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Evolution of Acquired Middle Ear Cholesteatoma in Patients With Ectrodactyly, Ectodermal Dysplasia, Cleft Lip/Palate (EEC) Syndrome

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Objective: To review an institutional experience with the surgical and clinical management of acquired middle ear cholesteatoma in patients with ectrodactyly, ectodermal dysplasia, cleft lip/palate (EEC) syndrome.
Study Design: Retrospective chart review.
Setting: Tertiary referral center.
Patients: Eight patients with medical history significant for EEC syndrome who underwent surgery for acquired middle ear cholesteatoma between 1996 and 2016.
Intervention(s): Appropriate surgical interventions at the time of admission.
Main Outcome Measure(s): History of ventilation tube insertion, status of the contralateral ear, surgical technique, cholesteatoma recidivism, presence of postoperative external auditory canal stenosis, pre and postoperative audiograms.
Results: Cholesteatoma was diagnosed in all patients, 3 (37.5%) unilateral and 5 (62.5%) bilateral, totalizing 13 ears. Six ears (46.2%) underwent a canal wall up mastoidectomy but required conversion to a canal wall down technique in a second procedure due to recurrent cholesteatoma. In the remaining seven ears (53.8%) a canal wall down mastoidectomy was performed. Of all meatoplasty performed, seven (53.8%) evolved with stenosis of the external auditory canal.
Conclusions: Our results suggest that most patients with EEC syndrome and middle ear cholesteatoma should be considered for a canal wall down mastoidectomy due to extensive disease and a high rate of recidivism. In addition, a high percentage of postoperative stenosis of the external auditory canal was found in this group. **Key Words:** Cleft palate—Ectodermal dysplasia—EEC syndrome—Middle ear cholesteatoma.

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Ectrodactyly, ectodermal dysplasia, cleft lip/palate (EEC) syndrome is a rare autosomal-dominant genetic disorder with great variability of expression and reduced penetrance. It affects approximately 1 in 18,000 newborns (1). Familial cases show an autosomal-dominant inheritance with marked intrafamilial and interfamilial variability. However, the majority of cases are sporadic (2).

The most common clinical manifestation is ectodermal dysplasia (ex: fine and sparse hair, nail dystrophy, hypo or anodontia and sweat glands alterations), which occurs in all patients. Other features of the syndrome include ectrodactyly (also known as split hand/foot malformation), cleft lip and/or palate, lacrimal duct abnormalities and genitourinary malformations (Fig. 1) (3,4).

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Differential diagnoses include other syndromes related to ectodermal dysplasia, such as Goltz Syndrome, Rapp Hodgkin Syndrome, Hay Wells Syndrome, and Christ Siemens Touraine Syndrome (5,6).

Mutations in the p63 gene, an important transcription factor during embryogenesis and differentiation of stem cells into stratified epithelium, are identified as the genetic cause of EEC syndrome. The p63 gene is a transcription factor from the same protein family as p53 and p73 and serves as a master regulator of epidermal development and differentiation (1,2).

Adequate ectodermal development is crucial for normal ear growth. There is an ectodermal component in each branchial arch and the first and second arch give rise to the auricle components (7).

The main otologic alterations described in patients with ectodermal dysplasia are: ear wax impaction, chronic serous otitis media, recurrent acute otitis media, stenosis of the external auditory canal, hearing loss and delay in language development (7–10).

Despite the high incidence of otologic manifestations in patients with ectodermal dysplasia and cleft

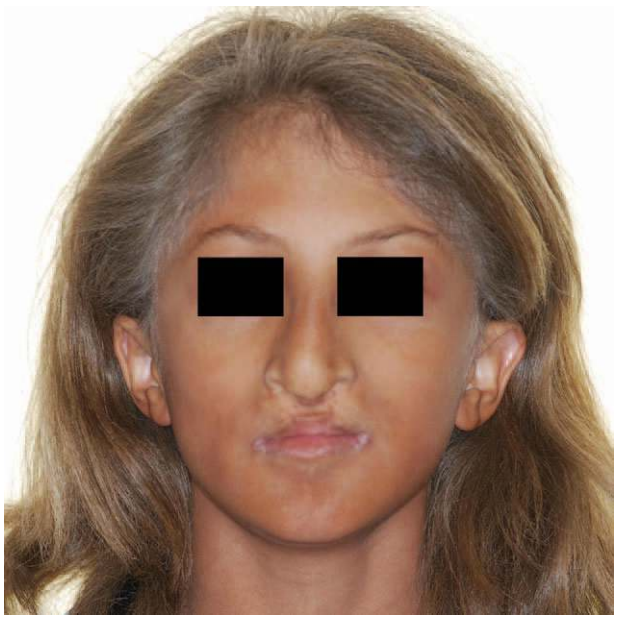

FIG. 1. Frontal view shows the patient's bilateral cleft lip and ectodermal dysplasia features.

palate, an association between EEC syndrome and acquired middle ear cholesteatoma has never been established.

This article aims to describe the evolution of acquired middle ear cholesteatoma in patients with EEC syndrome and to review an institutional experience with the clinical and surgical management of the disease.

METHODS

Subject Selection Criteria

Patients with EEC syndrome who underwent surgery for acquired middle ear cholesteatoma were selected. In all cases the clinical diagnosis of EEC syndrome was established by a geneticist using standard clinical criteria including history, physical examination, laboratory tests, and imaging studies.

This study was approved by the ethics committee of our institution and conducted in accordance with the ethical principles stated in the Helsinki Declaration.

All patients underwent hearing evaluation and a computed tomography study of the temporal bones before surgery.

Methodology

Retrospective chart review. The following data were collected: age, gender, history of cleft lip/palate repair surgery, history of ventilation tube insertion, status of the contralateral ear, surgical technique, cholesteatoma recidivism, presence of postoperative external auditory canal stenosis, pre and postoperative audiograms.

Audiological Testing

Audiometry was performed in a soundproofed booth with a loudspeaker positioned at 0° azimuth and at a distance of 1 m from the subject to obtain the mean thresholds for frequencies of 0.5, 1, 2, and 3 kHz, according to the guidelines of the Committee on Hearing and Equilibrium (11).

RESULTS

Eight patients with medical history significant for EEC syndrome underwent surgery for acquired middle ear cholesteatoma between 1996 and 2016. Their ages ranged from 14 to 34 years. The patient data, cleft type, history of ventilation tube insertion, and presence of external auditory canal stenosis are described in Table 1.

All patients presented surgically repaired cleft lip and palate. History of serous otitis media was found in all patients and seven (87.5%) underwent previous myringotomy and ventilation tube insertion.

Primary acquired epitympanic cholesteatoma was diagnosed in all patients, 3 (37.5%) unilateral and 5 (62.5%) bilateral, totalizing 13 ears.

In most cases, the decision to perform a canal wall up (CWU) or a canal wall down (CWD) mastoidectomy was made intraoperatively, based on mastoid anatomy and specific disease findings. Generally, in patients with adequate anatomy, condition of care and follow-up, the less invasive option was chosen in that period.

Seven ears (53.8%) underwent a CWD mastoidectomy. In the remaining six ears (46.2%) a CWU mastoidectomy was performed. However, patients submitted to a CWU mastoidectomy required a second surgery due to recurrent cholesteatoma, continuous suppuration, and tympanic membrane perforation.

TABLE 1. *Patient data*

Patient No	Age	Gender	Cleft Type	History of VT Insertion	Cholesteatoma	External Auditory Canal Stenosis
1	22 y	F	bcl/p	+	Bilateral	Bilateral
2	24 y	F	bcl/p	+	Unilateral Right	–
3	14 y	F	rcl/p	+	Bilateral	Bilateral
4	33 y	F	bcl/p	+	Unilateral Left	–
5	30 y	M	bcl/p	+	Bilateral	–
6	21 y	F	bcl/p	+	Bilateral	Bilateral
7	34 y	F	lcl/p	–	Unilateral Left	Unilateral Left
8	29 y	F	bcl/p	+	Bilateral	–

bcl/p indicates bilateral cleft lip/palate; F, female; lcl/p, left cleft lip/palate; M, male; rcl/p, right cleft lip/palate; VT, ventilation tube; y, years.

TABLE 2. *Postoperative complications and recurrent cholesteatoma extension in patients submitted to prior CWU mastoidectomy*

Patient No + Ear	1st Surgical Technique	Postoperative Complications	Recurrent Cholesteatoma	2nd Surgical Technique
1 Right	CWU	Otorrhea, TM perforation	E, Me	CWD
1 Left	CWU	Otorrhea, TM perforation	E, Me	CWD
3 Right	CWU	Otorrhea, TM perforation	Me	CWD
6 Left	CWU	Otorrhea	E	CWD
8 Right	CWU	Otorrhea, TM perforation	E, Me	CWD
8 Left	CWU	Otorrhea	E	CWD

CWD indicates canal wall down; CWU, canal wall up; E, epitympanum; Ma, mastoid; Me, mesotympanum; TM, tympanic membrane.

During the second procedure, surgeons found recurrent cholesteatoma, extensive disease, erosion of the posterior canal wall, and a contracted mastoid that led them to convert the procedure into a CWD mastoidectomy. Cholesteatoma extension and recurrence sites are described in Table 2.

Of all meatoplasty performed, seven (53.8%) evolved with stenosis of the external auditory canal (Fig. 2). All patients evaluated with unilateral cholesteatoma presented otologic abnormalities in the contralateral ear, such as conductive hearing loss and retraction of the tympanic membrane.

Preoperative average bone conduction threshold was 7.79 dB versus a 7.40 dB postoperative. While preoperative average air conduction threshold was 40.96 dB versus a 44.02 dB postoperative.

DISCUSSION

About 300 cases of EEC syndrome have been reported since its first description by Rudiger in 1970 (12). Ectodermal dysplasia is the most common clinical feature and it is present in all patients. Other major features of the syndrome include ectrodactyly, cleft lip and/or palate, lacrimal duct abnormalities, and genitourinary malformations (3,4).

The syndrome is caused by mutations in the p63 gene, an important transcription factor during embryogenesis and differentiation of stem cells into stratified epithelium. The p63 gene is essential for regenerative proliferation in epithelial development (1,6). Mice devoid of p63 fail to generate stratified epithelia and their appendages. The surface epithelium of p63 knockout mice consists only of a single layer of keratinocytes that results in dehydration and death of the animals within a few hours after birth (13).

This study demonstrated a high percentage of postoperative external auditory canal stenosis. This may be explained by mutations in the p63 gene whose isoforms are expressed throughout the basal layer of the epidermis and play a crucial role in the regulation of epidermal repair during wound healing and epidermal homeostasis. Mice with a germ line deletion of TAp63, a p63 isoform, developed alopecia, a severe blistering disease and wound-healing defects evidenced by a failure to completely heal wounds created on the epidermis (14,15).

Otologic abnormalities in EEC syndrome have been poorly described in the literature. However, it is plausible to expect a high incidence of pathologies since both ectodermal dysplasia and cleft palate are associated with poor Eustachian tube function and recurrent otitis media (7–10,16). In patients with ectodermal dysplasia the absence or hypoplasia of mucous glands results in abnormal functioning of the Eustachian tube and patients can develop chronic serous otitis media (7,8). There is also a

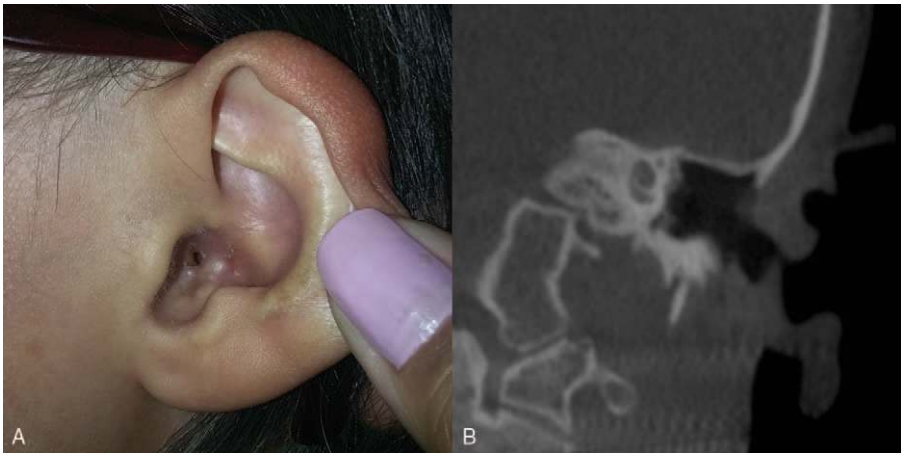

FIG. 2. Postoperative external auditory canal stenosis. (*A*) Left ear. (*B*) CT study of left temporal bone.

high prevalence of serous otitis media in patients with cleft palate. In this patients, the muscles responsible for dilating and opening the Eustachian tube are unable to contract properly and dilate the Eustachian tube, which is unable to balance pressure and drain secretions (16,17).

The results of this study suggest that most patients with EEC syndrome and acquired middle ear cholesteatoma should be considered for a CWD mastoidectomy due to extensive disease, difficult clinical control, and a high rate of recidivism. Status of the contralateral ear should also be considered, since all patients evaluated were found to have at least one otologic abnormality in the contralateral ear.

EEC syndrome is a complex entity that still needs elucidations and, despite the limitations of the study, the carrying out of prospective studies is unlikely due to the rarity of the condition. To our knowledge, this is the first study correlating EEC syndrome and acquired middle ear cholesteatoma.

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