Consideration of Median Cleft Lip With Frenulum Labii Superior

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Abstract: Median cleft lip is usually divided into true and false when being discussed. Owing to recent developments of diagnostic imaging methods that have improved the accuracy, the presence of an intermediate type of median cleft lip, which cannot simply be divided into true and false, has been suggested. However, the simple method of classification is still clinically valuable. We have previously reported in this Journal a case of median cleft lip with 2 upper labial frenums. In the present study, based on our experience with false median cleft lip, we set forth a hypothesis that 2 upper labial frenums can be found in true median cleft lip, whereas no upper labial frenum is found in false median cleft lip. A review of the results of previous Japanese cases (7 true and 4 false cases) supported our hypothesis. We also reviewed one of our cases of right cleft lip accompanied by holoprosencephaly and discuss the case from the developmental perspective. The shape of the upper labial frenum may be a factor that can be used for clinically classifying intermediate median cleft lip into either true or false in cases that are otherwise difficult to classify.

Key Words: Median cleft lip, cleft lip, labial frenum, facial cleft, holoprosencephaly

We previously reported a case of median cleft lip with 2 upper labial frenums. Based on subsequent experience on false median cleft lip cases, we developed a hypothesis that true median cleft lip sometimes has 2 upper labial frenums, whereas false median cleft lip has no upper labial frenum, and report here a case of true median cleft lip with a review of previous reports.

PATIENTS

Patient 1
This is our previously reported case. The baby was born at 39 + 4 gestation weeks with a birth weight of 2792 g after normal vaginal delivery in November 2000. The median cleft lip observed at birth resulted in the baby being brought to our surgical outpatient clinic. On examination, a median cleft affecting slightly more than half of the white part of the upper lip was observed (Fig. 1A). A pair of philtral ridges existed almost symmetrically, with a slight widening above the clef. An indentation at the median alveolar process and 2 upper labial frenums were observed (Fig. 1B). There were no evident abnormalities in the shape of the external nose and inter-orbital distance. We consulted our pediatric department for possible brain malformations including holoprosencephaly. Although holoprosencephaly was less likely on computed tomography, corpus callosal agenesis was suspected from the ventricular shape, which was confirmed by magnetic resonance imaging (MRI). Repair of median cleft lip was undertaken by simple closure under general anesthesia on March 9, 2001. Figure 1C and D show the patient 6 months after surgery.

Patient 2
The baby was born at 40 + 2 gestation weeks with a birth weight of 2384 g in November 2000. Cleft lip, jaw, and palate had already been observed in utero, and postnatal brain ultrasonography revealed corpus callosal defect and frontal lobe hypoplasia. Lobar type holoprosencephaly was diagnosed by MRI. Chromosome analysis detected 18p− syndrome. The baby presented median cleft lip and nasal columella and septum defects (Fig. 2A). There was no upper labial frenum (Fig. 2D). A few days after birth, seizure and hypernatremia were manifested and treated with anticonvulsants and DDA VP nasal spray (Kyowa Hakko Co, Tokyo, Japan). After controlling the seizure and hypernatremia, surgical repair of cleft lip was performed under general anesthesia at 9 months of age. To simultaneously repair the nasal columella defect, cleft lip closure with nasal columellar reconstruction surgery, as recommended by Shimizu et al., was undertaken. The 1-year outcome was favorable (Fig. 2B–E).

Patient 3
This is a case of right cleft lip associated with holoprosencephaly. The baby was born at 39 + 6 gestation weeks with a birth weight of 2982 g in January 2008. Holoprosencephaly was diagnosed by MRI at our pediatric department. Only right cleft lip was present, and nasal columella and floor were intact. Six months after birth, surgery was performed at an appropriate body weight. Upper labial frenum was not observed on complete examination during operation under general anesthesia (Fig. 3A, B).

RESULTS
In patient 1, there were 2 upper labial frenums. Although corpus callosal defect was confirmed, a diagnosis of holoprosencephaly was not given. We believe that this case is under the category of true median cleft lip. Patient 2 was a false median cleft lip without upper labial frenum. Patient 3 was a right cleft lip that was associated with holoprosencephaly without upper labial frenum.

REVIEW OF PREVIOUS CASES IN JAPAN
We reviewed previous cleft clip cases in Japan (7 true and 4 false cases).
The inclusion criteria were as follows:
1. Whether it is clear from the description if a case was true or false cleft lip, and
2. Details of upper labial frenum can be clearly determined from pictures or description.

Six cases of true median cleft lip were recognized as having 2 upper labial frenums (the clefts of 2 cases that, among them, were at the lower half). The other case had a single, thickened upper labial frenum. None of the 4 false median cleft lip cases had upper labial frenum (Table 1). In addition, 2 mild cases of false median cleft lip showed no upper labial frenum (Figs. 4 and 5).

**DISCUSSION**

Median clefts of the upper lip account for approximately 0.1% to 0.7% of patients with cleft lip and jaw. Median cleft lip is generally classified into true and false median cleft lips (Table 2). True median cleft lip is a splitting gap, whereas false median cleft lip is a tissue defect. That is, the former is caused by the failure of fusion of both medial nasal processes between the fifth and eight week of pregnancy, whereas the latter is considered as a subtype of holoprosencephaly (Fig. 6). Several classifications of false median cleft lip have been suggested in relation to brain malformations. The oldest is the classification of arhinencephaly into 5 subtypes proposed by Kundrat in 1882, in which the type that is associated with median cleft lip belongs to the third subtype.

On the other hand, in 1959, Yakovlev suggested the term holotelencephaly and stated, “while the rhinencephalon is hypoplastic, it always exists.” In 1964, DeMyer et al suggested another term, holoprosencephaly, claiming that the prosencephalon was not differentiated and stayed in a holistic state, and classified it into 5 subtypes based on the strong correlation with the face. False median cleft lip is regarded to fall under type IV of DeMyer classification. Later, Kumagai added type VI with normal facial features, and since then, holoprosencephaly has been discussed in these classifications of V or VI types (Table 3).
However, as the title (“the face predicts the brain”) meant, DeMyer classification was intended to predict brain malformations from the facial features. With the development of new diagnostic imaging techniques and improvement in accuracy, the occurrence of the intermediate type, which cannot be easily classified into true or false, has recently been suggested.\textsuperscript{1,3,4,8,26} Furthermore, the classification of true and false has been criticized as an old concept defined when diagnostic imaging techniques were not yet developed.\textsuperscript{1,3,7} Tange\textsuperscript{3} suggested the term midfacial hypoplasia, stating it as, “a single malformation due to the same pathogenetic mechanism, only with different periods of manifestation.” Although there is yet no consensus, we believe that it is inappropriate to define median cleft lip as true or false only by the presence of holoprosencephaly.

However, the significance of classification cannot be denied because the clinical differentiation between defect and splitting is extremely important in determining surgical techniques. That is, although true median cleft lip can be treated with simple closure of the cleft, false median cleft lip requires surgical techniques including reconstruction of the defect.

We also describe the embryology of upper labial frenum. Between the fifth and eighth embryonic weeks, left and right olfactory pits appear near the lower end of the frontonasal prominence and divide it into medial and 2 lateral nasal processes, between which each olfactory pit is located. Lateral portions of the upper lip are formed by medial extension of the left and right maxillary prominences originating from the first pharyngeal arch. Both maxillary prominences are fused with each other at the median line and ipsilateral medial nasal process. Therefore, the medial portion of the upper lip (philtrum) is formed by fusion of the maxillary prominence and medial nasal process.\textsuperscript{17,27,28} In addition, the degeneration of the labiogingival lamina, which is a band of ectodermal epithelial cells growing into the embryonic mesenchymal tissue, forms the labiogingival groove. The upper labial frenum connecting the upper lip to the gum is thought to be formed at this time from the remains of the labiogingival lamina at the midline.\textsuperscript{17} If an inhibiting mechanism against degeneration exists at the median labiogingival lamina, failure of such mechanism may cause holoprosencephaly. This degeneration occurs immediately after fusion of both bilateral medial nasal processes and bilateral maxillary prominences. This period is responsible for the development of false median cleft lip, which is regarded as prosencephalon differentiation failure, and just after the development of true median cleft lip, which is regarded as fusion failure of medial nasal processes. Taking these into consideration, the shape of the upper labial frenum is thought to reflect the development of median cleft lip from a relatively early period. As a result, if true median cleft lip is a cleft resulting from the failure of the fusion of the medial nasal processes, a cleft may develop at the median labiogingival lamina. Accordingly, 2 upper labial frenums may result from the failure of fusion of each frenulum developed separately. However, in false median cleft lip, where defect is the main pathogenetic mechanism, it is thought that the upper labial frenum and nasal columella and septum do not exist.

### TABLE 1. Literature Review (7 True and 4 False Cases)

<table>
<thead>
<tr>
<th>Type</th>
<th>No. Upper Labial Frenum</th>
<th>Publishing Year/Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>True 2</td>
<td>1965/Tange</td>
</tr>
<tr>
<td>2</td>
<td>True 2 (divided at the lower portion)</td>
<td>1965/Tange</td>
</tr>
<tr>
<td>3</td>
<td>True 2</td>
<td>1986/Takeda et al</td>
</tr>
<tr>
<td>4</td>
<td>True 2</td>
<td>1988/Idezuki et al</td>
</tr>
<tr>
<td>5</td>
<td>True 1 (thickened)</td>
<td>2004/Sakota et al</td>
</tr>
<tr>
<td>6</td>
<td>True 2 (divided at the lower portion)</td>
<td>2007/Onizuka</td>
</tr>
<tr>
<td>7</td>
<td>True 2</td>
<td>2007/Okada et al</td>
</tr>
<tr>
<td>8</td>
<td>False 0</td>
<td>1965/Tange</td>
</tr>
<tr>
<td>9</td>
<td>False 0</td>
<td>1985/Marumo et al</td>
</tr>
<tr>
<td>10</td>
<td>False 0</td>
<td>1988/Idezuki et al</td>
</tr>
<tr>
<td>11</td>
<td>False 0</td>
<td>1996/Hoshino et al</td>
</tr>
</tbody>
</table>

In 6 cases of true median cleft lip, 2 upper labial frenums were observed. The other case had a single, thickened upper labial frenum. None of the 4 false median cleft lip cases had an upper labial frenum.
The definition of the upper labial frenum also deserves consideration. The New Cyclopedic Medical Dictionary defines the term as "the vertical fold running at the median line (between the left and right maxillary incisors) between the oral vestibular mucosa and the frontal mucosa of the alveolar process." And the insertion site is known to vary with age.

Taking these facts into consideration, we regarded in this study only folds at cleft lips that compared with the adjacent vestibular mucosa of the upper lip, and the insertion sites are obviously lower facing toward the front of the alveolar process as the upper labial frenums. We excluded the folds made by pulling in examination and bandlike tissue at cleft borders inserted into the bone usually observed in cleft lip.

The shape of the upper labial frenum has not yet been discussed as one of the characteristic findings to differentiate true and false median cleft lips. We developed a hypothesis that true median cleft lip sometimes has 2 upper labial frenums, whereas false median cleft lip has no upper labial frenum. All previous reports in Japan supported our hypothesis. One may think that the presence of nasal columella and septum provides a sufficient condition for the clinical differentiation between true and false median cleft lips. However, the upper labial frenum was not observed in our case of right cleft lip associated with holoprosencephaly (Patient 3).

These finding interestingly suggest that the presence of holoprosencephaly, rather than the nasal columella and septum, should more specifically indicate the possibility of an upper labial frenum defect. Although it would be a repetition of the previous

**TABLE 2.** Concept of True and False Median Cleft Lips

<table>
<thead>
<tr>
<th>Appearance</th>
<th>True Median Cleft Lip</th>
<th>False Median Cleft Lip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
<td>Failure of fusion failure of both medial nasal processes in the embryonic period</td>
<td>Tissue defect</td>
</tr>
<tr>
<td>Symptoms</td>
<td>No brain malformations, increased interorbital distance, split nose, widened nose wing, and rounded nose tip</td>
<td>Brain malformations, increased interorbital distance, flat external nose without midportion of the lip, nasal columella, nasal septal cartilage, and midfacial bone defect</td>
</tr>
</tbody>
</table>

**TABLE 3.** Demyer and Kumagai Classification of Holoprosencephaly

<table>
<thead>
<tr>
<th>Classification</th>
<th>Facial Type</th>
<th>Facial Feature</th>
<th>Skull and Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Cyclopia</td>
<td>A single eyeball or partially split eyeball in a single orbit and proboscis instead of the nose</td>
<td>Microcrania and alobar holoprosencephaly</td>
</tr>
<tr>
<td>II</td>
<td>Ethmocephaly</td>
<td>Extremely short interorbital distance, but separated. Proboscis-shaped nose. Small skull and face. Defected midportion of the jaw, nasal septum, bone, and turbinates</td>
<td>Microcrania and alobar holoprosencephaly</td>
</tr>
<tr>
<td>III</td>
<td>Cebocephaly</td>
<td>Short interorbital distance, flat and incomplete nose in normal position, flat nose root with slightly elevated nose tip, and incomplete philtrum. No median cleft lip</td>
<td>Usually has alobar holoprosencephaly and microcrania</td>
</tr>
<tr>
<td>IV</td>
<td>With median cleft lip</td>
<td>Short interorbital distance, flat nose, defected philtrum, midportion of the jaw, nasal septum, and abnormal ethmoidal horizontal plate</td>
<td>Usually has alobar holoprosencephaly, microcrania, and sometimes trigonocephaly</td>
</tr>
<tr>
<td>V</td>
<td>With median philtrum-premaxilla angle</td>
<td>Short interorbital distance, flat nose, bilateral, and sometimes unilateral cleft lip</td>
<td>Microcrania, sometimes trigonocephaly, and semilobar or lobar holoprosencephaly</td>
</tr>
<tr>
<td>VI</td>
<td>Normal</td>
<td>Normal face and short interorbital distance</td>
<td>Frequent trigonocephaly, and semilobar or lobar holoprosencephaly</td>
</tr>
</tbody>
</table>
report, we had considered 2 different surgical techniques for Patient 1 (Fig. 7). These were simple closure for a cleft from fusion failure and an extension flap for a tissue defect. Regarding it as true median cleft lip, simple closure was performed, producing a good result with a less prominent groove at the lower nasal columella. Our hypothesis is expected to help differentiate equivocal cases such as patient 1 and clarify the pathogenetic mechanism of the intermediate type of median cleft lip.

CONCLUSIONS
Based on our experience of median cleft lip cases, we developed a hypothesis that true median cleft lip sometimes has 2 upper labial frenums, whereas false median cleft lip has no upper labial frenum. All previous reports in Japan supported our hypothesis. It is thought that the shape of the upper labial frenum can help differentiate the intermediate type of the median cleft lip which cannot be clearly classified as true or false.

REFERENCES