year-old patient with USH2A who was excluded from the regression analysis because of excessively good hearing threshold, which of considerable importance to explain some of the relevant differences in phenotypes based on different genotypes. By this an understanding of the related pathophysiology could be gained.

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olds against age for the 2 types of Usher syndrome at each frequency. Regression lines are shown only for the patients with USH2A, because the USH1B threshold data were non-Gaussian at most frequencies. It is clear, however, that the latter did not show any appreciable dependence on age. The USH2A can be optimally distinguished from USH1B at age younger than 40 years, according to the criterion that in USH2A the maximum tolerable thresholds are 70, 80, and 100 dB at 0.25, 0.5, and 1 kHz, respectively (dotted lines).

There was significant progression in hearing impairment, ie, the regression coefficient—here called annual threshold increase—differed significantly from 0, in the patients with USH2A at all frequencies (Figure 2, Table). Regression analysis (analysis of variance) showed that the annual threshold increases at 0.25 to 4 kHz were not significantly different (pooled value, about 0.7 dB/y), but the intercepts (decibel hearing level at age x = 0) differed significantly from 0, except at 0.25 kHz. The intercepts tended to be higher at the high frequencies, ie, assuming that the linear regression applies to the whole age range.

A longitudinal analysis on 13 patients with USH2A included in this study was previously performed by van Aarem et al.17 From these data, they concluded that in individual cases, USH2A can show progression in hearing impairment. We also performed a longitudinal analysis on progression of residual hearing of 8 patients with USH1B (data not shown), but found no evidence of any substantial progression in hearing impairment.

Hearing impairment has been regarded to be different in Usher syndrome type I and type II since definition of these clinical subtypes. Patients with Usher syndrome type I have been said to see themselves as deaf people going blind, whereas those with Usher syndrome type II regard themselves as visually impaired individuals with a hearing problem.18 This acknowledges the pertinent difference between the prelingually profoundly deaf patient with Usher syndrome type I and the moderately to severely hearing-impaired patient with Usher syndrome type II.

Moeller et al19 performed quantitative evaluation of hearing thresholds in 9 patients with Usher syndrome type I and type II. Many authors have used only descriptive terms to characterize the difference in hearing impairment between patients with Usher syndrome type I and type II.

Pakarinen et al21 compared Usher syndrome type III with types I and II and found mean hearing thresholds of about 90, 100, 105, and 110 dB at 0.25, 0.5, 1, and 2 kHz, respectively, in 79 patients with Usher syndrome type I. Hearing impairment in our USH1B population seemed to be more severe, with minimum hearing thresholds of 80, 95, 120, and 120 dB at 0.25, 0.5, 1, and 2 kHz, respectively. When analyzing the data from patients with Usher syndrome type II, Pakarinen et al21 reported hearing thresholds between 40 and 90 dB. Our patients with USH2A showed similar thresholds at the low frequencies but higher thresholds at the higher frequencies.

It proved possible to distinguish USH2A from USH1B by means of a simple audiogram criterion. This criterion applies only to patients younger than 40 years and the low frequencies (0.25-1 kHz). Higher ages and

![Figure 1. Synoptic audiogram of the threshold values measured in patients with Usher syndrome types 1B (USH1B) and 2A (USH2A). Triangles indicate out-of-scale measurements or vibrotactile thresholds; numbers, numbers of observations; asterisk, a patient with USH2A who was excluded from statistical analysis; and HL, hearing level.](https://jamanetwork.com/10/19/)

### Table: Statistics of Hearing Threshold by Frequency in USH1B and USH2A

<table>
<thead>
<tr>
<th>Frequency</th>
<th>0.25 kHz</th>
<th>0.5 kHz</th>
<th>1 kHz</th>
<th>2 kHz</th>
<th>4 kHz</th>
</tr>
</thead>
<tbody>
<tr>
<td>USH1B (n = 19)</td>
<td>Minimum value, dB HL</td>
<td>80</td>
<td>95</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>USH2A (n = 26)</td>
<td>Mean ± SD, dB HL</td>
<td>36.73 ± 14.49</td>
<td>50.96 ± 14.63</td>
<td>65.77 ± 15.92</td>
<td>72.88 ± 14.71</td>
</tr>
<tr>
<td>P95, dB HL</td>
<td>61</td>
<td>76</td>
<td>93</td>
<td>98</td>
<td>109</td>
</tr>
<tr>
<td>ATI, dB/y</td>
<td>0.81</td>
<td>0.75</td>
<td>0.66</td>
<td>0.58</td>
<td>0.75</td>
</tr>
<tr>
<td>y Intercept</td>
<td>5.70</td>
<td>22.01</td>
<td>40.24</td>
<td>50.65</td>
<td>49.36</td>
</tr>
<tr>
<td>−P50, correction for presbyacusis</td>
<td>0.70</td>
<td>0.63</td>
<td>0.53</td>
<td>0.34</td>
<td>0.31</td>
</tr>
</tbody>
</table>

*USH1B and USH2A indicate Usher syndrome types 1B and 2A; HL, hearing level; P95, 95th percentile threshold value; ATI, annual threshold increase; and −P50, correction for presbyacusis.*
Figure 2. Hearing thresholds according to age in patients with Usher syndrome types 1B (USH1B) and 2A (USH2A). Triangles indicate out-of-scale measurements or vibrotactile thresholds; numbers, numbers of observations; VTT, vibrotactile threshold; HL, hearing level; and asterisk, a patient with USH2A who was excluded from statistical analysis. The dotted lines separate both types of Usher syndrome by threshold at age younger than 40 years at frequencies of 0.25 to 1 kHz. The sloped line in each plot is the regression line for the patients with USH2A.
frequencies are inappropriate because of the relatively strong influences of progression and presbyacusis, which caused considerable overlap in threshold values between the 2 types. Exclusion of 1 patient with USH2A, who had excessively good hearing thresholds, did not have any favorable effects on these results.

We wished to find out whether apparent progression in hearing impairment could be attributed to presbyacusis. We therefore also corrected each patient’s threshold at each frequency by subtracting the 50th percentile presbyacusis threshold appropriate for the patient’s age and sex. An informal, tentative linear regression analysis was used, since a formal analysis was not permitted because the data were clearly biased by the presbyacusis correction. The results obtained indicated that progression was still detectable in the corrected threshold-on-age data at 0.25 to 1 kHz, but less so at 2 to 4 kHz (Table). It can therefore be concluded that the patients with USH2A as a group disclosed progression in hearing impairment that could not be explained by presbyacusis alone.

The rate of progression (annual threshold increase) in the present cross-sectional analysis of patients with USH2A seemed somewhat higher than the average progression in a longitudinal analysis of these patients.17 This might be explained by the fact that a single, last-visit threshold measurement tends to be more influenced by presbyacusis than are longitudinal measurements at a relatively young age.

In the patients with USH2A the rate of progression was fairly similar at all frequencies, with an annual threshold increase of 0.7 dB/y on average, but the intercepts, which we will call offset thresholds here, were different between the frequencies. The higher frequencies were clearly more affected at a very young age in USH2A.

We conclude that, not unexpectedly, patients with USH2A and USH1B can be easily distinguished by their hearing impairment at the low frequencies and at age younger than 40 years. This study shows that hearing impairment in our patients with USH2A can be characterized as progressive. If this applies to all patients with USH2A, the phenotype probably needs to be redefined.

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