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The deafness, pre-auricular sinus, external ear anomaly and commissural lip pits syndrome – otological, vestibular and radiological findings

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Abstract

Commissural lip pits, pinna dysplasia, pre-auricular sinus and hearing loss constitute a recently described autosomal dominant branchial arch syndrome. In a large family, eight out of the 74 members were also affected by conductive hearing loss. No inner ear abnormalities could be demonstrated on the CT scans. In three patients (four ears) out of four patients (six ears), exploratory tympanotomy revealed serious ossicular chain anomalies. In one ear, round window aplasia was also present. Long-term hearing improvement could only be achieved in one ear.

Key words: Deafness, congenital; Chromosome abnormalities, auto-somal dominance; Hearing loss, conductive; Branchial region

Introduction

Various autosomal dominant hereditary branchial arch syndromes with symptoms including pinna dysplasia, pre-auricular sinus and congenital conductive or mixed hearing loss have been described. The best known examples are the branchio-oto-renal (BOR) syndrome and the Treacher-Collins syndrome or mandibulofacial dysostosis (McKusick, 1992). Gene linkage has recently been successful for these two syndromes. The BOR syndrome has been linked to chromosome 8q and the Treacher-Collins syndrome to chromosome 5q (Dixon *et al.*, 1991; Kumar *et al.*, 1992).

The results of clinical examination of the family described in this paper indicate that this is a new autosomal dominant inherited syndrome, whose symptoms comprise pre-auricular sinus, commissural lip pits, external ear anomaly and also mixed or conductive hearing loss (MIM No. 120502) (Marres and Cremers, 1991; McKusick, 1992). At present, gene linkage studies are being performed on this family to investigate whether the distinction between this syndrome and the branchial arch syndromes mentioned above can be supported by the results of gene linkage studies.

The otological aspects of this syndrome are described in more detail, together with the findings and results of middle ear surgery.

Patients and methods

The proband was examined at the Nijmegen University Hospital, Department of Otorhinolaryngology, for the evaluation of congenital hearing loss. A request for genetic counselling subsequently arose. This led to further differentiation and analysis of the features in the proband and that of several members of his family. Although it could be concluded that the hearing loss, pinna dysplasia and pre-auricular sinus displayed an autosomal dominant inheritance pattern, it was difficult to distinguish these symptoms from those of the branchio-oto-renal (BOR) syndrome (Table I).

We were recently offered the opportunity to perform a detailed family study on the 74 family members. All the members underwent otorhinolaryngological examination, including micro-otoscopy and all of them older than 3.5 years (n = 66) also underwent pure tone audiometry. The findings of this examination are shown in the pedigree (Figure 1). The study results led us to the conclusion that this might be a new autosomal dominant branchial arch syndrome (Marres and Cremers, 1991).

The features of this syndrome were: conductive or mixed hearing loss, pre-auricular sinus or cyst, external ear anomalies and commissural lip pits (Figures 2 and 3). Contrary to the BOR syndrome, there were no renal anomalies or cervical fistulae. One or more features were found in 20 of the members which could be attributed to this syndrome. Within this group, eight were also suffering from hearing loss (Tables II and III). Their data formed the subject of this study. Ear surgery was performed on four members (six ears) and six members, underwent high resolution CT scanning of the middle and inner ear. Vestibular examination with electronystagmography and computer analysis was performed in three cases. The tests included velocity step tests and caloric tests, as well as smooth pursuit and cylindrical-screen optokinetic nystag-

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TABLE I
THREE BRANCHIAL ARCH SYNDROMES. THE PENETRATION AND VARIATION OF THE FEATURES ARE NOT PRESENTED

Features	The Treacher-Collins syndrome	The BOR syndrome	The present (new) syndrome in this pedigree
Pinna dysplasia	+	+	+
Pre-auricular sinus	+	+	+
Ear appendage	+	+	–
Aural atresia	+	+	–
High arched or cleft palate	+	+	–
Hearing loss	+	+	+
Cervical fistula	–	+	–
Renal anomalies	–	+	–
Hypoplasia or aplasia of facial bones	+	–	–
Commissural lip pits	–	–	+
Vestibular hypofunction	–	+	–

+, Feature compatible with the syndrome; – , feature not described in association with the syndrome (see Cremers and Fikkers-van Noord, 1980; Marres and Cremers, 1991; Marres *et al.*, 1993).

mus tests. Furthermore it was assessed whether any gaze nystagmus (visual fixation in lateral gaze) or spontaneous nystagmus (eyes open in the dark) occurred.

Results

Patient 1 (III-7 in Figure 1)

In 1962, the male proband, aged eight years, was referred to the Department of Otorhinolaryngology because of suspected bilateral congenital hearing loss. His medical history did not reveal any aetiological factors. Physical examination showed bilateral pinna dysplasia and a pre-auricular sinus (Table II). Recently as part of a family study, commissural lip pits were also found to be present (Marres and Cremers, 1991). Hearing thresholds were obtained by regular pure tone audiometry from 1962 to 1991 (Table III). A hearing aid was fitted at our subunit for paediatric audiology. He received personal tuition to help with his schooling.

To improve his conductive hearing loss, exploratory tympanotomy was performed on his right ear at the age of 12 years. The incus and malleus were found to be mobile but there was a plump ankylotic stapes. The long process of the incus was fragile and too short. There was no bony contact between the incus and the stapes. The round and oval windows were found to be normal, the facial nerve had a normal course and the bony canal was intact. Stapedectomy was performed and a 3.5 mm teflon wire piston was interposed onto the incus. The hearing improved post-operatively from about 50 to 20 dB hearing threshold. The patient no longer found it necessary to wear a hearing aid (Table IV).

Exploratory tympanotomy on the left side was performed at the age of 26 years. Stapes reflexes were not measured pre-operatively. During surgery, the malleus was found to be hypermobile, the long process of the incus was almost absent and the stapes was malformed and fixed through ankylosis to a normal-sized oval window. The facial nerve showed no abnormalities in its course and he had an intact bony canal. A teflon wire piston, with a length of 5 mm, was interposed between the malleus and vestibule after stapedotomy. His post-operative hearing remained unsatisfactory, so the ear was re-explored to improve the teflon interpositioning. This achieved a mean hearing gain of 25 dB. However, during follow-up, the hearing thresholds increased (Table IV) and the same procedure was repeated. Again, piston interpositioning was improved in combination with re-opening of the oval window. The teflon wire piston was attached around the neck of the malleus without removing the head of the malleus. Only the neck of the malleus and part of the handle were detached from the tympanic membrane. However, in the follow-up period, the wire of the piston penetrated the tympanic membrane and was extruded. The same surgical technique was subsequently repeated in combination with a fascia underlay technique to cover and support the piston–malleus connection. These repeated operations on the left ear were mainly conducted at the request of the patient, who had experienced what it meant to be able to hear with both ears and was highly motivated to have the situation restored.

Patient 2 (III-30 in Figure 1)

The patient was a 25-year-old woman. Her clinical features and pre-operative hearing thresholds are presented in Tables I and II. Exploratory tympanotomy of the left ear had been performed at the age of 16 years elsewhere

TABLE II
PATIENT CHARACTERISTICS. NUMBERS IN BRACKETS REFER TO THE PEDIGREE SHOWN IN FIGURE 1

Patient no.	Pre-auricular sinus		Commissural lip pit		External ear anomaly	
Ear	Right	Left	Right	Left	Right	Left
1 (III-7)	+	+	+	+	+	–
2 (III-30)	+	–	–	–	+	–
3 (II-10)	cyst	–	–	–	+	+
4 (IV-5)	+	–	–	–	–	–
5 (III-6)	–	–	+	–	+	–
6 (III-4)	–	+	–	–	–	–
7 (IV-7)	+	+	+	+	+	+
8 (IV-8)	+	+	–	–	+	+

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TABLE III

ELEVATED HEARING THRESHOLDS OF EIGHT PATIENTS WITH ASSOCIATED ANOMALIES AS SHOWN IN TABLE II. THE FIRST NUMBER REPRESENTS THE AIR CONDUCTION THRESHOLD (IN dB HL), THE SECOND NUMBER (IF MEASURED) IS THE SENSORINEURAL HEARING THRESHOLD. (IF THE PATIENT UNDERWENT EAR SURGERY, THE PRE-OPERATIVE THRESHOLDS ARE PRESENTED)

Patient no.	Ear	Frequency					
		250	500	1000	2000	4000	8000
1	Left	40	45/0	45/5	35/5	40/5	45/0
	Right	50	45/0	45/5	55/10	50/10	45/5
2	Left	50	40/15	50/10	45/20	65/25	75
	Right	10	10	10	20	35	50
3	Left	20	20/10	10/0	10/0	25/0	45/30
	Right	65	70/10	70/10	75/45	75/30	80
4	Left	60	35/0	30/0	25/0	30/5	45/40
	Right	50	40/0	25/0	20/0	20/0	50/25
5	Left	60	50/10	25/5	20/10	40/55	45/30
	Right	30	20/5	10/5	10/10	15/55	45/40
6	Left	15	10	5	5	15	30
	Right	50	40/5	40/5	35/10	40/0	45/5
7	Left	–	60	55/0	50/10	45/5	65
	Right	–	55/10	60/5	35/10	20/0	30/10
8	Left	50	45/5	40/5	25/10	30/15	45
	Right	50	50/0	45/0	40/5	35/0	45

owing to congenital conductive hearing loss; it was her wish to have binaural hearing. Disconnection of the incudo-stapedial joint was found, because the long process of the incus was too short. Autologous cortical bone had been used to reconstruct the ossicular chain.

Seven years later, she was referred to the Nijmegan University Hospital, Department of Otorhinolaryngology, because of progressive hearing loss. The conductive hearing threshold in her left ear had increased. During exploratory tympanotomy, the autologous incus, which was found to be in its original position, was removed. The incus was normal except for the long process which was much too short. The suprastructure of the stapes was malformed and somewhat curved. The mobility of the stapes in the oval window was considered to be normal. The facial nerve was normal. The autologous incus was transformed and interposed to reconstruct the ossicular chain. Her hearing level did not improve post-operatively (Table IV).

Patient 3 (II-10 in Figure 1)

A 58-year-old woman with unilateral mixed hearing loss was examined. Her syndromal features are shown in Table II and her mixed unilateral hearing loss is presented in Table III. She had been experiencing progressive hearing loss in her right ear. As there was a sensorineural component in her hearing loss, a CT scan of the petrosal bones was performed to trace inner ear malformations. No abnormalities were found. Exploratory tympanotomy revealed several congenital anomalies of the ossicular chain and other middle ear malformations; there was a plump incus and the long process of the incus was absent. The stapes suprastructure was also absent and the stapedial footplate was fixed. Besides these ossicular chain abnormalities, aplasia of the round window was suspected. This was in contrast to the CT scan which demonstrated a normal round window. However a bony plate could be demonstrated covering the round window (Figure 4). The facial nerve followed a normal course through the bony canal.

Consequently and in view of a reasonable hearing threshold in her left ear, no attempt was made to improve her hearing (Table IV).

Patient 4 (IV-5 in Figure 1)

A 15-year-old girl was referred to the Department of Otorhinolaryngology, at the age of seven years, with complaints of otitis media with effusion. The features are presented in Table II. During follow-up, chronic otitis media developed resulting in bilateral perforation of the tympanic membranes. At the age of 12 years, exploratory tympanotomy and myringoplasty was performed on her right ear because of serious conductive hearing loss; the ossic-

TABLE IV

POST-OPERATIVE HEARING THRESHOLDS. THE FIRST NUMBER REPRESENTS THE AIR CONDUCTION THRESHOLD (IN dB HL), THE SECOND NUMBER (IF MEASURED) IS THE SENSORINEURAL HEARING THRESHOLD

Patient no	Ear	Follow-up (years)	Frequency (Hz)					
			250	500	1000	2000	4000	8000
1	Right	22	25	20/0	20/5	10/10	35/20	45/30
	Left	1	40	50/5	35/20	20/15	30/5	70/20
	Left	0.5	40	45/5	45/5	30/15	60/15	55/25
	Left	4.5	50	45/0	45/5	55/10	80/30	120
	Left	2	60	45/10	40/5	25/20	70/35	80
2	Left	7	50	40/15	50/10	45/20	60/45	75
	Left	1	50	45/10	45/10	30/20	45/30	80
3	Right	1	60	65/25	70/10	85/45	75/40	80
4	Right	1	15	15/5	20/5	5/0	5/5	40/25
	Left	2	65	50/5	25/5	25/5	45/15	65

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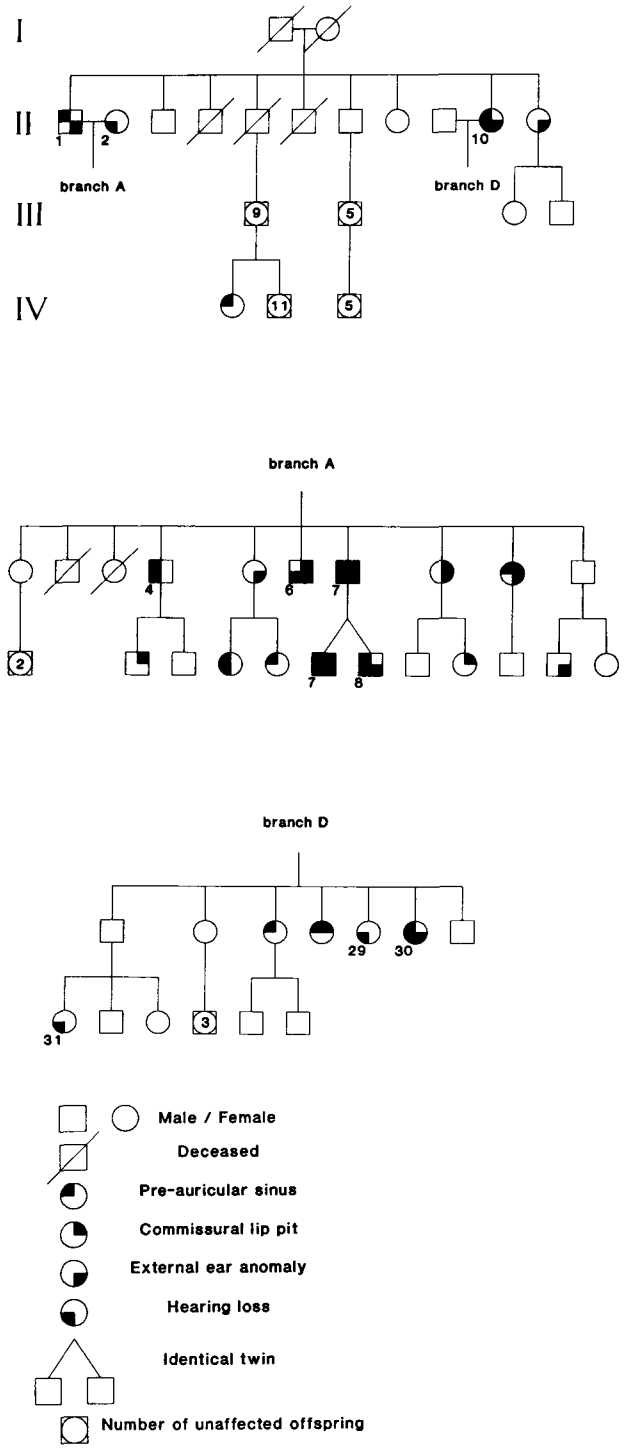

FIG. 1

Pedigree of four generations of a family. All the family members in three generations were examined (n = 74). All who were older than 3.5 years were tested audiologically (n = 66).

ular chain and facial nerve were found to be normal. The post-operative results were satisfactory (Table IV). Two years later, the same procedure was performed on the left side. Again, there were no abnormalities besides perforation of the tympanic membrane. Unfortunately, perforation of this side recurred during the first year of follow-up. Her hearing loss was considered to be a residual consequence of chronic otitis media.

Patient 5 (III-6 in Figure 1)

The bilateral hearing loss of this 36-year-old male patient was confirmed by means of audiometry. It was not possible to elicit the stapes reflex on the left side. His medical history indicated chronic otitis media of the right ear and otoscopy revealed perforation of the tympanic membrane. Owing to the presence of perforation of the tympanic membrane in the right ear and the patient's history, it is very likely that the hearing loss was the result of previous otological disease. Therefore, it was unclear whether the hearing loss was caused by a congenital middle ear anomaly, despite the presence of the other features and the absence of a stapes reflex on the left side (Table II). The patient was not troubled by his hearing loss and found it unnecessary to have a hearing aid fitted or to undergo exploratory tympanotomy.

Patients 6, 7 and 8 (III-4, IV-7 and IV-8 in Figure 1, respectively)

These patients were also found to have hearing loss besides the other syndromal features (Tables II and III). Stapedial reflexes could not be elicited in any of them. Patient 6 had no previous history of otological disease and otological examination did not reveal any abnormalities besides the pre-auricular sinus in the left ear. However, his hearing loss was only demonstrated on the right side and he had never considered a hearing aid or surgery.

Patients IV-7 and IV-8 (identical twins) were considered to be too young for surgery, so hearing aids were fitted for hearing rehabilitation at the age of three years when their hearing loss was first demonstrated. The paediatric audiology unit is currently giving counsel to the children and their parents and has an advisory function with regard to the children's schooling. Both patients had a negative otological anamnesis and history, so their hearing loss can provisionally be attributed to the underlying syndrome in view of the other features present.

High-resolution CT scanning (1 mm slices in coronal and transverse directions) of the inner ears in patients number 1, 3, 5, 6, 7 and 8, showed no abnormalities of the inner ear structures, especially no cochlear dysplasia.

Patients 1 and 5 showed vestibular hyper-reactivity of their velocity step (VS) responses, i.e. the initial velocities (V) were too high compared to the confidence limits reported in 1986 by Theunissen *et al.* Caloric responses in patient 1 were normal. Patient 6 had normal VS responses but a marginally pathological caloric side difference of 25 per cent with small response on the left side. In all three cases tested, the results of the other vestibular and oculomotor tests were normal.

In the pedigree, three other cases with hearing loss are presented (see Figure 1): patient II-2 (spouse), III-29 and IV-31. The hearing loss of patient II-2 was mixed and showed a slowly progressive character. No stapes reflexes could be elicited. The hearing loss was probably based on otosclerosis. The hearing loss in patients III-29 and IV-31 can be attributed to chronic otitis media. In view of the absence of any other features, these patients appear to be phenotypically unaffected.

Discussion

We consider the syndrome described in this study to be

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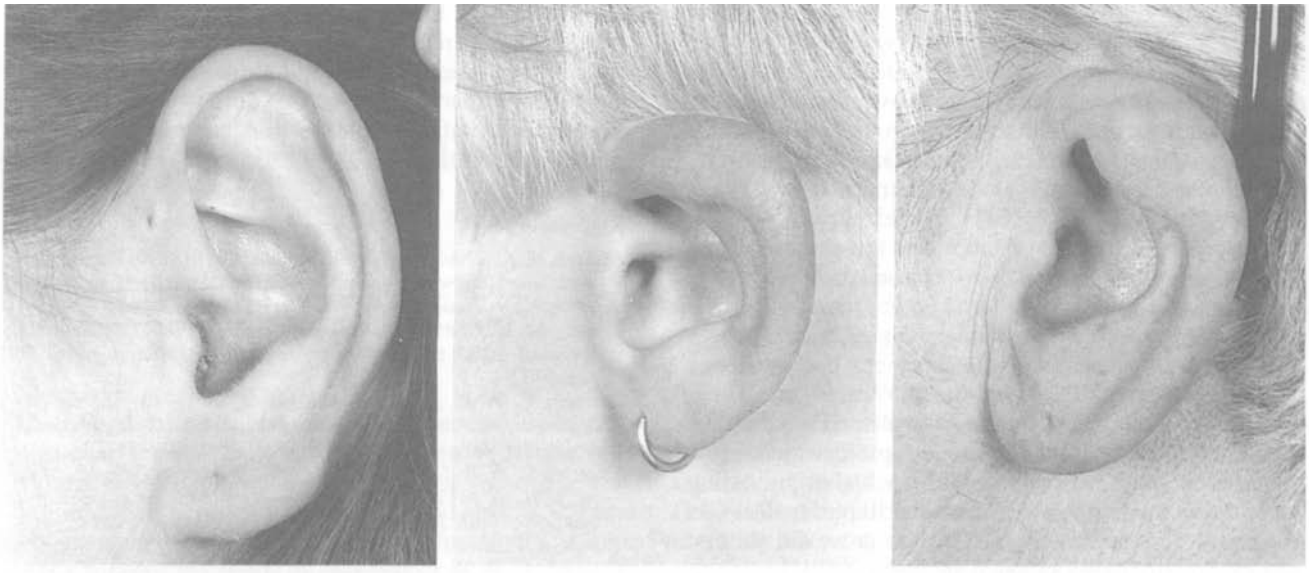

FIG. 2
Pre-auricular sinus with (middle) and without (left) pinna dysplasia. Pinna dysplasia without pre-auricular sinus (right).

a separate syndrome, despite the similarities with a few documented branchial arch syndromes. The greatest similarities exist between this syndrome and the branchio-oto-renal (BOR) syndrome, referred to in the past as the ear pits deafness syndrome (Melnick *et al.*, 1976; Cremers and Fikkers-van Noord, 1980).

The distinction made between the branchio-oto-renal syndrome and the branchio-oto (BO) syndrome in the literature proved to be incorrect because no investigation had been made of the kidneys of the patients who were suffering from the branchio-oto-(renal) syndrome (i.e. the ear pits deafness syndrome) (Melnick *et al.*, 1978; Cremers and Fikkers-van Noord, 1980). In the near future gene-linkage studies are expected to give the final answer to this. The absence of any renal anomalies in the family described in this paper, the absence of cervical fistulae or sinuses, and the presence of commissural lip pits, are motives for distinguishing this syndrome from the BOR syndrome.

Earlier literature surveys and our own work on the BOR syndrome have shown that only 15 per cent of people with the BOR syndrome present with ear pits and deafness without cervical fistulae (Cremers and Fikkers-van Noord, 1980). The observation that none of the people in this fully-investigated family, comprising 74 members, were found to have cervical fistulae, supports the assumption that this anomaly should be differentiated from the BOR syndrome.

The commissural lip pits must be distinguished from the paramedian lip pits which are associated with facial clefting (Cheney *et al.*, 1986). Commissural lip pits do not generally have any clinical significance. However, in a recent report, mention was made of a unilateral lip pit in combination with an ectopic salivary cyst and an aberrant parotid duct (Arriaga *et al.*, 1990). The morphogenesis of these lip pits cannot be attributed solely to a branchial cleft anomaly. A possible explanation is that only partial fusion took place between the maxillary process and the mandibular process in the 6th to 8th week of embryonic development.

The best known examples of branchial arch syndrome

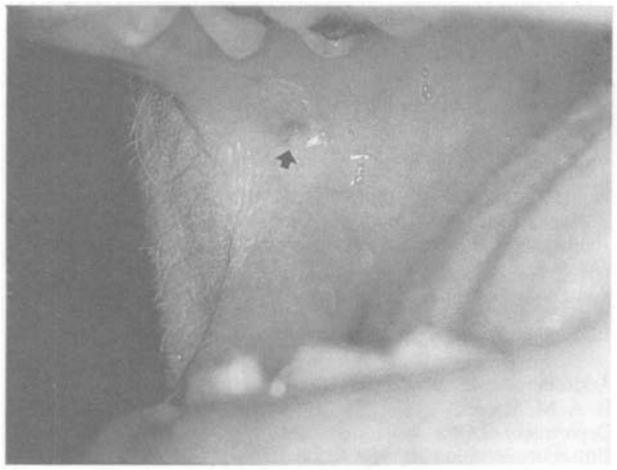

FIG. 3
Commissural lip pit (arrowed).

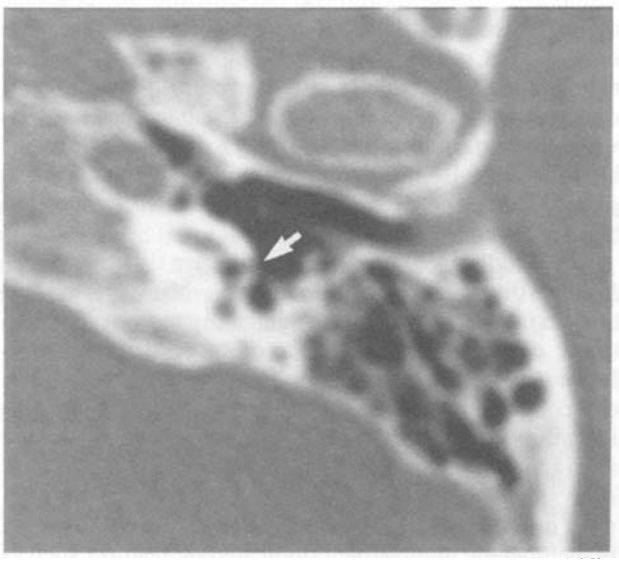

FIG. 4
Axial CT scan (right ear, patient 3) showing a normal round window covered by a bony plate (arrowed).

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anomalies with associated hearing loss are the Treacher-Collins syndrome and the BOR syndrome. Another example is autosomal dominant inherited hemifacial microsomia. The anomalies of the ossicular chain and middle ear associated with these syndromes are generally more severe than those encountered in ears with a congenital middle ear anomaly alone (Cremers *et al.*, 1981; Cremers and Teunissen, 1991). For example, a combination of stapes footplate fixation and the absence of the long process of the incus is often seen and there is a higher incidence of dysplasia of the oval and/or round windows, which is an expression of more extensive branchiogenic involvement. Dysplasia of the inner ear has also been described in the BOR syndrome (Won *et al.*, 1977; Cremers *et al.*, 1981). This can be explained as being the result of impeded growth of the otic capsule, which is surrounded by a layer of cartilage of branchial origin during early development (Van de Water and Represa, 1991). In the new syndrome described in this paper we did not find any evidence of developmental anomalies of the inner ear. The cases we examined did not show any signs of vestibular hypofunction, which was found to be a typical characteristic in half of the cases with the BOR syndrome (Cremers *et al.*, 1981). However, the number of patients examined (n = 3) in this study was too small to draw any definitive conclusions.

The middle ear anomalies revealed by exploratory tympanotomy in our group of patients all showed involvement of the long process of the incus with additional stapes footplate ankylosis in three out of the four operated ears. In one case, dysplasia of the oval window was also present. Stapes surgery produced only one successful long-term result: patient III-7 (right ear) in whom the piston had been fixed to the incus. In one patient, suspected aplasia of the round window prevented us from attempting to repair the severe congenital ossicular chain anomaly. Malleovestibulopexy achieved only a temporary hearing improvement in one ear; improving the surgical techniques may lead to better results. For example, partly detaching the malleus from the tympanic membrane may be preferable. If the results are not expected to be favourable using this technique, it may even be worthwhile to consider myringochordovestibulopexy, which has recently been introduced (Cremers *et al.*, 1993). Although the long-term results were favourable in only one out of four ears with ossicular chain anomalies, for the patient in question who was suffering from bilateral hearing loss, this was a major breakthrough. By improving the surgical techniques and gaining experience with such anomalies, success rates can be expected to steadily increase.

The middle ear anomalies described in this paper confirm that the ossicular chain anomalies with associated features in this new syndrome are generally more severe than usual; consequently the chance of successful surgery is lower (Cremers and Teunissen, 1991). In the case of bilateral congenital hearing loss, fitting the patients with hearing aids is still the best solution. Surgery can be considered as an alternative to hearing aids. The chances of achieving a successful result with reconstructive surgery for the treatment of other syndromes with congenital hearing loss and branchiogenic involvement (indicated by features such as pinna dysplasia, e.g. the BOR syndrome and the Treacher-Collins syndrome) are at present smaller than those for congenital ossicular chain anomalies (Teunissen, 1992; Marres *et al.*, 1993). In this new syndrome described here it is possible that the middle ear anomalies will be more serious than normal, which may have an unfavourable influence on successful surgery. However, this does not mean that the situation is so unfavourable that middle ear surgery should not be considered.

References

Arriaga, M. A., Dindzans, L. J., Bluestone, C. D. (1990) Parotid duct communicating with labial pit and salivary cyst. *Archives of Otolaryngology, Head and Neck Surgery* **116:** 1445–1447.

Cheney, M. L., Cheney, W. R., LeJeune, F. E. (1986) Familial incidence of labial pits. *American Journal of Otolaryngology* **7:** 311–313.

Cremers, C. W. R. J., Fikkers-van Noord, M. (1980) The ear pits deafness syndrome. Clinical and genetic aspects. *International Journal of Pediatric Otorhinolaryngology* **2:** 309–322.

Cremers, C. W. R. J., Thijssen, H. O. M., Fischer, A. J. E. M., Marres, E. H. M. A. (1981) Otological aspects of the ear pits deafness syndrome. *ORL Journal Otorhinolaryngological Related Specimens* **43:** 223–239.

Cremers, C. W. R. J., Teunissen, E. (1991) The impact of a syndromal diagnosis on surgery for congenital minor ear anomalies. *International Journal of Pediatric Otorhinolaryngology* **22:** 59–74.

Cremers, C. W. R. J., Marres, H. A. M., Brunner, H. G. (1993) Neo-oval window technique and myringo-chorda-vestibulopexy in the BOR syndrome. *Laryngoscope* **103:** 1186–1189.

Dixon, M. J., Read, A. P., Donnai, D., Colley, A., Dixon, J., Williamson, R. (1991) The gene for Treacher-Collins syndrome maps to the long-arm of chromosome 5. *American Journal of Human Genetics* **49:** 17–22.

Kumar, S., Kimberling, W. J., Kenyon, J. B., Smith, R. J. H., Marres, H. A. M., Cremers, C. W. R. J. (1992) Autosomal dominant branchio-oto-renal syndrome – localization of a disease gene to chromosome 8q by linkage in a Dutch family. *Human Molecular Genetics* **1:** 491–495.

Marres, H. A. M., Cremers, C. W. R. J. (1991) Congenital conductive or mixed deafness, pre-auricular sinus, external ear anomaly and commissural lip pits: an autosomal dominant inherited syndrome. *Annals of Otorhinolaryngology* **100:** 928–932.

Marres, H. A. M., Cremers, C. W. R. J., Marres, E. H. M. A., Vreugde, J. P. (1993) Ear surgery in the Treacher-Collins syndrome. *Annals of Otology, Rhinology and Laryngology* (submitted).

McKusick, V. A. (1992) *Mendelian Inheritance in Man*, 10th Edition, Vol. 1, Johns Hopkins University Press, Baltimore, pp 168, 169, 253, 694, 695.

Melnick, M., Bixler, D., Nance, W. E., Silk, K., Yune, H. (1976) Familial branchio-oto-renal dysplasia: a new addition to the branchial arch syndromes. *Clinical Genetics* **9:** 25–34.

Melnick, M., Hodes, M. E., Nance, W. E., Yune, H., Sweeney, A. (1978) Branchio-oto-renal dysplasia and branchio-oto dysplasia: two distinct autosomal dominant disorders. *Clinical Genetics* **13:** 425–442.

Teunissen, B. (1992) *Major and minor congenital anomalies of the ear. Classification and surgical results.* Thesis, University of Nijmegen, The Netherlands, pp 57–74.

Theunissen, E. J. J. M., Huygen, P. L. M., Folgering, H. T. (1986) Vestibular hyper-reactivity and hyperventilation. *Clinical Otolaryngology* **11:** 161–169.

Van de Water, Th.R., Represa, J. (1991) Tissue interactions and growth factors that control development of the inner ear: neural tube-otic anlage interaction. *Annals of New York Academy of Sciences* **630:** 116–128.

Won, K. H., Gayler, B. W., Shimizu, H. (1977) Genetic hearing loss with pre-auricular sinus and branchiogenic fistula. *Archives of Otolaryngology, Head and Neck Surgery* **103:** 676–680.

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