A Family With Autosomal Dominant Inherited Dysmorphic Small Auricles, Lip Pits, and Congenital Conductive Hearing Impairment

Sacha M. P. Koch, MD; Shrawan Kumar, PhD; Cor W. R. J. Cremers, MD, PhD

Design: We examined 3 generations in a family for congenital conductive hearing impairment, dysmorphic small auricles, and lip pits.

Setting: Department of Otorhinolaryngology, University Hospital Nijmegen, Nijmegen, the Netherlands.

Results: Seven members of the family had bilateral dysmorphic auricles. Three subjects had either a pit or dimple in the lip. Two subjects had congenital conductive hearing impairment.

Conclusion: Using gene linkage, we confirmed that these autosomal dominant inherited branchial anomalies present a new separate branchial arch syndrome.


THREE GENERATIONS of a family were examined for congenital conductive hearing impairment, dysmorphic small auricles, and lip pits. These autosomal dominant inherited branchial anomalies represent a separate branchial arch syndrome as confirmed by gene linkage studies. Seven members of the family had bilateral dysmorphic small auricles. Three subjects had a dimple or pit in the lip. Two subjects also had congenital conductive hearing impairment.

More than 50 genetic syndromes with congenital conductive hearing impairment have been reported. Some branchiogenic syndromes occur fairly frequently and are well delineated, such as the autosomal dominant inherited branchio-oto-renal (BOR) syndrome, the autosomal dominant inherited Treacher Collins syndrome (mandibulofacial dysostosis), and hemifacial microsomia (oculoauriculovertebral spectrum). All these branchiogenic syndromes affect multiple organs. Another rare branchiogenic syndrome has been described only in combination with other characteristics, such as pinnal abnormalities, congenital hearing impairment, and lip pits. Individuals with this syndrome described by Marres and Cremers have ear pits, lop-ears, congenital hearing impairment, and commissural lip pits. The latter syndrome can be differentiated from the above-mentioned syndromes, but in the case of incomplete penetrance, this differentiation may be difficult in some individuals.

The results of clinical examination of the 3 generations of the present family suggest a new autosomal dominant inherited syndrome. We found bilateral dysmorphic small pinnae, congenital conductive hearing impairment, and lip pits or dimples. The anomalies are presumably developmental defects in the first and second branchial arch that occurred during the sixth and seventh weeks of gestation, resulting in an auricle abnormality (first and second arch) and an abnormal incus and stapes (first and second arch).

RESULTS

In 1997, the male proband (Figure 2, III: 1), aged 13 years, was referred to the Department of Otorhinolaryngology of the University Hospital Nijmegen for evaluation of congenital hearing impairment. The results of a physical examination showed bilateral dysmorphic small auricles (Figure 1, E). There were no preauricular sinuses or second branchial arch fistulas, but there were bilateral commissural lip pits. The results of otoscopy showed a somewhat straight handle of the malleus and relatively small external auditory canals but no severe abnormali-
SUBJECTS AND METHODS

The proband (the eldest of 6 children) was referred to the Department of Otorhinolaryngology, University Hospital Nijmegen, Nijmegen, the Netherlands, because of a unilateral congenital conductive hearing impairment. A congenital anomaly of the ossicular chain was suspected in view of the accompanying bilateral small dysmorphic auricles (Figure 1, E). After performing successful unilateral surgery for the congenital conductive hearing impairment, we received permission to conduct a clinical investigation of his family. The family comprised 3 generations with several affected members (Figure 2). The parents, the brothers, sister, and almost all paternal aunts agreed to take part in our clinical investigation. Clinical and otorhinolaryngological examinations were performed, including microotoscopy, pure-tone audiometry, and photographs of the auricles. Previous audiograms taken elsewhere were obtained. Permission could not be obtained to perform ultrasonographic investigation of the kidneys. Blood samples were taken for gene linkage studies.

In the right ear, he had 60-dB conductive hearing loss and a 60-dB speech perception threshold, with 100% discrimination (Figure 3). There were complaints of occasional tinnitus. Computed tomographic scans of the temporal bones showed normal pneumatization of the middle ear and mastoid bones. The facial nerve had a normal course, and its bony canal was intact. There was no sign of an enlarged vestibular aqueduct. We observed normal inner ears and normal bilateral internal auditory canals. To improve the conductive hearing impairment, exploratory tympanotomy was performed on his right ear. The long process of the incus was found to be too short, the stapes was monopodal, and there was congenital fixation of the footplate. The incus and the stapedial crurae were removed. Stapedectomy was performed, and a modified piston (modified Teflon platinum Cremers piston; Richards Co, Memphis, Tenn) was interposed onto the handle of the malleus (length of 5.5 mm measured from the middle eye with a diameter of 0.6 mm). This modified piston has an extra loop of wire to ensure a tight fit around the malleus. Thus, mallevestibuloplexy was performed. His auditory threshold improved postoperatively from about 60 to 25 dB (Figure 4), but sensorineural hearing loss was present at the high frequencies. The tinnitus did not diminish.

The father (Figure 2, II:2) of the proband was 31 years old. The results of physical examination showed bilateral dysmorphic small auricles (Figure 1, C). We did not observe preauricular sinuses, second branchial arch fistulas, or commissural lip pits. The results of otoscopy showed bilateral normal tympanic membranes. His audiogram was normal.

The proband’s paternal grandfather (Figure 2, I:1) was dead. The family said that he had had the same bilateral dysmorphic small pinnae. No hearing impairment had been noted.

The youngest sister (Figure 2, II:8) of the proband’s father was aged 28 years. She also had bilateral dysmorphic small auricles. We did not observe preauricular sinuses, second branchial arch fistulas, or commissural lip pits. The results of otoscopy and audiometry were normal.

The proband’s 9-year-old sister (Figure 2, III:4) had bilateral dysmorphic small pinnae (Figure 1, F). We did not observe preauricular sinuses or second branchial arch fistulas. A lip dimple on the right side was noted. The results of otoscopy and audiometry were normal.

The proband’s 2 brothers were dizygotic twins aged 6 years (Figure 2, III:5 and III:6). Subject III:5 had bilateral dysmorphic small auricles (Figure 1, A). We did not observe preauricular sinuses, second branchial arch fistulas, or commissural lip pits. The results of one otoscopy showed signs of recent otitis media on the right side, while the left bony external auditory canal appeared to ascend slightly. Repeated pure-tone audiometry was performed, and the results showed a conductive hearing loss of 30 to 40 dB in the right ear and 20 dB in the left ear.

Subject III:6 (Figure 2) also had bilateral dysmorphic small auricles (Figure 1, B). We did not see preauricular sinuses or second branchial arch fistulas. On the right side, there was a lip dimple. The results of otoscopy showed a well-aerated middle ear cleft and slight myringosclerosis on the left side. The audiogram demonstrated conductive hearing loss of 25 dB in the right ear and 35 dB in the left ear. The speech perception threshold was in agreement with the pure-tone audiogram. He experienced acute otitis media only once as shown by the otitis media of the left ear.

The 40-year-old mother of the proband (Figure 2, II:1) had normal auricles (Figure 1, D). We did not observe preauricular sinuses, second branchial arch fistulas, or commissural lip pits. The results of otoscopy and audiometry were normal. She did not have the syndrome.

Subjects III:2 and III:3 (Figure 2) were dizygotic twin boys aged 12 years. The results of physical examination of subject III:2 showed normal auricles (Figure 1, G). We did not observe preauricular sinuses, second branchial arch fistulas, or commissural lip pits. The results of otoscopy showed normal tympanic membranes. The audiogram in subject III:2 was normal. He did not have the syndrome.

The other twin (Figure 2, III:3) also had normal auricles (Figure 1, H). We did not observe preauricular sinuses, second branchial arch fistulas, or commissural lip pits. The results of otoscopy showed normal tympanic membranes. His audiogram was normal. He did not have any features of the syndrome.

The eldest proband’s paternal aunt (Figure 2, II:3) was aged 39 years. The results of physical examination showed slight anteversion in the auricles, but we did not observe preauricular pits, branchial fistulas, or lip pits. There were no complaints of hearing loss. She did not
have the syndrome. She had 6 children who did not have the syndrome.

The proband’s paternal aunt (Figure 2, II:4) was aged 38 years. During the physical examination, we observed normal auricles and no preauricular pits, branchial fistulas, or lip pits. There were no complaints of hearing loss. She did not have the syndrome.

Subject II:5 was the proband’s paternal aunt (Figure 2), who was aged 39 years. She could not be included in this family report. Neither dysmorphic auricles nor hearing impairment were noted in the medical history. She probably did not have the syndrome.

Subject II:6 (Figure 2), aged 35 years, was another sister of the proband’s father. The results of physical examination showed normal auricles. We did not observe preauricular pits, branchial fistulas, or lip pits. There were no complaints of hearing loss. She did not have the syndrome. She had 2 children; they did not have the syndrome.

The proband’s paternal aunt (Figure 2, II:7) was aged 32 years. During the physical examination, we observed a normal left auricle and a right auricle that was surgically corrected to repair anteverision. We did not observe preauricular pits, branchial fistulas, or lip pits. The
results of otoscopy showed normal tympanic membranes. There were no complaints of hearing loss. She did not have the syndrome.

Gene linkage studies were performed to see whether linkage could be confirmed for the BOR syndrome or the syndrome described by Marres and Cremers.\textsuperscript{2} We screened for closely linked markers on chromosome 8q and 1q in this family.\textsuperscript{5,6} The 2-point results presented in Table 1 for both the chromosomes indicate that the syndrome was not linked to either 1q or 8q regions.

**COMMENT**

The syndrome described herein has a branchiogenic origin. We evaluated 6 affected family members with dysmorphic small auricles, and 2 of them had a congenital conductive hearing impairment. In 3 subjects, a lip pit or dimple was seen. No other branchiogenic features were present. On the basis of clinical features of this family, it is obvious that the BOR syndrome, the Treacher Collins syndrome, and autosomal dominant inherited hemifacial microsomia can be excluded.

Individuals with another syndrome that resembles the BOR syndrome have preauricular sinuses, dysmorphic auricles, commissural lip pits, and congenital conductive or mixed hearing impairment,\textsuperscript{2,3} without second branchial arch fistulas. The pattern of inheritance is autosomal dominant. In 2 large families with this syndrome, gene linkage to chromosome 1q31 was found.\textsuperscript{7} The high incidence of preauricular sinuses and the absence of this feature in the present family makes it unlikely that they have the same syndrome. Gene linkage

---

**Figure 2.** The pedigree demonstrates the proband and the autosomal dominant transmission of the dysmorphic small auricle in the proband’s father, paternal grandfather, paternal aunt, 1 sister, and 1 brother.

**Figure 3.** Preoperative audiogram demonstrates a conductive hearing loss, a 60-dB speech reception threshold, and 100% discrimination. A, Right ear. B, Left ear.

**Figure 4.** One-year postoperative audiogram demonstrates a reduction in the auditory threshold from about 60 dB to 25 dB; sensorineural hearing loss was present at the high frequencies. A, Right ear. B, Left ear.
studies7 showed that those syndromes have a different genetic background. Various other rare syndromes with an autosomal dominant pattern of inheritance were considered before a final diagnosis was made (Table 2). Two other syndromes with features somewhat similar to those in the present family but with an autosomal recessive pattern of inheritance were also excluded.8,9 Dysmorphic auricles are believed to be an autosomal dominant inherited trait.10,15 Congenital hearing impairment could have been missed during the first clinical investigation,15 but the findings were confirmed later using the results of pure-tone audiometry and otoscopy.10 Congenital ossicular chain anomalies and malformed auricles with an autosomal dominant pattern of inheritance have been seen in a few families.11-13 Gorlin et al1 considered that these were 3 distinct syndromes. Escher and Hirt11 reported thickened earlobes and hereditary congenital conductive hearing impairment caused by congenital incudostapedial malunion in an extensive study of 4 generations of a family. Congenital ossicular anomalies of the incus

Table 1. Two-Point Results of Gene Linkage Studies

<table>
<thead>
<tr>
<th>Marker</th>
<th>Recombination Factor α*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td>Chromosome 1q</td>
<td></td>
</tr>
<tr>
<td>D1S2654</td>
<td>−0.33</td>
</tr>
<tr>
<td>D1S2757</td>
<td>−1.46</td>
</tr>
<tr>
<td>D1S1723</td>
<td>−1.38</td>
</tr>
<tr>
<td>D1S422</td>
<td>0.57</td>
</tr>
<tr>
<td>D1S2622</td>
<td>−0.50</td>
</tr>
<tr>
<td>D1S2655</td>
<td>−0.33</td>
</tr>
<tr>
<td>Chromosome 8q</td>
<td></td>
</tr>
<tr>
<td>D8S279</td>
<td>−1.00</td>
</tr>
<tr>
<td>D8S286</td>
<td>−0.55</td>
</tr>
<tr>
<td>D8S530</td>
<td>−1.00</td>
</tr>
<tr>
<td>D8S533</td>
<td>−0.32</td>
</tr>
<tr>
<td>D8S534</td>
<td>−0.68</td>
</tr>
</tbody>
</table>

* Lod scores were calculated assuming α male is equivalent to α female. The recombination factor α for 0.0 is −∞.

Table 2. Reports of Other Rare Syndromes*

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Hereditary Transmission</th>
<th>Hearing Loss</th>
<th>Pinnal Anomaly</th>
<th>External Auditory Canals</th>
<th>Ossicles</th>
<th>Inner Ear</th>
<th>CNS</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marres and Cremers,2 1991</td>
<td>AD</td>
<td>+</td>
<td>+</td>
<td>Pinna dysplasia</td>
<td>–</td>
<td>–</td>
<td>Stapes and incus</td>
<td>–</td>
</tr>
<tr>
<td>Schweitzer et al,4 1984</td>
<td>AD</td>
<td>+</td>
<td>–</td>
<td>Hyperbolus and cup</td>
<td>–</td>
<td>–</td>
<td>Stapes, incus, and malleus</td>
<td>–</td>
</tr>
<tr>
<td>Mengel et al,8 1969</td>
<td>AR</td>
<td>+</td>
<td>–</td>
<td>Small pinnae and antverted helix</td>
<td>Bilateral or unilateral</td>
<td>–</td>
<td>Stapes, incus, and malleus</td>
<td>–</td>
</tr>
<tr>
<td>Cantu et al,9 1978</td>
<td>AR</td>
<td>+</td>
<td>+</td>
<td>Type I to III microtia</td>
<td>Bilateral or unilateral</td>
<td>Excessively small</td>
<td>Stapes, incus, and malleus</td>
<td>Thick cochlea</td>
</tr>
<tr>
<td>Kessler,10 1967</td>
<td>AD</td>
<td>–</td>
<td>–</td>
<td>Type I microtia and dysmorphic helix</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Escher and Hirt,11 1968</td>
<td>AD</td>
<td>+</td>
<td>–</td>
<td>Excessive lobus helix</td>
<td>Hyperplasia and hyperlobus</td>
<td>–</td>
<td>–</td>
<td>Stapes and incus</td>
</tr>
<tr>
<td>Wilmot,12 1970</td>
<td>AD</td>
<td>+</td>
<td>–</td>
<td>Helix and hyperplasia</td>
<td>Hyperlobus and hyperplus</td>
<td>–</td>
<td>–</td>
<td>Stapes and incus</td>
</tr>
<tr>
<td>Konigsmark and Gorlin,13 1976</td>
<td>AD</td>
<td>+</td>
<td>+</td>
<td>Excessive lobus and pinnae</td>
<td>–</td>
<td>Small</td>
<td>Stapes</td>
<td>–</td>
</tr>
<tr>
<td>Wildervank,14 1962</td>
<td>AD</td>
<td>+</td>
<td>–</td>
<td>Atresia due to flap</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

* CNS indicates central nervous system; AD, autosomal dominant; plus sign, characteristic is present; minus sign, characteristic is not present or not reported; and AR, autosomal recessive.
and stapes superstructure, thickened lop auricles, and micrognathia were described by Schweitzer et al in a small study of 3 generations of a family. Wilmot described a mother and her 2 sons with dysmorphic auricles, congenital anomalies of the long process of the incus and stapes superstructure, and stapes footplate ankylosis. All 3 subjects had congenital conductive hearing impairment. Wilmot’s report includes photographs of 3 right auricles of the 3 affected family members. It is mainly the superior helix that is dysplastic.

The present family has a separate syndrome, but it may have been reported before by Wilmot. As congenital hearing impairment was not present in all the members of the present family, gene linkage studies will have to show whether the syndromes reported by Potter and Kessler have a common genetic background. The presence of lip pits or dimples has not been mentioned in the reports by Potter and Kessler. In agreement with the results of Wilmot, reconstructive surgery of the ossicular chain by means of malleovestibulopexy improved the proband’s congenital conductive hearing impairment.

Accepted for publication December 3, 1999.

Reprints: Cor W. R. J. Cremers, MD, PhD, Department of Otorhinolaryngology, University Hospital Nijmegen, PO Box 9101, 6500 HB Nijmegen, the Netherlands.

REFERENCES


