Audiologic Findings in Saethre-Chotzen Syndrome

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Background: Hearing loss has been described in Apert syndrome but is poorly documented in other craniosynostosis disorders.
Methods: The authors retrospectively reviewed the audiologic and otologic records of patients with Saethre-Chotzen syndrome to define the incidence, type, and extent of hearing loss. Only patients with documented audiologic examinations were included. Hearing loss was categorized by American Speech-Language-Hearing Association guidelines (i.e., mild, 26 to 40 dB; moderate, 41 to 55 dB; moderate/severe, 56 to 70 dB; severe, 71 to 90 dB; and profound, >90 dB).
Results: Twenty-nine patients met inclusion criteria. Mean age at initial audiologic evaluation was 6.7 years (range, 0.7 to 24.5 years). Seventeen patients (59 percent) had at least one abnormal audiogram; in 15 patients, the deficit was mild. Eight patients demonstrated sensorineural hearing loss. Five cases resolved and, thus, had been mischaracterized. Six patients had conductive hearing loss on at least one examination; follow-up testing in four patients revealed normal hearing. Two patients had unspecified hearing loss by sound field method. One patient had mixed hearing loss on consecutive audiograms. Twenty-one patients (72 percent) had normal hearing on their last audiogram.
Conclusions: Most patients with Saethre-Chotzen syndrome had hearing loss at some point during childhood. This was typically mild and correlated with middle ear abnormality and eustachian tube dysfunction. Usually, the hearing deficit resolved. Early mischaracterization of mixed hearing loss or conductive hearing loss as sensorineural hearing loss was common. (*Plast. Reconstr. Surg.* 127: 2014, 2011.)

Hearing loss has been reported in most types of syndromic craniosynostosis, including Apert syndrome,[1–4] Pfeiffer syndrome,[5] Muenke syndrome,[6,7] Crouzon syndrome,[8,9] and others.[9–14] The type and extent of the auditory deficit differs among these disorders. For example, studies have demonstrated that the majority of patients with Apert syndrome (*FGFR2* mutation) develop permanent low-frequency conductive hearing loss as a result of chronic otitis media,[1–4,15,16] whereas sensorineural hearing loss in this condition is quite rare. In contrast, nearly all patients with Muenke syndrome (Pro250Arg mutation of *FGFR3*) demonstrate low-frequency sensorineural hearing loss,[6,7] which is presumed to be caused by abnormal patterning of auditory sensory epithelial cells in the organ of Corti.[17]

Saethre-Chotzen syndrome is an autosomal dominant craniosynostotic disorder of variable expression occurring in one in 25,000 to one in 50,000 live births.[18] Characteristic features include bilateral or unilateral coronal synostosis, ptosis of the eyelids, small ears with prominent helical crura, low frontal hairline, and brachydactyly. Although craniosynostosis is typically considered a major criterion for the clinical diagnosis, in one series, synostosis was found in only 64 percent of patients with features of Saethre-Chotzen syndrome.[19] Another report described a family in which only 25 percent of those with a positive *TWIST* mutation had craniosynostosis.[20,21] Furthermore, genetic confirmation of the diagnosis is not always definitive. Of 24 patients (four families) with a clinical diagnosis of Saethre-Chotzen, Nascimento and colleagues found that none had an iden-

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tifiable *TWIST* mutation.[22] Another report found that only 71 percent of clinically diagnosed patients have an identifiable *TWIST* mutation.[23] Thus, in some patients, the diagnosis can be elusive and determined only by more subtle clinical findings.

This syndrome was initially described in 1931 by Saethre,[24] and auditory findings were not mentioned in the original report. However, conductive hearing loss was observed in the three patients reported 1 year later by Chotzen.[25] Since that time, hearing impairment in Saethre-Chotzen syndrome has been mentioned infrequently in several case reports and small series,[13,26–30] and a large series failed to distinguish the type of loss.[19] In light of the incomplete information available in the literature, we undertook this study to better characterize the incidence, type, and degree of hearing loss in patients with Saethre-Chotzen syndrome.

MATERIALS AND METHODS

After institutional review board approval, patients treated at our craniofacial center with a diagnosis of Saethre-Chotzen between 1978 and 2008 were identified and their records were reviewed. Patients were considered to have Saethre-Chotzen if they had a documented *TWIST* mutation, or had typical physical findings consistent with the diagnosis as ascertained by a clinical geneticist or our most experienced author (J.B.M.).

Data collected included date of birth, sex, family history of Saethre-Chotzen or hearing loss, relevant physical findings, date and results of all audiologic and otologic assessments, operative treatment of middle or inner ear abnormality, and computed tomographic findings when available. Patients were only included if they had an audiometric evaluation performed at our institution by a certified audiologist. A pure-tone average was calculated from the hearing thresholds at 500, 1000, 2000, 4000, and 8000 Hz for all audiograms. When possible, both bone and air conduction thresholds were evaluated and the diagnosis of conductive, sensorineural, mixed, or unknown hearing loss was made for each ear. Behavioral observational audiometry (sound field testing) was performed if patients were unable to cooperate with conventional audiologic testing. The degree of hearing loss was categorized according to American Speech-Language-Hearing Association guidelines (i.e., mild, 26 to 40 dB; moderate, 41 to 55 dB; moderate/severe, 56 to 70 dB; severe, 71 to 90 dB; and profound, >90 dB).

Tympanographic results were reviewed to determine compliance of the tympanic membrane and were classified as type A, B, or C. Type A is considered normal. Type B is flat and corresponds to middle ear effusion, occlusion of the external auditory canal with cerumen, perforation of the tympanic membrane, or presence of a pressure equalizing tube. Type C tympanogram usually indicates eustachian tube dysfunction or mastoid abnormality. These results were compared with the pure-tone averages to assist in distinguishing sensorineural hearing loss and conductive hearing loss in young patients.

RESULTS

A total of 55 patients had a diagnosis of Saethre-Chotzen syndrome. Of these, 27 were excluded: 26 did not have a recorded audiogram obtained at our institution; the diagnosis could not be confirmed in one patient. Of the remaining 29 patients, 59 percent were female ($n = 17$) (Table 1) and 66 percent of them ($n = 19$) had family members with the same diagnosis. Mean age at initial audiologic evaluation was 6.7 years (range, 0.7 to 24.5 years) (Table 1). Seventeen (59 percent) had at least one abnormal hearing test, and in all but two patients (patients 8 and 19), the deficit was mild. Eight patients demonstrated sensorineural hearing loss on at least one examination; however, subsequent examinations in seven patients revealed either normal hearing ($n = 5$) or persistent sensorineural hearing loss ($n = 2$). Six patients had conductive hearing loss on at least one examination. Follow-up testing in four showed normal hearing in all. Two patients who could not cooperate with standard audiologic testing protocols had unspecified hearing loss according to the sound field method; of these, one (patient 23) had a subsequent normal hearing test. Lastly, one patient (patient 8) had mixed hearing loss on two consecutive examinations.

Tympanometry was performed on all patients at the time of the audiometric examination. On initial tympanometry, 10 patients were classified as type A (normal), 17 were classified as type B, and two were type C; one could not tolerate tympanometry (patient 28). On follow-up evaluation, five patients improved from type B tympanometry to type A, consistent with improvement in eustachian tube function.

Two patients underwent computed tomography of the temporal bones specifically to investigate the middle and inner ear. One patient had dysmorphic vestibules and lateral semicircular canals bilaterally. The other patient had a narrowing of the cartilaginous portion of the external auditory canal, underpneumatized mastoid air cells bilaterally with partial opacification, an air-fluid level within the

Table 1. Results of Audiometry and Tympanometry and Surgical Management

Patient	Sex	Family Members with Saethre-Chotzen Syndrome	Age at Audiography (yr)	Audiography Results	Tympanometry*		Surgical Management
					Right	Left	
1	M	Yes	2.6	CHL (unilateral), mild	A	A	PET × 2
			3.1	Normal	A	A	
2	F	No	5.8	Normal	C	C	None
3	M	Yes	7.6	SNHL (bilateral), mild	B	B	PET × 4
			10.6	Normal	B	B	
			10.8	Normal	B	B	
			15.8	Normal	B	B	
4	F	Yes	23.3	Mixed (bilateral), mild	B	B	PET
5	F	Yes	1.1	SNHL (bilateral), mild	B	B	None
6	M	Yes	9.9	Normal	A	A	None
			12.1	Normal	A	A	
			15.4	Normal	A	A	
			17.4	Normal	A	A	
7	F	Yes	3.2	Normal	B	B	PET × 2
			4.1	Normal	B	B	
			4.3	SNHL (bilateral), mild	B	B	
			6.7	Normal	B	B	
8	F	Yes	24.5	Normal	B	B	None
			31.7	Mixed (unilateral), moderate/severe	A	A	
			37.8	Mixed (unilateral), moderate/severe	A	A	
9	F	Yes	9.3	CHL (unilateral), mild	B	B	PET × 5
			10.6	SNHL (bilateral), mild	A	A	
			13.1	Normal	A	A	
10	F	Yes	1.0	Normal	A	B	None
11	F	No	7.8	Normal	A	A	None
			9.1	Normal	B	B	
			10.2	Normal	A	A	
12	F	No	5.8	Normal	B	B	PET
			7.3	SNHL (unilateral), mild	B	B	
			10.7	Normal	A	A	
13	M	Yes	7.2	CHL (unilateral), mild	B	B	None
			9.3	Normal	A	A	
14	M	Yes	3.1	Normal	B	B	None
			7.6	Normal	B	B	
15	M	No	17.3	CHL (unilateral), mild	A	A	None
16	M	No	14.1	Normal	A	A	PET
			14.7	Normal	A	A	
17	F	No	5.8	SNHL (bilateral), mild	A	A	PET × 2
			8.2	SNHL (bilateral), mild	A	C	
			11.6	SNHL (bilateral), mild	A	A	
18	F	Yes	3.8	Normal	A	A	None
19	M	No	4.1	SNHL (bilateral), moderate/severe	A	A	PET
			22.1	SNHL (bilateral), profound	A	A	
20	M	Yes	0.7	Normal	B	B	PET × 3
			2.3	SNHL (bilateral), mild	B	B	
			3.8	Normal	A	A	
			9.5	Normal	B	B	
			12.2	Normal	B	B	
21	M	No	6.0	Normal	A	A	None
			9.1	Normal	A	A	
22	F	Yes	<1	CHL (unilateral), mild	A	A	PET × 2
			1.9	Normal	A	A	
			6.4	CHL (unilateral), mild	C	C	
			7.9	Normal	A	A	
23	F	Yes	1.0	Bilateral, mild (SF)	A	B	None
			1.1	Bilateral, mild/moderate (SF)	B	B	
			1.8	Bilateral, mild/moderate (SF)	A	A	
			2.3	Normal	A	A	
24	F	Yes	8.5	Normal	C	C	None
25	F	Yes	2.1	Normal	B	B	None
26	F	Yes	2.1	Normal	B	B	None
27	F	Yes	2.1	Normal	B	B	None
28	M	No	2.5	Mild (SF)	—	—	None
29	M	No	10.9	CHL (unilateral), mild	B	B	PET

M, male; F, female; CHL, conductive hearing loss; SNHL, sensorineural hearing loss; Mixed, conductive plus sensorineural hearing loss; SF, sound field; PET, pressure-equalizing tubes.

*Tympanometry types: A, normal; B, flat (consistent with fluid in the middle ear); and C, negative middle ear pressure (consistent with eustachian tube dysfunction).

left mastoid antrum, severe thickening and retraction of the tympanic membranes bilaterally, asymmetric scattered opacifications in the middle ear spaces, and slightly dysmorphic ossicles.

DISCUSSION

This study showed that over one-half of our patients with Saethre-Chotzen syndrome had abnormal hearing on at least one audiologic assessment during childhood. This is considerably greater than the 3.1 percent reported prevalence of hearing loss for children and adolescents in the general population.[31] In most instances, the hearing loss was mild, which corresponds to other published reports,[19] and the deficit improved to normal or nearly normal in time. Nine of the patients had an abnormal hearing test that normalized over time. Of these, four had earlier evidence of sensorineural hearing loss (patients 3, 7, 12, and 20), three had conductive hearing loss (patients 1, 13, and 22), one had separate audiograms showing sensorineural hearing loss on one and conductive hearing loss on the other (patient 9), and the last patient had an abnormal hearing by sound field screening (patient 23). Because true sensorineural hearing loss does not resolve, it is likely that the four patients with sensorineural hearing loss actually had conductive hearing loss. This conclusion is supported by the observation that each had a type B tympanogram, consistent with middle ear effusion, and all were managed with pressure-equalizing tubes at some time. This false assignment arises because some children have difficulty completing the full audiologic test and may be unable to perform standard masking techniques used to differentiate sensorineural hearing loss from conductive hearing loss. In these instances, audiologists can use techniques such as sound field testing with behavioral observation, visual reinforcement, and conditioned play audiometry. These modalities are less accurate than pure-tone and speech audiometry, but they do provide a reasonably accurate audiologic assessment in young children.

Gradual improvement of hearing loss in our patients with Saethre-Chotzen syndrome suggests a temporal improvement in eustachian tube function and is in contrast to observations in other craniosynostotic syndromes. Rajenderkumar and colleagues found that although less than 6 percent of Apert syndrome patients had evidence of conductive hearing loss in infancy, 56 percent eventually developed permanent mild to moderate conductive hearing loss as a result of persistent otitis media (observed in 93 percent of patients).[3] These authors observed sensorineural hearing loss in only 3 percent (two of 70) of their study group. The authors documented that insertion of pressure-equalizing tubes did not reduce the risk of developing conductive hearing loss, although nearly half of the patients had only one set of tubes. In another series, 90 percent of patients with Apert syndrome had hearing loss, and the majority had conductive hearing loss.[4] Inner ear anomalies, such as dilation of the vestibule, malformed semicircular canals, and cochlear dysplasia, were found in all patients. The authors attributed some, but not all, conductive hearing loss to these anomalies.

Overall, seventy-two percent (21 of 29) of our patients with Saethre-Chotzen syndrome had normal hearing at the time of their last audiologic examination. Of the eight patients who did not have normal hearing on their last examination, two (patients 5 and 28) were younger than 3 years at their last assessment, making it impossible to predict whether the audiologic deficit persisted. Nevertheless, the finding of bilateral sensorineural hearing loss in patient 5 makes this finding more ominous. Patient 29 had mild conductive hearing loss at age 10.9 years and, although this may represent a permanent condition, his age precludes such a conclusion. Five patients had permanent hearing loss. One patient (patient 15) had mild conductive hearing loss at age 17 years and, given his age, we considered this permanent. Four patients had a sensorineural component to their audiologic deficit. Two patients (patients 17 and 19) had sensorineural hearing loss on repeated examinations, and two other patients (patients 4 and 8) had mixed hearing loss evident on audiograms obtained in their adult years. The 14 percent rate of sensorineural involvement in our study group was higher than had been previously reported, and was significantly higher than the 0.88 percent prevalence reported in the general population.[32] Most series of Saethre-Chotzen patients have described mixed hearing loss,[30] conductive hearing loss,[27,28] or did not distinguish the type of loss.[19,25,29] There is only one prior reported case of pure sensorineural hearing loss in Saethre-Chotzen syndrome.[13]

Sensorineural hearing loss has been reported in up to 95 percent of patients with Muenke syndrome (Pro250Arg mutation of *FGFR*),[7,17] and has been reported rarely in other craniosynostosis syndromes. Such an association is not completely unexpected because most of the fibroblast growth factor ligands (FGF) and receptors (FGFR) are expressed during development of the central nervous system, cranial nerves[33,34] and the inner ear neurosensory structures.[35–45] In patients with Muenke syndrome, *FGFR3* overexpression is postulated to have a direct

impact on the development of the inner ear sensory organ. Constitutive activation of *fgfr3* in a murine model results in abnormalities of the sensory cells in the organ of Corti and the apical region of the cochlear duct.[17] Because *TWIST* is an upstream modulator of *FGFR*,[46,47] the loss-of-function mutation in Saethre-Chotzen syndrome may alter middle and inner ear development and function. Even if such effects were not evident in childhood, we question whether they could lead to an accelerated decline of normal hearing with age. To this point, one patient in our study (patient 8) had a normal audiogram at 24 years of age and subsequently developed persistent moderate to severe mixed hearing loss in one ear (confirmed by two separate audiograms over a 6-year span) in his fourth decade. In addition, one 23-year-old patient (patient 4) had a single audiologic test demonstrating mixed hearing loss that, given her age, is considered permanent. It is possible that the seemingly minor risk of permanent hearing loss associated with the diagnosis of Saethre-Chotzen syndrome in childhood may increase abnormally as these patients age. This hypothesis cannot be proven by our data; further studies on older patients are warranted.

Historically, early care of infants and children with syndromic forms of craniosynostosis has focused on the sutural fusions and associated craniofacial anomalies. The prevalence and developmental consequences of hearing loss in these children warrants particular attention. Deafness has been linked to delays in early learning, cognitive development, and social adaptation.[48,49] Auditory dysfunction has been associated with deficits in complex motor activities and balance.[50] Early identification and management of hearing loss may reduce these harmful secondary effects. Cochlear implants can help to restore hearing function in patients with sensorineural hearing loss, and early implantation can result in improved language and speech development.[51–53] Management of middle ear effusion may minimize the risk of permanent conductive loss. Furthermore, persistent conductive hearing loss in childhood has been associated with the development of sensorineural hearing loss later in life.[54] Although hearing in our patients with conductive hearing loss was eventually restored, it is impossible to know whether even a temporary deficit has some incremental impairment on early speech, language, or cognitive development. Although some studies have shown evidence of subtle early developmental impairment in children with persistent middle ear effusion,[55,56] other reports have not.[57,58]

Many of our patients who underwent tube placement had improved hearing on a subsequent audiogram, but it is unclear whether this procedure was responsible for the observed trend toward improved hearing over time. The effect of this procedure is controversial. Up to 30 percent of children younger than 3 years will demonstrate a middle ear effusion on routine otoscopic examination.[59] It has been conventional wisdom that grommet insertion to drain middle ear effusion reduces the risk of conductive hearing loss in selected patients.[60,61] However, some authors suggest that middle ear effusion, and consequent conductive hearing loss, resolves spontaneously in most normal children and the benefits of pressure-equalizing tube placement are questionable.[59,62–64] In some instances, tubes may actually worsen hearing[65] and scar the tympanic membrane.[66]

There are limitations to our study that warrant discussion. First, the number of patients in this study was limited by the rarity of the diagnosis and because we only included patients who had a comprehensive audiologic examination from our institution. Second, we included patients seen over a 30-year period; therefore, some patients were treated before widespread availability of genetic testing. Saethre-Chotzen syndrome has phenotypic variability that makes it susceptible to underdiagnosis[67] or misdiagnosis as Pfeiffer or Muenke syndrome.[18] Some earlier reports incorrectly labeled patients with Muenke syndrome (Pro250Arg mutation of *FGFR3*) as having Saethre-Chotzen syndrome,[19,68] although these are clearly separate entities.[69] In the absence of genetic testing, we included only patients with clinical findings that are considered unique to this syndrome such as low-set frontal hairline, blepharoptosis, small ears, bifid distal phalanx of great toe, and syndactyly of toes 2 and 3.[69,70] Despite rigorous clinical scrutiny, it is possible that some of our patients may have been mislabeled as having Saethre-Chotzen syndrome. Nevertheless, even genetic testing is not conclusive (i.e., up to one-third of patients with a clinical diagnosis have no identifiable *TWIST* mutation).[19] Third, serial audiologic follow-up was inconsistent and, in some cases, lacking. One possible reason is that many patients had normal or very minor hearing loss and further audiologic assessment was deemed unnecessary. In addition, as a large tertiary care facility that draws patients from many neighboring and distant areas, follow-up can be inconsistent. It is possible that some patients underwent audiologic assessment in their local community. Lastly, the need for systematic audiologic assessment in this patient population has been historically underappreciated. Nearly 50 percent of our patients with Saethre-Chotzen syndrome were excluded from the study because they had no audiologic examination on record.

Given the paucity of meaningful information on this topic, this omission is not surprising.

The majority of patients with Saethre-Chotzen syndrome demonstrate hearing loss during childhood. In most instances, this is the result of poor eustachian tube function and improves with age. However, a small percentage with sensorineural hearing loss do not improve. The role of the *TWIST* gene mutation is this patient population is unclear and warrants further investigation. It is our hope that this investigation will draw attention to the importance of audiologic evaluation in the patient population.

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