Audiological Profile of Children and Young Adults With Syndromic and Complex Craniosynostosis

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Objectives: To determine syndrome-specific type, severity, and prevalence of hearing loss to facilitate follow-up and treatment.

Design: Tertiary pediatric hospital craniofacial clinic survey study. If insufficient or no data were available for a child, he or she was referred to an audiologist for pure-tone audiometry.

Setting: Academic research facility.

Patients: Information was gathered regarding 132 children and young adults with craniosynostosis.

Main Outcome Measures: The primary outcome was hearing assessment of children and young adults with various types of craniosynostosis. A secondary outcome was inference regarding the incidence of otitis media among children and young adults with craniosynostosis.

Results: We found mild or moderate hearing loss in 44.0% of patients with Apert syndrome, in 28.5% with Crouzon syndrome, in 62.1% with Muenke syndrome, in 28.6% with Saethre-Chotzen syndrome, and in 6.7% with complex craniosynostosis. Hearing loss was conductive in most patients with Apert, Crouzon, and Saethre-Chotzen syndromes and it was predominantly sensorineural in patients with Muenke syndrome.Sensorineural hearing loss at lower frequencies was found only in patients with Muenke syndrome.

Conclusions: Most patients with syndromic and complex craniosynostosis have recurrent otitis media with effusion, causing episodes of conductive hearing loss throughout their lives. Sensorineural hearing loss can occur in all 4 syndromes studied but is the primary cause of hearing loss in children and young adults with Muenke syndrome. For patients with these syndromes, we recommend routine visits to the general practitioner or otolaryngologist, depending on national standards of care, to screen for otitis media with effusion throughout life. We also advise early screening for sensorineural hearing loss among children and young adults with these syndromes.

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Methods

A cross-sectional survey was conducted among 146 patients aged 4 to 18 years with syndromic or complex craniosynostosis treated at the Dutch Craniofacial Center, Erasmus Medical Center–Sophia, Rotterdam, the Netherlands. All diagnoses were made by a geneticist based on the results of genetic analysis. If no syndrome diagnosis could be made and 2 or more sutures were closed, craniosynostosis was defined as complex. Because Crouzon and Pfeiffer syndromes often cannot be distinguished genetically, we considered them a homogeneous group in this study.

If no audiological information was available at our center, we contacted the parents or their child by mail to inquire about the results of testing performed elsewhere. In the Netherlands, hearing screening is performed in the first week of life, in primary school, and in secondary school. If screening results are aberrant, the child will be referred to an otolaryngologist or audiologist. If a patient had been

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seen by an otolaryngologist or audiologist, informed consent was obtained to acquire audiological data. Information was gathered regarding audiometric results, episodes of otitis media, inserted ear plugs, and the use of hearing aids. If the patient never had been seen by an otolaryngologist or audiologist, he or she was referred to an audiologist for single pure-tone audiometry. Patients were excluded if no audiological information was available and if they did not respond to or consent to our inquiry. A pure-tone average (with average losses at 0.5, 1.0, and .0 kHz) of 20- to 40-dB hearing loss was classified as mild and 41- to 70-dB hearing loss as moderate.

**RESULTS**

Of 132 patients aged 4 to 18 years with syndromic or complex craniosynostosis, audiological information was available at our center for 27 patients. The other 119 patients were contacted by mail, of whom 105 (88.2%) responded. Of 105 respondents, 62 had previously visited an otolaryngologist or audiologist and 43 had not. Of 43 who were referred for single pure-tone audiometry, we received information regarding 19 patients.

The total group for whom audiological information was sought consisted of 132 children and young adults (Table). Of these 132 children, 25 had Apert syndrome, 42 had Crouzon syndrome, 29 had Muenke syndrome, 21 had Saethre-Chotzen syndrome, and 15 had complex craniosynostosis. The mean age at the time of review was 11.5 years, and the mean age at the last hearing test was 8.8 years. Sixty-six patients (50.0%) were male.

Of 132 children and young adults, 108 (81.8%) had been seen at least once by an otolaryngologist or audiologist, and 88 (66.7%) had undergone audiometry at least once. Among those who underwent audiometry, 19 patients had Apert syndrome, 29 had Crouzon syndrome, 23 had Muenke syndrome, 10 had Saethre-Chotzen syndrome, and 7 had complex craniosynostosis. The distribution of hearing loss severity in the ear with better hearing is given in the Table.

The average hearing loss severity in the ear with better hearing across patients per frequency was calculated and is given in the Table.

### Table. Severity of Hearing Loss in the Better Ear

<table>
<thead>
<tr>
<th>Hearing Loss</th>
<th>Patient Group, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Apert Syndrome (n=25)</td>
</tr>
<tr>
<td>None</td>
<td>14 (56.0)</td>
</tr>
<tr>
<td>Mild</td>
<td>6 (24.0)</td>
</tr>
<tr>
<td>Moderate</td>
<td>5 (20.0)</td>
</tr>
<tr>
<td></td>
<td>Crouzon Syndrome (n=42)</td>
</tr>
<tr>
<td>None</td>
<td>30 (71.4)</td>
</tr>
<tr>
<td>Mild</td>
<td>8 (19.0)</td>
</tr>
<tr>
<td>Moderate</td>
<td>4 (9.5)</td>
</tr>
<tr>
<td></td>
<td>Muenke Syndrome (n=29)</td>
</tr>
<tr>
<td>None</td>
<td>11 (37.9)</td>
</tr>
<tr>
<td>Mild</td>
<td>14 (48.3)</td>
</tr>
<tr>
<td>Moderate</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td></td>
<td>Saethre-Chotzen Syndrome (n=21)</td>
</tr>
<tr>
<td>None</td>
<td>15 (71.4)</td>
</tr>
<tr>
<td>Mild</td>
<td>6 (28.6)</td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Complex Craniosynostosis (n=15)</td>
</tr>
<tr>
<td>None</td>
<td>14 (93.3)</td>
</tr>
<tr>
<td>Mild</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
</tr>
</tbody>
</table>

There is a high prevalence of hearing loss among children with syndromic craniosynostosis; this is reflected in the high proportion (66.7%) of patients who had visited an otolaryngologist or audiologist at least once before this study. In most cases, recurrent otitis media with effusion has resulted in conductive hearing loss. Sensorineural hearing loss or mixed hearing loss occurred in all syndromes but especially among patients with Muenke syndrome. If present, hearing loss in patients with Saethre-Chotzen syndrome is mild and hearing loss is absent in most patients with complex craniosynostosis.

Small studies show a high prevalence of congenital hearing loss due to ossicular chain fixation and/or absent external ear canals; larger studies show a much lower prevalence of congenital hearing loss and indicate that recurrent otitis media with effusion is the main cause of conductive hearing loss in syndromic craniosynostosis. Several risk factors for the development of recurrent otitis media with effusion are present in patients with syndromic craniosynostosis, including small nasopharynx, short and dysfunctional eustachian tube, obstructive sleep apnea, and cleft palate.

Apert syndrome is caused by an S252W or P253R mutation in the FGFR2 gene (OMIM 176943). This syndrome is characterized by craniosynostosis of coronal sutures, midface hypoplasia, obstructive sleep apnea, complex syndactyly of hands and feet, and mental retardation. Studies of patients with Apert syndrome describe a high incidence of conductive hearing loss, predominantly caused by recurrent otitis media with effusion.
sion and congenital stapes fixation. Superior semicircular channel dehiscence has been described in Apert syndrome as a cause of conductive hearing loss with larger air-bone gaps at lower frequencies. In effect, superior semicircular channel dehiscence creates a third window, which causes pseudoconductive hearing loss.

Crouzon syndrome is caused by several mutations in FGFR2 that differ from those in Apert syndrome. All sutures can be affected. Children with Crouzon syndrome have exophthalmus, midface hypoplasia, and a high prevalence of obstructive sleep apnea and raised intracranial pressure; however, their mental development is nearly normal in most cases. Among patients with Crouzon syndrome, studies describe conductive hearing loss, sensorineural hearing loss, and mixed hearing loss, caused by recurrent otitis media with effusion, ossicular chain fixation, and external auditory canal atresia. Although Crouzon syndrome has the lowest prevalence of hearing loss, 35.0% of patients have mild or moderate hearing loss. The same air-bone gaps as in Apert syndrome are seen, but they are larger at lower frequencies.

Muenke syndrome is caused by a P250R mutation in FGFR3 (OMIM 134934). In most cases, 1 or 2 coronal sutures are affected. Muenke syndrome is associated with a mild phenotype, but patients can have developmental and behavioral problems. A high prevalence of hearing loss is reported in Muenke syndrome, predominantly of the sensorineural type and worse at lower frequencies. Sensorineural hearing loss probably results from an influence of the FGFR3 mutation on development of the inner ear. This hearing loss was not found in patients with other forms of craniosynostosis, making it specific to Muenke syndrome. This is relevant for counseling; because the phenotype of Muenke syndrome varies, low-frequency sensorineural hearing loss may be the sole expression of the syndrome.

Saethre-Chotzen syndrome has a mild phenotype and is caused by deletions or mutations in the TWIST1 gene (OMIM 601622). In most cases, coronal sutures are affected. This syndrome is characterized by ptosis of the upper eyelid. The literature pertaining to hearing in patients with Saethre-Chotzen syndrome is limited. A high prevalence of hearing loss with a hearing aid always should be considered. Insertion of grommets does not prevent the development of permanent hearing loss, especially if ear discharge is present. Therefore, early management of hearing loss with a hearing aid always should be considered. Doing so will optimize auditory access and speech and language, since many developmental problems are seen in children with these syndromes.

In conclusion, regular checkups for middle ear function and hearing are indicated at least until age 18 years for patients with Apert syndrome and those with Crouzon syndrome. Depending on national standards of care, these checkups can be performed by an otolaryngologist or general practitioner. Patients with persistent otitis media with effusion or significant hearing loss should be referred to an otolaryngologist. Patients with Apert, Crouzon, Muenke, and Saethre-Chotzen syndromes...
Mathijssen had full access to all the data in the study and Toll, de Gier, and Mathijssen.

References