Median Cleft of the Lower Lip and Mandible: Case Reports, a New Embryologic Hypothesis, and Subdivision

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Median clefts of the lower lip and mandible are rare. In the literature so far, about 62 cases have been described. In addition, three more patients are presented here. These cases show a broad variation in the severity of this deformity, ranging from a simple notch in the vermilion to a complete cleft of the lip involving the tongue, the chin, the mandible, the supporting structures of the median of the neck, and the manubrium sterni.

Several hypotheses concerning the pathogenesis of median clefts of the lip and mandible have been proposed. Most authors consider it to be a failure of fusion of the first pair of branchial arches or failure of mesodermal penetration into the midline.

From our embryologic point of view, however, instead of paired branchial arches, only one first branchial arch develops during the early embryonic period ($\leq$17 mm crown-rump length). Within this first branchial arch, two mandibular processes grow out, separated by a groove in the median. These mandibular processes do not fuse but merge during the late embryonic period ($\geq$17 mm to $\leq$60 mm crown-rump length). In the same developmental period, there is formation of the lip and the alveolar process and the anlage and outgrowth of one membrane bone center in each mandibular process, resulting in the formation of the mandible with its symphysis.

As a consequence of the preceding, we propose the following subdivision of the median clefts of the lip and/or mandible: Hypoplasia of the mandibular processes during the early embryonic period will lead to the severest cleft of the mandible extending into the neck. During the late embryonic period, the less severe median clefts will develop. Disturbances of the outgrowth of bone centers of the mandible, resulting in nonformation of its symphysis, cause clefting of the mandible with involvement of all related soft tissues. Defects in the merging process produce just a notch of the vermilion or a higher cleft of the lower lip with or without involvement of the alveolar process of the mandible.

In conclusion, the variety of the clefts in the median of the lower lip and/or mandible as well as the low rate of incidence can be explained by the embryologic hypothesis proposed here. (*Plast. Reconstr. Surg.* 97: 313, 1996.)

Median clefting deformities of the lower lip and/or mandible are rare congenital anomalies. The first report was by Couronné.[1] In 1966, Monroe[2] conducted a comprehensive review of the literature and listed a total of 26 cases. Fujino et al.[3] produced an update in 1970 in which they described a total of 35 subjects. The last overview emanated from Rey et al.[4] in 1982. At this moment, a total of about 62 cases are available in the literature. In our clinic, 2 more patients with this clefting deformity have been seen in the last 10 years. We describe here the features of our patients and of one more patient of Dr. Denys Montandon.

Overall, there is a broad variation in the severity of this failure, ranging from a simple notch in the vermilion[5] to a (complete) cleft of the lip involving both the tongue and the mandible,[6–14] the chin,[15–20] and supporting structures of the median of the neck and the manubrium sterni.[21–23]

Several hypotheses concerning the pathogenesis of this clefting deformity have been proposed in the literature. Most authors consider it to be a failure of fusion of the first pair of branchial arches[4–6,11,13,15,17,21] or a failure of mesodermal penetration into the midline,[3,8,9,14,18] i.e. merging.[24] Others suggest external factors such as position in utero.[7,20]

External factors, as indicated in the last theory, can easily be excluded because of the fact that the localization of the clefting deformity of the mandible concerns the median in all cases described. In contrast, fusion and merging of swellings are normal developmental processes

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during embryogenesis.[24,25] According to Smits-van Prooije et al.[26] and Vermeij-Keers et al.,[25,27] the fusion process can be subdivided into three phases: (1) outgrowth of swellings (mesodermal cores covered by an epithelium), (2) apposition and adhesion of these swellings with interposition of a double-layered epithelial plate, and (3) disappearance of that plate by programmed cell death (apoptosis) resulting in fusion of the mesodermal cores of the swellings. Examples of this fusion process concern the formation of the primary and secondary palates.

During outgrowth of the first pair of branchial arches, however, such an epithelial plate has never been observed in the median. Therefore, it has been stated that instead of the first branchial arches,[28–31] there is only one arch with two mandibular processes (swellings) separated by a groove in the median.[25,32] This groove continues in the occipital direction in the body of the future tongue, also a derivative of the mandibular processes, and will disappear by merging.[24,29]

It is generally accepted that disturbance of the fusion process causes common clefting deformities such as complete clefts of the lip and alveolar process of the upper jaw and those of the soft and hard palates.[27] Other clefts of the upper jaw, like Tessier's cleft numbers 4 and 5,[33] and clefts of the mandible, however, are rare, and therefore, it is most likely that additional morphogenetic processes, such as formation of the lip and alveolar process and the differentiation of the mesoderm into bone centers and musculature, play a key role in these clefting deformities.[32,34]

In view of the preceding, all cases available in the literature and those presented here with clefting deformities of the lower jaw have been evaluated concerning the involvement of the lip, tongue, floor of the mouth, alveolar process, and basis of the mandible, chin, hyoid, and median of the neck up to the sternal corpus. On the basis of these clinical and embryologic data, a new hypothesis and subdivision concerning median clefts of the lip and mandible will be proposed. Possible associated anomalies are congenital heart deformities,[2,15–17,22,23] cleft palate,[2,3,5,12,16,18] facial anomalies (such as submental epidermoid cysts,[11,12] hemifacial microsomia,[7] Pierre Robin anomaly,[5] eye and ear deformities[3,7,16,22,23]), hand anomalies[2,10] (such as syndactyly, brachydactyly, and polydactyly), foot deformities[10,16] (such as club foot and ectrodactyly), and chromosomal aberrations.[2,4] None of these anomalies is specific. Some of these associated anomalies are seen in our patients as well.

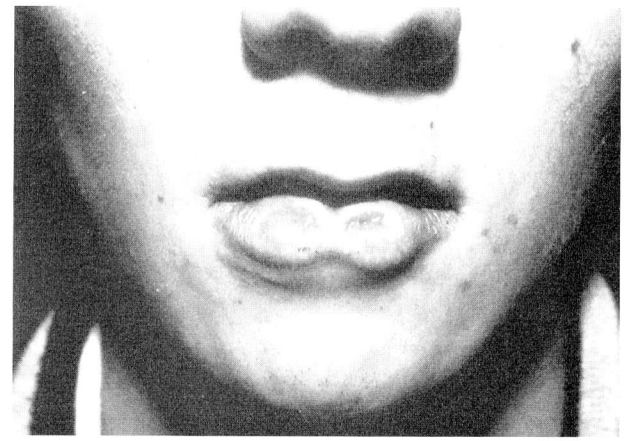

FIG. 1. *Case 1.* Before operation; a simple notch in the vermilion of the lower lip. This deformity mimicks lower lip pits. *(The photograph is printed with special permission of Dr. Montandon.)*

CASE REPORTS

The mildest form of cleft lower lip presents with a hardly noticeable dimple in the lower lip.

Case 1

This patient presented to Dr. Denys Montandon, of Geneva, several years ago. This case represents the least severe form of cleft lower lip. Only a small notch in the vermilion of the lower lip is seen (Fig. 1). The alveolar process and the basis of the mandible were intact; there was no hypodontia. This deformity mimicked lower lip pits.

Before and during operation, however, no cysts or sinuses were found. The deformity was treated with a Z-plasty (Fig. 2).

More severe forms of clefts in the lower lip present with ankyloglossia and an extension of the cleft through the mandible.

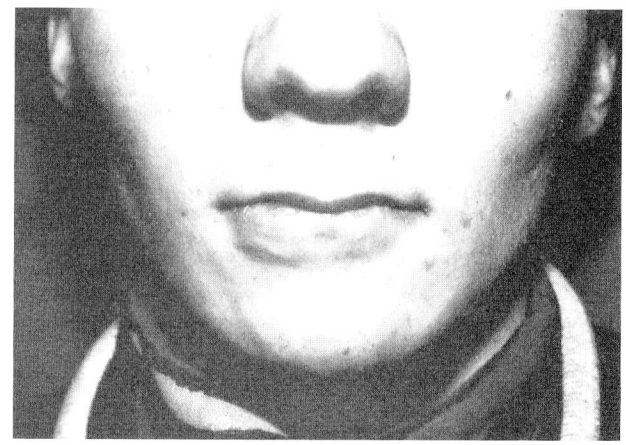

FIG. 2. *Case 1.* After operation; a Z-plasty has been performed. *(The photograph is printed with special permission of Dr. Montandon.)*

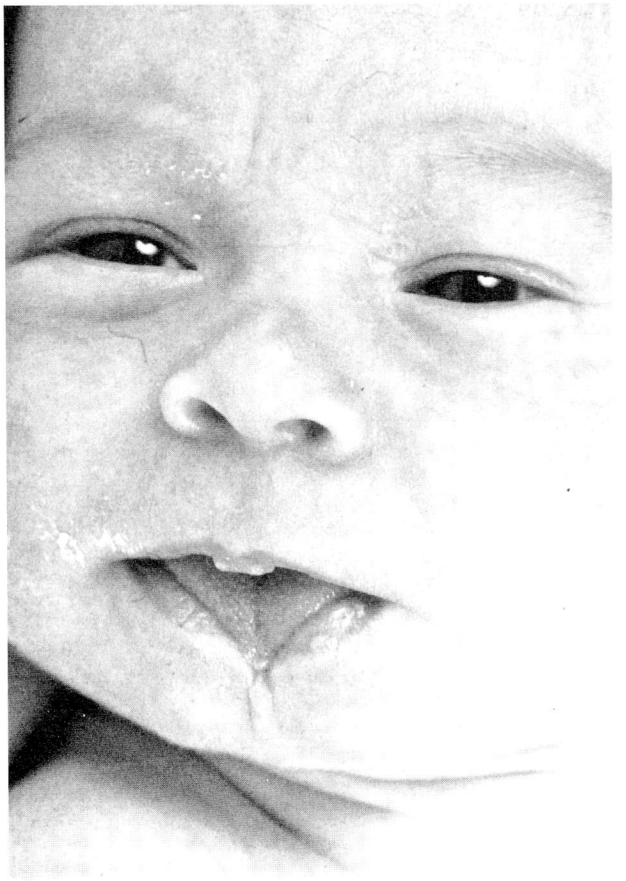

FIG. 3. *Case 2.* One week old, in frontal view. Complete cleft of the lower lip and mandible with ankyloglossia.

Case 2

B.K., a female patient, was born on March 30, 1983, after a normal gestation of 37.5 weeks. She weighed 3200 gm and was a first-born child. The pregnancy had been uneventful. The mother had known exposure neither to medication nor to radiation. There was no family history of congenital anomalies. The patient was admitted to Sophia Childrens Hospital on April 19, 1983.

On admission, the child demonstrated a complete cleft of the lower lip, with an ankyloglossia; the tethered tongue was attached to the vermilion border of the cleft lip (Figs. 3 and 4). The alveolar process and the basis of the mandible also showed a complete cleft. The contour of the upper face and head was normal, as were the structures of the neck, including the hyoid and sternum. Furthermore, physical examination revealed severe cardiac anomalies, as an univentricular heart, tricuspidalis atresia, a double-outlet right ventricle, and a coarctatio aortae. An echo of the skull and brain showed agenesis of the corpus callosum. There were no anomalies seen in the abdomen or extremities. X-rays of the skull are, unfortunately, not available. Examination of the chromosomes showed a normal female 46XX karyotype. Despite carefully controlled medical treatment, including an operation for the coarctatio aortae, the child failed to thrive and died of heart failure on May 30, 1983. No plastic surgical operations were performed on her.

The severest cleft that we have seen in our patients includes the lower lip, the mandible, the chin, and a contracture of the neck.

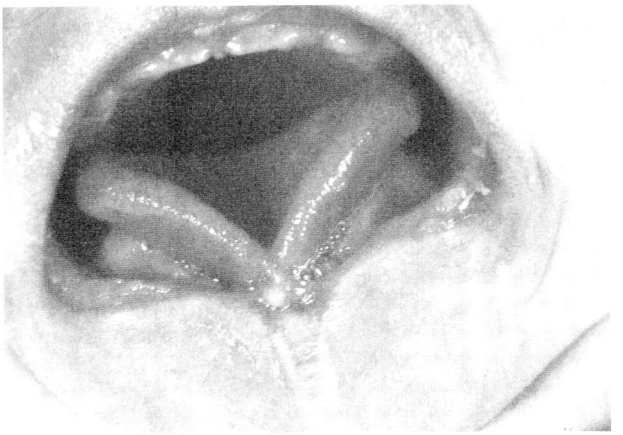

FIG. 4. *Case 2.* Detail of the deformity. The tongue is not cleft but attached to the lip and mandible.

Case 3

A.B., a girl, was born on July 17, 1992, after a normal gestation of 40 weeks. She weighed 3080 gm and was a first-born child; the pregnancy had been uneventful. The mother used labetalol (an antihypertensive drug), 300 mg/day, from long before to somewhat after her pregnancy. No teratogenic effects of this drug are known.[5,9] There was no known exposure to radiation during pregnancy, and there was no family history of congenital anomalies. The girl was admitted to the Sophia Childrens Hospital on July 31, 1992.

On admission, the child demonstrated a complete cleft of the lower lip, chin, and alveolar process and basis of the mandible. Furthermore, she had an ankyloglossia, i.e., a tethered tongue, attached to the vermilion border of the lower lip, and a contracture of the neck (Figs. 5 and 6). The contour of the upper face and head was normal. The hyoid and sternum were intact. There were no anomalies found in the thorax, the abdomen, or the extremities. Radiographic investigation confirmed agenesis of the symphysis mandibulae. Esophageal-stomach passage was normal, as was an echo of the skull. Examination of the chromosomes showed a normal 46XX karyotype. The child was operated on on October 5, 1992 (Figs. 7 to 9).

The contracture of the neck was released by excision of a fibrinous chord and a Z-plasty. The ankyloglossia was corrected; the tongue was released, and the "bifid" part was closed. The two ends of the mandible were approximated with absorbable sutures in order to facilitate closure of the skin. Further operations will be necessary in the future. We are planning to close the mandibular gap when the child is about 10 years old, in order to preserve growth of the mandible and teeth. However, in a regular check in our outpatient clinic, we found that both edges of the cleft mandible were crossing, so we are forced to perform an osteosynthesis of the mandible in the near future.

DISCUSSION

Clinical Data

All patients described here and in the literature showed defects in the median of the lower lip. In addition, other derivatives of the first branchial arch, such as the alveolar process and basis of the mandible, chin, and tongue, can be

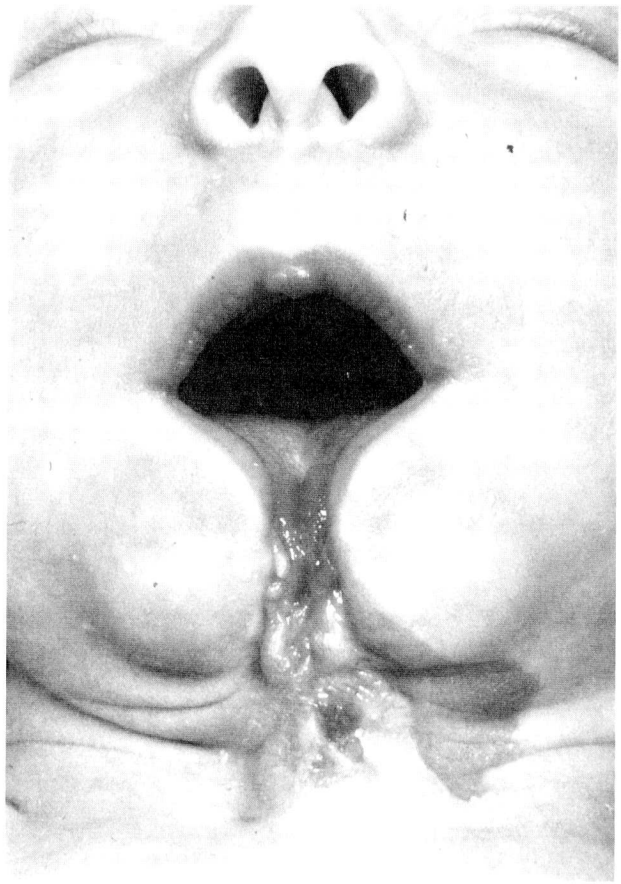

FIG. 5. *Case 3.* One week after birth, in frontal view. Complete cleft of the lower lip, chin, and mandible, ankyloglossia, and chord with contracture of the neck. The triangular zone left of the chord in the neck is caused by irritation from saliva. It disappeared spontaneously.

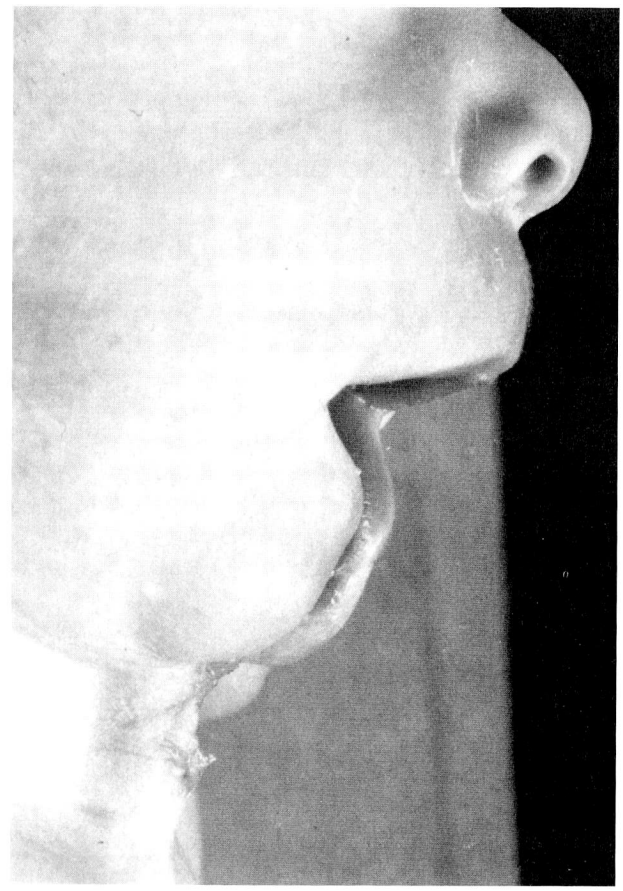

FIG. 6. *Case 3.* In lateral view. The chord with contracture of the neck is clearly visible.

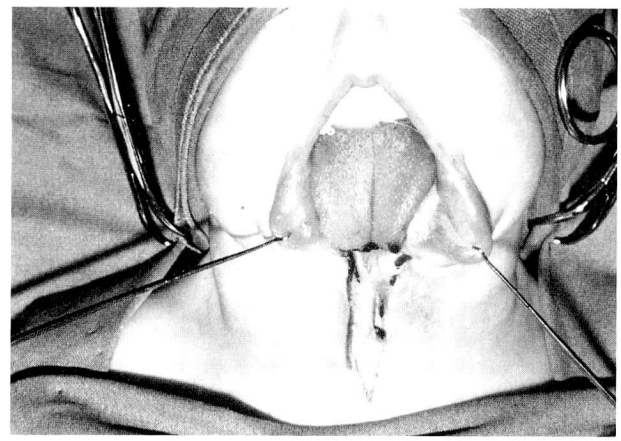

FIG. 7. *Case 3.* Preoperative view with outlining of the contracture of the neck.

involved in these median clefts, as seen in two of our subjects. Only three patients mentioned in the literature showed the most severe cleft, including the tongue and the floor of the mouth and extending in the median of the neck up to the sternum. In addition, the hyoid and the manubrium sterni can be agenetic.[21–23]

Embryologic Data

It is generally accepted that disturbances taking place early during embryogenesis cause more severe congenital malformations than those taking place during later developmental stages. This statement, however, does not apply to all the clefting deformities in the median of the mandible, as will be stipulated hereafter.

In brief, the development of the head and neck area can be subdivided into an early ($\leq$17 mm crown-rump length) and late ($\geq$17 to $\leq$60 mm crown-rump length) embryonic period.[25] During the early period, i.e., the first 7 weeks of development, just rostral of the buccopharyngeal membrane and bilateral of the outflow tract of the heart, both the mandibular processes forming the first branchial arch are visible in 8 to 10 somite human embryos. They are separated from each other by a shallow groove in the median, i.e., the intermandibular groove, situated in front of the outflow tract of the heart (Fig. 10). Therefore, the basis of the interman-

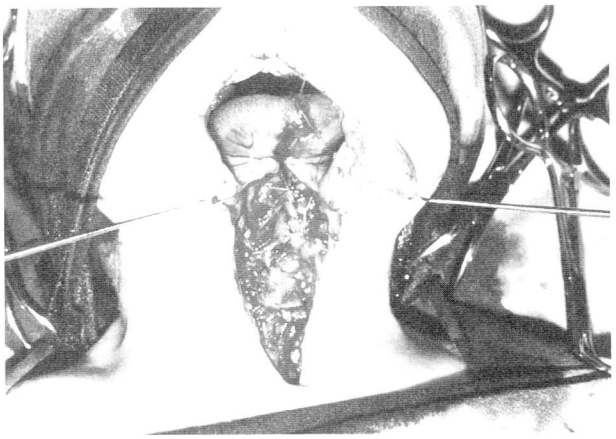

FIG. 8. *Case 3.* Perioperative view after excision of the neck chord and release of the tongue.

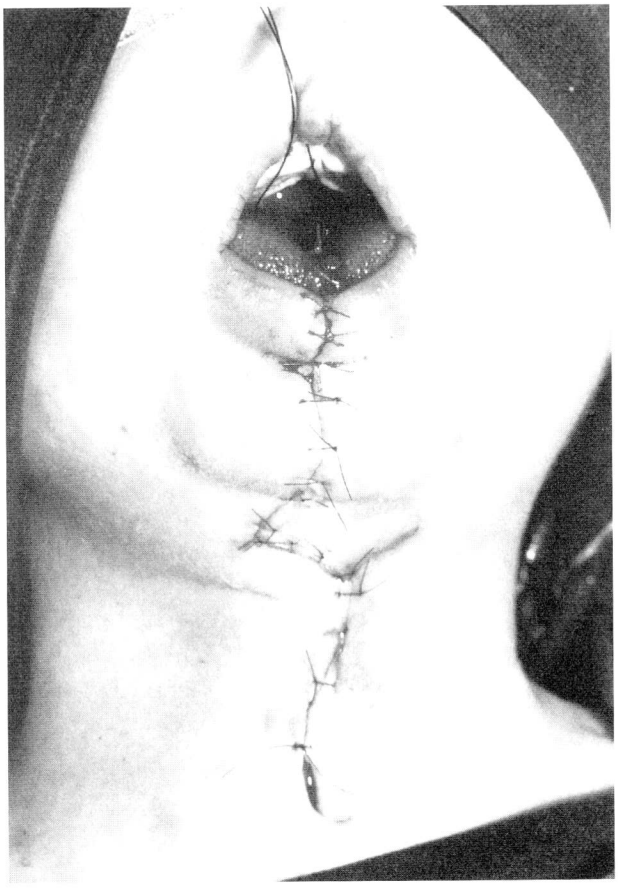

FIG. 9. *Case 3.* Final result after the operation.

dibular groove coincides with the cranial part of the future sternum and thoracic wall.

Subsequently, these processes grow out in rostral and cranial directions and move away from the heart without fusion in the median. The remaining otherwise paired branchial/pharyngeal arches exhibit neither a groove nor a fusion process in the median of the neck. Bilaterally, they show their ectodermal grooves,

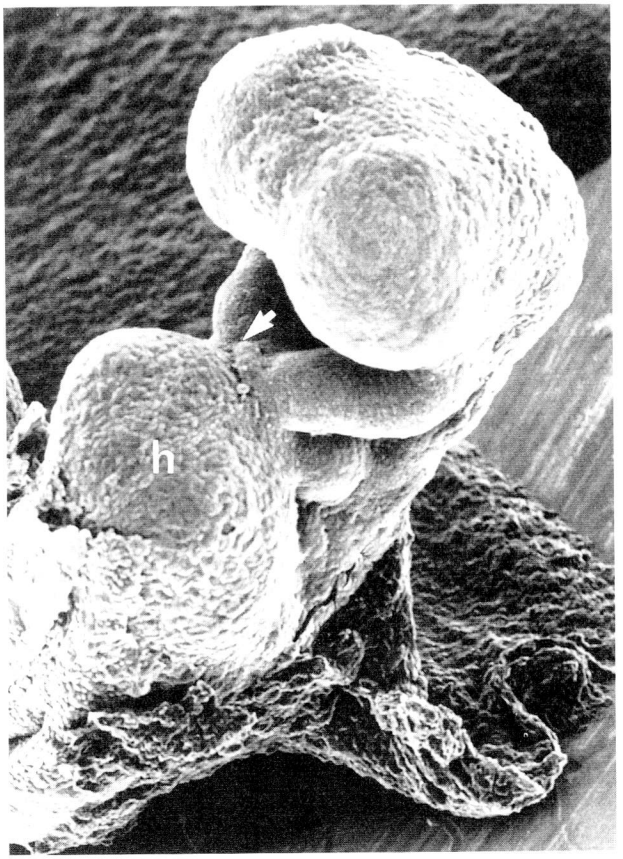

FIG. 10. Murine embryo in the early embryonic period, oblique view. Arrow points at the intermandibular groove between both mandibular processes, localized rostrally of the heart (*h*).

grow out in a caudal direction, and fuse with each other and with the retrobranchial ridge.[27]

During this outgrowth of the mandibular processes, including the intermandibular groove, the floor of the stomodeum has been formed with the anlage of the body of the tongue. This anlage is indicated by three swellings: rostrally, paired lateral swellings separated by the intermandibular groove, and occipitally, the unpaired tubercle, i.e., the tuberculum impar, wedged in between the lateral swellings.[28] After rupture of the buccopharyngeal membrane in human embryos of 2.5-mm crown-rump length (about 23 somites), by apoptosis, the stomodeum communicates with the pharynx.[37] The floor of the pharynx consists of the other branchial arches separated from each other by transverse grooves. They form the root of the tongue.[28,29] In the median of the pharynx, a groove or fusion of these arches has never been observed.

Within the mesodermal compartment of the mandibular processes, Meckel's cartilage will develop at the end of the early embryonic pe-

riod. The late embryonic period (i.e., from 7 weeks up to the end of the first trimester of pregnancy) is characterized by merging of the mandibular processes (i.e., squeezing out of the intermandibular groove), formation of the lower lip and alveolar process of the mandible, and development (17 mm crown-rump length) and outgrowth of one membrane bone center in each mandibular process in substitution for Meckel's cartilage. In other words, Meckel's cartilage does *not* convert into the definitive mandible.[28] Each bone center develops centrally in the core of the mandibular process and grows out in a rostral as well as occipital direction, enclosing both Meckel's cartilage and the inferior alveolar nerve. Simultaneously, differentiation of the musculature of the mandibular processes takes place. The symphysis mandibulae has been formed in embryos of about 25-mm crown-rump length and will ossify during the first year postnatally.[27]

Conclusions, Hypothesis, and Subdivision

From the normal embryologic processes described above, it is most likely that hypoplasia of the mandibular processes during the early embryonic period causes the most severe clefting deformity of the mandible, with a bifid tongue and/or ankyloglossia, and extension of the cleft into the cranial half of the thoracic body wall. Agenesis of the cranial bone centers of the sternum and lack of ossification of the corpus of the hyoid result during the late developmental period. Disturbances of the outgrowth of both bone centers of the definitive mandible, resulting in nonformation of its symphysis, cause clefting of the mandible during the late embryonic period. And as a consequence, all soft tissues, including the ectoderm and musculature of the tongue, lower lip, and chin, can be more or less involved in this clefting deformity, i.e., according to Vermeij-Keers and van der Meulen a secondary cleft.[32,34]

In the literature, about 50 percent of cases have been described with a cleft of the tongue, i.e., a bifid tongue, in all patients except 4 combined with ankyloglossia. A bifid tongue can be explained as a persistent intermandibular groove, i.e., a merging defect of the tongue. Careful study of the photographs of the patients described in the literature reveals that many so-called bifid tongues actually are not cleft at all but show an "open book" deformity, caused by the ankyloglossia, mimicking a cleft.

In the slightest clefting form, the lower lip shows just a notch of the vermilion or a higher cleft of the ectoderm and underlying musculature of the lip but without or with slight involvement of the alveolar process of the mandible, such as agenesis of the medial incisors. Such cases can be explained by insufficient outgrowth of the lip, most probably due to incomplete merging of the mandibular processes. These less severe clefts develop in the same embryonic period as the disturbances of outgrowth of the bone centers of the mandible. Therefore, the statement, "the sooner the defect in embryogenesis, the severer the deformation," does not count for all median clefting deformities of the mandible.

Recommendations

In view of the preceding, it will be clear that these clefting deformities are very rare and appear in many different grades. In order to describe and classify the extension of the defect, attention should be paid to the following aspects:

Involvement of Soft Tissues. Clefts of the *lower lip*; these can be partial or up to the mentolabial crease. The cleft may extend through the *chin* as a whole or may end only a few millimeters below the vermilion border. Involvement of the *tongue*; this can be a real bifid tongue or an "open book" deformity caused by ankyloglossia.

Involvement of Bony Structures. The alveolar process and/or basis of the *mandible* can be affected. The *hyoid* may be cleft or even absent. The cleft can extend through the *neck*; cysts, chords, or contractures may accompany the cleft. Even the *sternum* may be involved in the cleft; the manubrium and the upper part of the corpus can be affected. A roentgenogram and/or a CT scan is indispensable in order to measure the width of the cleft of the mandible.

Associated anomalies occur quite often.

In the follow-up it is important to monitor the development of the *dentition*. It is clear that the therapy fully depends on the findings during examination. In general, most authors tend to free the tongue and close the lower lip as soon as possible. This is logical in view of the functions of the tongue and lip in sucking and swallowing and, in later stages, in speech.

The discussion about the timing of the treatment of the mandibular defect is not closed yet. Most authors prefer to wait until "later stages" (usually about 8 to 10 years of age) in order to prevent damage of the tooth buds during operation of the mandible. On the other hand,

careful osteosynthesis of the basis of the mandible (1) cannot harm these buds, (2) may be necessary (as in our third case), (3) may be advantageous for the development of the teeth, and (4) may be of benefit for a normal outgrowth of the upper and lower jaws in relation to each other. Again, this timing also depends on the severity of the clefting deformity. The cleft may be so wide that it is impossible to close the defect of the mandible in an early stage.

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REFERENCES

1. Couronné (of Rouen), A. Observation d'un bec-de-lièvre, compliqué de fentes à la voûte palatine. *Ann. Clin. Soc. Méd.-Prat. Montpellier* (2s) 6: 107, 1819.
2. Monroe, C. W. Midline cleft of the lower lip, mandible, and tongue with flexion contracture of the neck: Case report and review of the literature. *Plast. Reconstr. Surg.* 38: 312, 1966.
3. Fujino, H., Kyoshoin, Y., and Katsuki, T. Median cleft of the lower lip, mandible, and tongue with midline cervical cord: A case report. *Cleft Palate J.* 7: 679, 1970.
4. Rey, A., Vazquez, M. P., Jennequin, P., and Marie, M. P. Fentes labio-mandibulaires. A propos d'un cas. Revue de la littérature. *Rev. Stomatol. Chir. Maxillofac.* 83: 39, 1982.
5. Ranta, R. Incomplete median cleft of the lower lip associated with cleft palate, the Pierre Robin anomaly or hypodontia. *Int. J. Oral Surg.* 13: 555, 1984.
6. Keith, A. Congenital malformations of palate, face and neck. *Br. Med. J.* 2: 363, 1909.
7. Braithwaite, F., and Watson, J. A report on three unusual cleft lips. *Br. J. Plast. Surg.* 2: 38, 1949.
8. Ecker, H. A. Medial clefts of the lips. *Am. J. Surg.* 96: 815, 1958.
9. Millard, D. R., Jr., Lehman, J. A., Jr., Deane, M., and Garst, W. P. Median cleft of the lower lip and mandible: A case report. *Br. J. Plast. Surg.* 24: 391, 1971.
10. Iregbulem, L. M. Median cleft of the lower lip. *Plast. Reconstr. Surg.* 61: 787, 1978.
11. Surendran, N., and Varghese, B. Midline cleft of the lower lip with cleft of the mandible and midline dermoid in the neck. *J. Pediatr. Surg.* 26: 1387, 1991.
12. Chidzonga, M. M., and Shija, J. K. Congenital median cleft of the lower lip, bifid tongue with ankyloglossia, cleft palate and submental epidermoid cyst: Report of a case. *J. Oral Maxillofac. Surg.* 46: 809, 1988.
13. Marcadé, E., Babut, J. M., Pailheret, J. P., and Allouis, M. Fente médiane de la lèvre inférieure. *Ann. Chir. Plast.* 26: 148, 1981.
14. Martinot-Duquennoy, V., Bardot, J., and Magalon, G. Fente médiane de la lèvre inférieure. A propos d'une observation. *Ann. Chir. Plast. Esthet.* 36: 480, 1991.
15. Sherman, J. E., and Goulian, D. The successful one-stage surgical management of a midline cleft of the lower lip, mandible, and tongue. *Plast. Reconstr. Surg.* 66: 756, 1980.
16. Ashley, L. M., and Richardson, G. E. Multiple congenital anomalies in a stillborn infant. *Anat. Rec.* 86: 457, 1943.
17. Stewart, W. J. Congenital median cleft of the chin. *Arch. Surg.* 31: 813, 1935.
18. Abrahamsom, P. D. Bilateral congenital clefts of the lower lip. *Surgery* 31: 761, 1952.
19. Russel, A. G., and Staley, C. E. Congenital cleft mandible: Report of a case. *J. Oral Surg.* 19: 257, 1961.
20. Knowles, C. C., Littlewood, A. H. M., and Bush, P. G. Incomplete median cleft of the lower lip and chin with complete cleft of the mandible. *Br. Dental J.* 127: 337, 1969.
21. Morton, C. B., and Jordan, H. E. Median cleft of lower lip and mandible, cleft sternum and absence of basihyoid. *Arch. Surg.* 30: 647, 1935.
22. Davis, A. D. Medial cleft of the lower lip and mandible. *Plast. Reconstr. Surg.* 6: 62, 1950.
23. Park, S., and Takushima, A. Median cleft of the lower lip, mandible and manubrium: A case report. *J. Craniomaxillofac. Surg.* 21: 189, 1993.
24. Patten, B. M. *Human Embryology*, 2nd Ed. London: Churchill-Livingstone, 1953.
25. Vermeij-Keers, Chr., Mazzola, R. F., van der Meulen, J. C., Strickler, M., and Raphael, B. Cerebro-craniofacial and craniofacial malformations: An embryological analysis. *Cleft Palate J.* 20: 128, 1983.
26. Smits-van Prooije, A. E., Vermeij-Keers, Chr., Poelmann, R. E., Mentink, M. M. T., and Dubbeldam, J. A. The neural crest in presomite to 40-somite murine embryos. *Acta Morphol. Neerl. Scand.* 23: 99, 1985.
27. Vermeij-Keers, Chr., Hartwig, N. G., and De Water, R. Cell deposition and degeneration in relation to cleft lip formation. *J. Anat.* 173: 236, 1990.
28. Arey, J. B. *Developmental Anatomy*, 7th Ed. Philadelphia: Saunders, 1965.
29. Hinrichsen, K. V. *Human Embryologie: Lehrbuch und Atlas der Vorgeburtlichen Entwicklung des Menschen*. Berlin: Springer-Verlag, 1990.
30. Moore, K. L., and Persaud, T. V. N. *The Developing Human: Clinically Oriented Embryology*, 5th Ed. Philadelphia: Saunders, 1993.
31. Larsen, W. J. *Human Embryology*. New York: Churchill-Livingstone, 1993.
32. Vermeij-Keers, Chr. Craniofacial Embryology and Morphogenesis: Normal and Abnormal. In M. Stricker, J. C. van der Meulen, B. Raphael, and R. Mazzola (Eds.), *Craniofacial Malformations*. Edinburgh: Churchill-Livingstone, 1990.
33. Tessier, P. Anatomical classification of facial, craniofacial and latero-facial clefts. *J. Maxillofac. Surg.* 4: 69, 1976.
34. van der Meulen, J. C. Classification of Craniofacial Malformations. In M. Stricker, J. C. van der Meulen, B. Raphael, and R. Mazzola (Eds.), *Craniofacial Malformations*. Edinburgh: Churchill-Livingstone, 1990.
35. Gerard, J., Blazquez, G., Lardoux, H., Beausejour, B., Faurie, C., Rousset, D., and Flouvat, B. Action de deux beta-bloquants sur l'hypertension arterielle pen-

dant la grossesse. Resultats d'une etude prospective sur 56 femmes enceintes hypertendues traitees par atenolol et labetalol. *J. Gynaecol. Obstet. Biol. Reprod. Paris* 12: 891, 1983.

36. Gerard, J., Blazquez, G., Mounac, M., Giraud, P., Jeuffroy, A., and Lardoux, H. Traitement de l'hypertension arterielle gravidique par un alpha-betabloquant: 58 cas traites par labetalol. *Rev. Fr. Gynaecol. Obstet.* 79: 713, 1984.
37. Poelmann, R. E., Dubois, S. V., Hermsen, C., Smits-van Prooije, A. E., and Vermeij-Keers, Chr. Cell degeneration and mitosis in the buccopharyngeal membranes in the mouse embryo. *Anat. Embryol.* 171: 187, 1985.