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Prevention and management of hearing loss in syndromic craniosynostosis: A case series

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ABSTRACT

Objective: To assess the audiological profile in a cohort of children affected by syndromic craniosynostosis.
Methods: Eleven children with Apert syndrome ($n = 4$), Saethre-Chotzen syndrome ($n = 3$), Muenke syndrome ($n = 2$), Crouzon syndrome ($n = 1$) and Pfeiffer syndrome type 1 ($n = 1$) were submitted to a complete audiologic evaluation including otoscopy, pure-tone audiometry, tympanometry and acoustic reflex testing, ABR, otoacustic emissions, temporal bone High Resolution CT (HRCT) scan. The main outcome measures were prevalence, type and severity of hearing loss, prevalence of chronic otitis media, correlation with the time of first surgical correction.
Results: Seven of 11 patients (64%) presented hearing loss (HL), conductive in 3/7 patients (43%) and mixed in 4/7 (57%). No patients showed a purely sensorineural HL. All hearing impaired patients displayed middle ear disorders: the patients with conductive HL had otitis media with effusion (OME) and 3/4 patients with mixed HL showed tympanic alterations or cholesteatoma. A bilateral vestibular aqueduct enlargement was detected by HRCT scan in one normal hearing patient. The ABRs resulted normal in all cases.
Conclusion: Our study confirms the high prevalence of otologic diseases in such patients. In contrast with previous studies, middle ear disorders were responsible for the hearing impairment also in patients with mixed HL due to secondary inner ear damage. These findings restate the necessity of a close audiologic follow-up. We did not detect the specific ABR abnormalities previously reported, possibly because of an early correction of the cranial vault malformations.

1. Introduction

Craniosynostosis, the premature fusion of one or more cranial sutures, is a relatively common congenital defect, affecting about 1 in 2100 to 2500 live births [1,2]. Syndromic craniosynostoses, accounting for less than 20% of cases [3], are characterized by the synostosis of multiple sutures in association with extracranial malformations, typically involving limbs, heart and central nervous system. This group includes more than 100 syndromes, the commonest being Apert (OMIM #101200), Crouzon (OMIM #123500) and Pfeiffer syndrome (OMIM #101600), all caused by heterozygous mutations in *FGFR1-2* genes, Muenke syndrome (OMIM #602849), caused by a heterozygous Pro250Arg mutation in *FGFR3* gene, and Saethre-Chotzen syndrome (OMIM #101400), caused by heterozygous mutations or deletions in *TWIST1* gene.

Hearing loss (HL) is a common complication of syndromic craniosynostosis. In most patients, HL is mostly conductive, resulting from recurrent otitis media secondary to impaired eustachian tube function, abnormal anatomy of the nasopharynx and/or cleft palate [4–8]. Conversely, a mild-to-moderate low frequency sensorineural HL has been commonly detected in Muenke syndrome, likely as a direct disruption of the *FGFR3*

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Pro250Arg mutation on the development of cochlear sensory epithelia [9]. Moreover, congenital malformations of the temporal bone, such as auditory canal stenosis or atresia, ossicular malformations or fixation and inner ear anomalies, have been reported as possible but extremely uncommon cause of HL in craniosynostosis [4–8]. Interestingly, specific abnormalities in auditory brainstem responses (ABR), including prolonged I-to-III interpeak latency and absent/dysmorphic wave II, have been described in patients affected by FGFR2 craniosynostosis. These anomalies have been hypothetically related to a compression of the auditory nerve in its passage through the internal auditory meatus and/or the posterior fossa [10].

The aim of this study was to assess the otologic and audiological profiles, inclusive of ABR evaluation, in a cohort of patients affected by syndromic craniosynostosis.

2. Materials and methods

The cohort included 11 patients recruited between January 2008 and October 2010. Informed consent was obtained prior to the inclusion in the study from a parent or legal guardian. Specifically, four patients were affected by Apert syndrome, one by Crouzon syndrome, two by Muenke syndrome, one by Pfeiffer syndrome type 1 and 3 by Saethre-Chotzen syndrome. The clinical diagnosis was confirmed by molecular analysis in all cases. There were nine male patients (82%) and two female patients (18%), aged 4–15 years (mean age 8.5 years). First cranial vault remodeling was performed in 10/11 patients within the 6th month of life (mean age 4 months) and in one case at the age of 12 months. Patients' clinical and molecular data are summarized in Table 1.

Each patient was submitted to a complete otologic evaluation including otoscopy, hearing assessment by pure-tone audiometry (PTA) at 0.25–0.5–1–2–4–8 kHz, tympanometry and acoustic reflex testing, ABR and otoacoustic emissions. In addition, a temporal bone High Resolution CT scan was performed in all patients.

ABRs were recorded using standard procedures with the EP 25 device (Amplifon, Italy), placing an active electrode on the forehead, a reference electrode on the earlobe of the stimulated side and a ground electrode on the contralateral earlobe. Both ears were tested while patients were lying down relaxed, but not sedated, in a quiet environment. Stimuli consisted of 0.1 ms clicks through TDH 49 earphones presented at 100 dB SPL if the patient was normal hearing (i.e. better than 25 dB at all frequencies tested at pure tone audiometry) and at 115 dB SPL if impaired hearing. Stimulation rate was 11 Hz, using 1000 sweeps, and responses were filtered through a bandpass set at 100 Hz and at 3000 Hz. Wave I, III and V latencies and interwave (I–III, III–V, I–V) latencies were measured and compared with our laboratory standards [11] and literature data [12]. For this study, we set the limit for normal hearing at 25 dB both for air (AC) and bone conduction (BC) thresholds for all the tested frequencies. We referred to conductive hearing loss when AC was worse than 25 dB for one or more frequencies with normal BC; we referred to mixed hearing loss when both AC and BC were worse than 25 dB with BC better than AC.

3. Results

Four of 11 patients (36%) had normal hearing, defined as a hearing threshold better than 25 dB, and 7/11 (64%) presented HL. Mean PTA thresholds observed in the patients are reported in Table 2. The degree of HL ranged from mild to moderate; mean air (AC) and bone conduction (BC) hearing thresholds at 0.5–1–2–4 kHz were 35.5 and 11.5 dB, respectively.

Hearing loss was conductive in 3/7 patients (43%) and mixed in 4/7 (57%). The former group of patients had 28.5 dB AC and 10.8 dB BC mean hearing thresholds; the latter had 38.4 dB AC and 13 dB BC mean hearing thresholds. No patients showed purely sensorineural HL. The mean age of normal hearing patients was 5.75 years (SD 1.71), compared with 10.14 years (SD 2.67) of the hearing impaired group; the difference is statistically significant at Student's t-test ($p < 0.05$).

All the patients presenting HL displayed a history of recurrent otitis media. At the time of examination otitis media with middle ear effusion (OME) persisted in 3/3 (100%) patients with conductive HL, as confirmed by otoscopy, flat tympanograms and absence of acoustic reflexes. Of these patients two had TWIST mutations; the one with FGFR2 mutation eventually developed cholesteatoma on one ear and tympanic atelectasis on the other. On the contrary 3/4 (75%) patients with mixed HL showed at otoscopic examination, the sequelae of severe middle ear disventilative disorders, such as tympanic retractions, atelectasis or perforations and cholesteatomatous otitis. None of these patients had an unaffected side. All these patients had FGFR2 mutations. The remaining patient with mixed HL presented on both sides normal otoscopy with type A tympanogram and absence of acoustic reflexes; these findings were compatible with ossicular fixation, although we did not have any surgical verification. This patient had Apert syndrome (mutation S252W FGFR2). None of the patients with FGFR3 and FGFR1 mutations had hearing loss.

High Resolution CT scan resulted normal in all cases, with the exception of one patient displaying a bilateral enlargement of vestibular aqueduct and normal hearing. No patients complained of tinnitus or dizziness.

Finally, OAE were absent in all the hearing impaired patients and the ABR recording showed normal latencies and wave morphology in each tested ear, consistent with PTA thresholds. We found no significant differences between hearing impaired and normal patients ($p > 0.05$ at Student's t-test, Table 3).

Table 1
Patients' clinical and molecular data.

Case	Diagnosis	Mutation	Sex	Age (years)	Age at diagnosis	Age at first vault remodelling
1	Apert	S252W FGFR2	M	9	at birth	6 months
2	Apert	P253R FGFR2	F	10	at birth	2 months
3	Apert	S252W FGFR2	M	15	at birth	12 months
4	Apert	P253R FGFR2	F	11	at birth	4 months
5	Crouzon	D336G FGFR2	F	10	3 months	3 months
6	Muenke	P250R FGFR3	F	6	5 months	5 months
7	Muenke	P250R FGFR3	F	5	2 months	3 months
8	Pfeiffer	P252R FGFR1	M	4	2 months	5 months
9	Saethre-Chotzen	K145N TWIST	F	8	3 months	3 months
10	Saethre-Chotzen	R154T TWIST	F	6	2 months	4 months
11	Saethre-Chotzen	R116L TWIST	F	10	at birth	6 months