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Original Research

Uncommon associations with cleft palate: Plausibility of postclosure opening as a cause of cleft palate

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ABSTRACT

Objective: Current consensus from numerous animal studies has emerged that disturbances at any stage of palatal development can cause cleft palate. However, several clinical cases of uncommon forms of cleft palate that may have resulted from rupture after palatal fusion have been previously reported and treated. This hypothesis of postclosure opening as a cause of cleft palate was reviewed in the literature.
Materials and methods: We reviewed Japanese and English-language literature describing uncommon forms of cleft palate, which included palatal remnants, perforation, and divided nevi. In addition, a retrospective chart review of over 1300 cleft palate repairs performed by the authors was done.
Results: There were many reports of palatal remnants and perforations, but no reports of divided nevi on the cleft palate. Our retrospective chart review revealed that 12 cases may have resulted from postclosure opening, with 5 cases due to epithelial remnants on the hard palate, 5 cases of cleft palate with perforation, 1 case of a palatal sinus, and 1 case of a divided nevus over the cleft.
Conclusions: Epithelial remnants did not seem to be evidence of a postclosure opening event, because they were found in 23–85% of intact palates. However, perforation of the hard palate and a divided nevus on the cleft cannot be explained by embryology, which might indicate postclosure opening as a cause of the cleft. Clinical or animal studies are required to test this hypothesis further.

1. Introduction

Both in humans and mice, secondary palate development is a dynamic process, and is composed of four stages [1]. Stage 1 (vertical growth) is characterized by formation of the palatal shelves from the bilateral maxillary processes, which develop vertically on either side of the tongue. During stage 2 (elevation), the bilateral palatal shelves elevate to a horizontal position above the dorsum of the tongue. It is postulated that rapid alterations of cell proliferation and extracellular matrices including hyaluronate and glycosaminoglycan help to attain this horizontal orientation of the shelves [2]. During stage 3 (adhesion), the palatal shelves contact each other in the midline. Many genes are expressed both in the medial edge epithelium (MEE) and the mesenchyme for the next stage. During stage 4 (fusion), the MEE of the approximating palatal shelves are fused via several desmosome contacts to form a midline seam. The fate of MEE cells is to undergo apoptosis, migration, or epithelial-mesenchymal transformation coincident with the process of palatal fusion and disappearance of MEE [3–5].

Most authors agree that cleft palate (CP) results from disturbances at any stage of secondary palate development [6,7]. In animal studies, disturbance of palatal shelf growth, delay or failure of the shelf elevation, disturbance of shelf fusion, failure of medial edge mesenchymal cell death, postclosure opening, and failure of mesenchymal consolidation have all been postulated to cause CP [6,8,9].

On the other hand, several cases of CP that could not explained by standard embryological events have been reported [10–12], including epithelial remnants [13] and perforation of the palate [14]. Kitamura [15,16] suggested that such CPs were caused by postclosure opening (also described as postfusion rupture). However, there have been few animal studies to support this theory [17,18].

Herein we review the literature that describes cases of CP with causes to suggest a postclosure opening phenomenon. In addition, we present our series of similar conditions, and revisit the notion that our hypothesis is a potential cause of CP.

☆ Asian AOMS: Asian Association of Oral and Maxillofacial Surgeons; ASOMP: Asian Society of Oral and Maxillofacial Pathology; JSOP: Japanese Society of Oral Pathology; JSOMS: Japanese Society of Oral and Maxillofacial Surgeons; JSOM: Japanese Society of Oral Medicine; JAMI: Japanese Academy of Maxillofacial Implants.

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Table 1
Uncommon associations with cleft palate that might suggest a postclosure opening phenomenon.

Association	Case(s)	Source	Present case(s)
Epithelial remnants	11 fetuses with CL/P and 6 fetuses with CP 1 infant with soft palate cleft 4 infants with CL/P and 1 infant with SMCP	Kitamura, 1991 [16] Shimizu et al., 1994 [20] Richard et al., 2000 [13]	4 infants with CP and 1 infant with SMCP
Perforation[a]	1 child with hard palate cleft 5 children with hard palate cleft 3 children with CL/P and 1 child with SMCP 1 adolescent with CP 1 infant, 2 children, and 1 adult with SMCP 11 cases of hard palate cleft and 2 cases of SMCP (age not clarified) 1 neonate with hard palate cleft	Lynch et al., 1966 [10] Fara, 1971 [14] Cheng and Zhou, 1998 [21] Aslan et al., 2002 [11] Mehendale and Sommerlad, 2003 [22] Butow et al., 2008 [23] Engelbrecht et al., 2013 [12]	1 infant with perforation of CP and 4 infants with adhesion of soft palate associated with SMCP
Divided nevus	Not reported		1 child with compound nevus divided over the cleft palate

[a] Anecdotal reports of adults with untreated SMCP associated with perforation due to trauma or stomatitis are excluded.

2. Materials and methods

2.1. Review of the literature

We reviewed the English and Japanese literature reporting uncommon associations with CP, including epithelial remnants (also known as epithelial cysts or Epstein pearls), perforation (also reported as sinus, adhesion, or fenestration) and divided nevus. We also reviewed the literature describing animal studies on the mechanisms for clefting, including a mouse model that forms spontaneous clefts, and studies on teratogens that act on secondary palate development. PubMed was used to search English-language literature, and Ichushi Web was used for Japanese-language literature. Case reports and literature older than 50 years were excluded.

2.2. Retrospective chart review of patients

One co-author (Y.S.) has treated more than 800 patients with CP during his more than 30 years of clinical experience at Showa University Hospital. Although most of the older medical charts were unavailable, cases of CP associated with uncommon conditions were personally recorded by the co-author (Y.S).

In addition, we have volunteered our services for plastic surgery missions in several developing nations. In particular, since the time 20 years ago that the coauthor (Y.S.) established a cleft lip and palate mission in association with local surgeons and humanitarian organizations in Nepal [19], around 900 cleft lip and/or palate (CL/P) repairs have been performed, more than half (approximately 500) of which were CP repairs. With regard to clinical cases of CP possibly caused by postclosure opening such as remnants, perforation, and divided nevus, a retrospective chart review of those patients was carried out by one co-author (Y.S.).

3. Results

3.1. Review of the literature

Our literature search revealed several reports of uncommon associations with CP (Table 1). Kitamura [16] reported that epithelial remnants were found in 17 human fetuses with CP or CL/P, and 6 fetuses with CP developed remnants. Others reported infants with CP or CL/P who developed epithelial remnants [13,20].

There have been many reports on CP associated with perforation [10–12,14,21–23]. This condition can be classified into two forms; fistula/perforation/adhesion of the submucous cleft palate (SMCP), and perforation of the hard palate. A few reports on perforation of the SMCP were published but not listed in Table 1 as they are case reports of adult patients that suffered perforation from minor trauma or stomatitis [24,25]. To our knowledge, there have been no reports on divided nevus with CP in any body of medical literature.

3.2. Clinical case examples

Our retrospective chart review revealed that at least 11 cases demonstrated uncommon associations with CP, which included 5 cases of epithelial remnants, 5 cases of perforation, and 1 case of divided nevus (Table 1). In addition, though the association with CP was unclear, a case of palatal sinus was thought to suggest an incomplete form of perforation. Clinical case examples are described as follows.

3.2.1. Epithelial remnants

A female newborn infant was referred to us for cleft palate (Fig. 1). During oral examination, two cysts were found along the left edge of the soft palate. When palatoplasty was performed at the age of one, the small cystic lesion was removed. Histopathological examination revealed that the cysts were surrounded by multiple epithelial linings. Whorls of keratin were present inside the cysts. A diagnosis of epithelial remnants was made.

3.2.2. Adhesion

A female newborn infant with CP was referred to us (Fig. 2). Oral examination revealed a mucosal adhesion of the soft palate. The cleft was repaired at the age of one according to the Furlow technique.

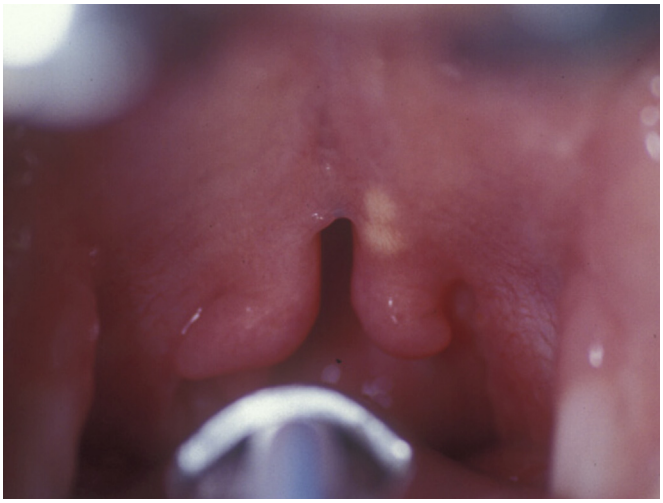

Fig. 1. Photograph of an infant with a cleft of the soft palate. Epithelial remnants are seen as two white cysts along the left edge of the cleft.

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