

The Cervical Vertebrae as a Factor in the Etiology of Cleft Palate

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As knowledge about the cleft lip and palate anomaly increases, it becomes apparent that there may be a number of potential etiological factors.

Curtis and Walker (3) have established that cleft palate is a separate entity from cleft lip either with or without cleft palate. Cleft lip appears to have a strong genetic basis (probably involving two recessive genes) and also an environmental component. Cleft palate, however, seems to be primarily due to environmental factors, with a limited genetic etiology.

Recent studies have revealed that many teratogenic agents are capable of causing clefts of the lip and palate in animals (5). Currently, emphasis has been on abnormalities in cellular metabolism induced by deficiencies in essential substances, excesses of normally occurring substances, or by the introduction of foreign substances. The older theories of mechanical interferences with development have received less attention.

There is evidence that individuals with clefts of the lip and palate have a high incidence of associated congenital anomalies (6, 9, 17, 20). These associated anomalies may be manifestations of one extensive primary defect, they may be distinct entities but with a common teratogenic agent, they may be secondary to a primary defect, or they may be distinct entities produced by different teratogenic agents.

A thorough study of the embryology of the primary and secondary palates and those structures in which associated anomalies occur might provide a basis for identifying clefts of different etiological types.

This study is an attempt to demonstrate the developmental relationship that exists between the vertebral column in the cervical region and the facial structures, and to relate this association to the etiology of cleft palate.

Sample

Records on 342 individuals with cleft lip and/or cleft palate were obtained from the Maxillo-Facial Clinic of the Hospital for Sick Chil-

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TABLE 1. Distribution of the sample according to sex and cleft-type.

	<i>Lip Only</i>	<i>Lip and Palate</i>		<i>Palate Only</i>	<i>Total</i>
		<i>Unilateral</i>	<i>Bilateral</i>		
Male	20	90	42	38	190
Female	18	44	25	65	152
Total	38	134	67	103	342

dren, Toronto. The sample consisted of children with either complete cleft lip and palate, complete cleft lip only, or complete cleft palate only. Age of subjects ranged from four to 19 years. The sex and cleft type distribution of the sample is shown in Table 1.

It is important to estimate whether this sample is representative of the cleft population. A bias may occur with reference to the more severe associated congenital anomalies, since children with such anomalies in addition to clefts are more likely, perhaps, to be referred to this hospital. The sample may, therefore, have a higher proportion of associated congenital anomalies than would a purely random sample.

The noncleft controls were obtained from the Burlington Orthodontic Research Centre in Burlington, Ontario. Since the incidence of vertebral anomalies in a normal population was expected to be very low, 800 controls were examined. The male:female ratio was approximately even. Another possible bias stems from the fact that attendance at the Burlington Centre was voluntary. There is the possibility, then, that children with severe neck deformities would not be brought to the centre by their parents, or if mental retardation was also associated, the children might be attending special schools in other parts of the province.

Racial or ethnic origins were very similar; the bulk of both samples trace their ancestry to the British Isles, most of the remainder are originally from Western Europe.

Thus both the cleft and noncleft samples are reasonably representative of the Ontario populations from which they were drawn, with a possible minor variance in incidence of severe vertebral anomalies.

Method

Standard cephalometric radiographs oriented in the lateral, antero-posterior, and oblique views were used for diagnosing anomalies of the vertebrae. Although cephalometric radiographs are not particularly suited for identifying vertebral anomalies in general, they are satisfactory for determining either absence of part or all of a vertebra or fusion between two or more vertebrae, and these are the essential characteristics with which this paper is concerned.

An arbitrary classification was devised based on the severity of the anomaly: a) *mild* conditions with no clinical significance, usually one

vertebrae was involved or there was fusion of only two vertebrae (Figure 1), b) *moderate* conditions which were of slight or moderate clinical significance with two or more vertebrae involved (Figure 2), and c) *severe* conditions with gross involvement of all or almost all of the cervical vertebrae. These conditions were reflected in a limitation of movement with a shortening of the neck (Figure 3).

Classification of the anomalies in this way had several advantages.

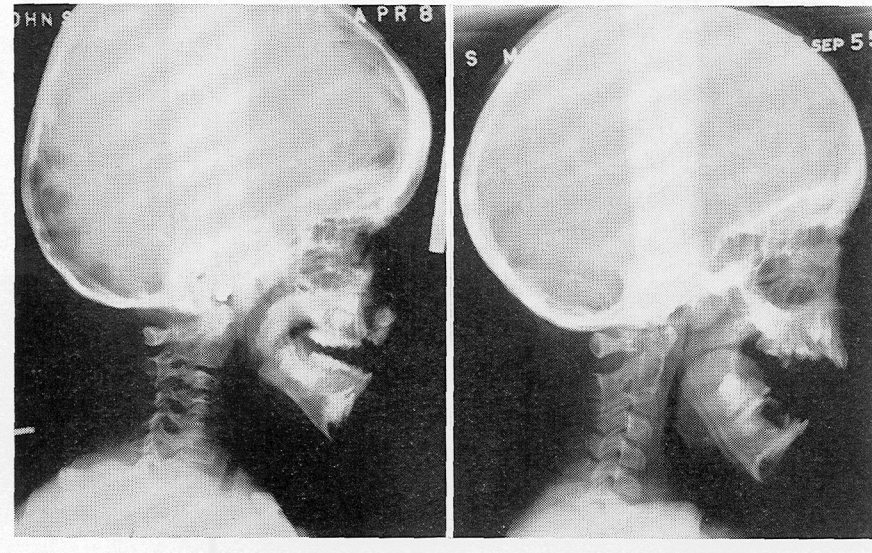


FIGURE 1. Two x-ray films showing mild vertebral involvement.

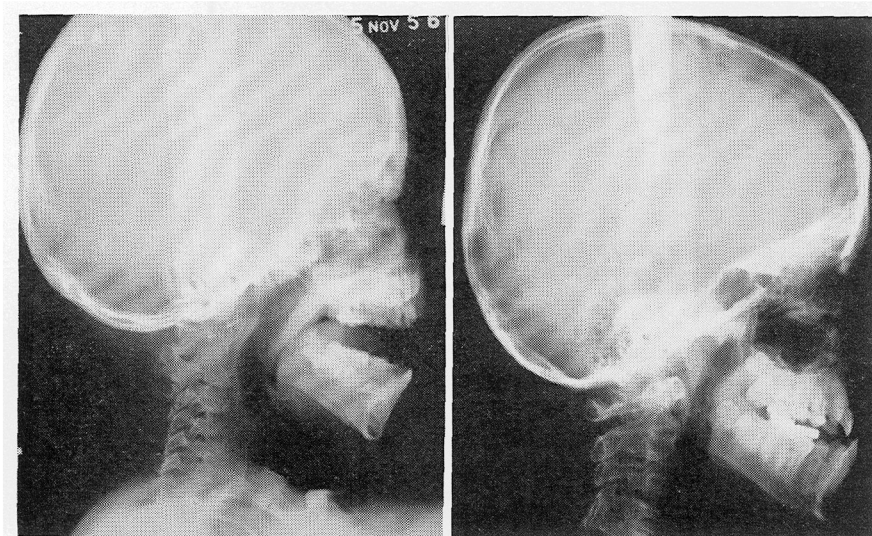


FIGURE 2. Two x-ray films showing moderate vertebral involvement.

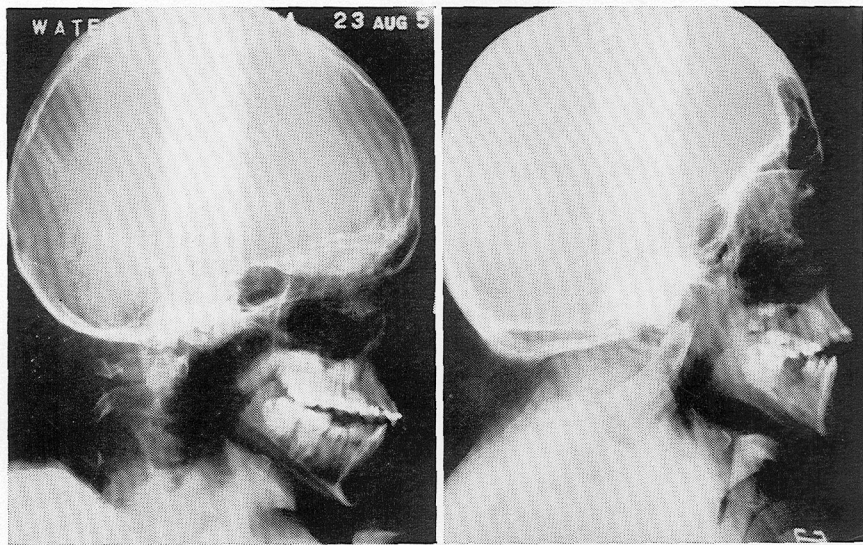


FIGURE 3. Two x-ray films showing severe vertebral involvement.

Not only the incidence but the degree of involvement in the two samples could be compared. More importantly, the quality of the x-rays and the difficulty in diagnosing the anomalies could lead to sizable errors in the determination of *mild* conditions and thus in the overall incidence. The *moderate* and *severe* conditions, however, were quite easily detectable and the data regarding these two types would be accurate.

Linear and angular cranial base measurements (Figures 4 and 5) were recorded for those individuals with vertebral anomalies to determine the effect of the malformation on the adjacent cranial base.

Findings

The number and type of anomalies identified in the cleft and noncleft samples are presented in Table 2. Statistical analysis revealed a highly significant difference between the incidence of vertebral anomalies in the cleft and in the noncleft samples, even though the incidence of mild anomalies was almost identical in the two samples. There was also a highly significant difference in the incidence of severe vertebral anomalies between the cleft palate group and the other cleft-type groups.

The findings with regard to size and configuration of the cranial base (Table 3) serve only to indicate trends because of the inadequacy in sample size and the complication of age and sex differences. However, a comparison with the values established for normal individuals (17) and those with clefts indicated that the ratios of basi-occiput to the remainder of the cranial base were considerably different. It was evident that the basi-occiput was defective in growth. The configuration of the

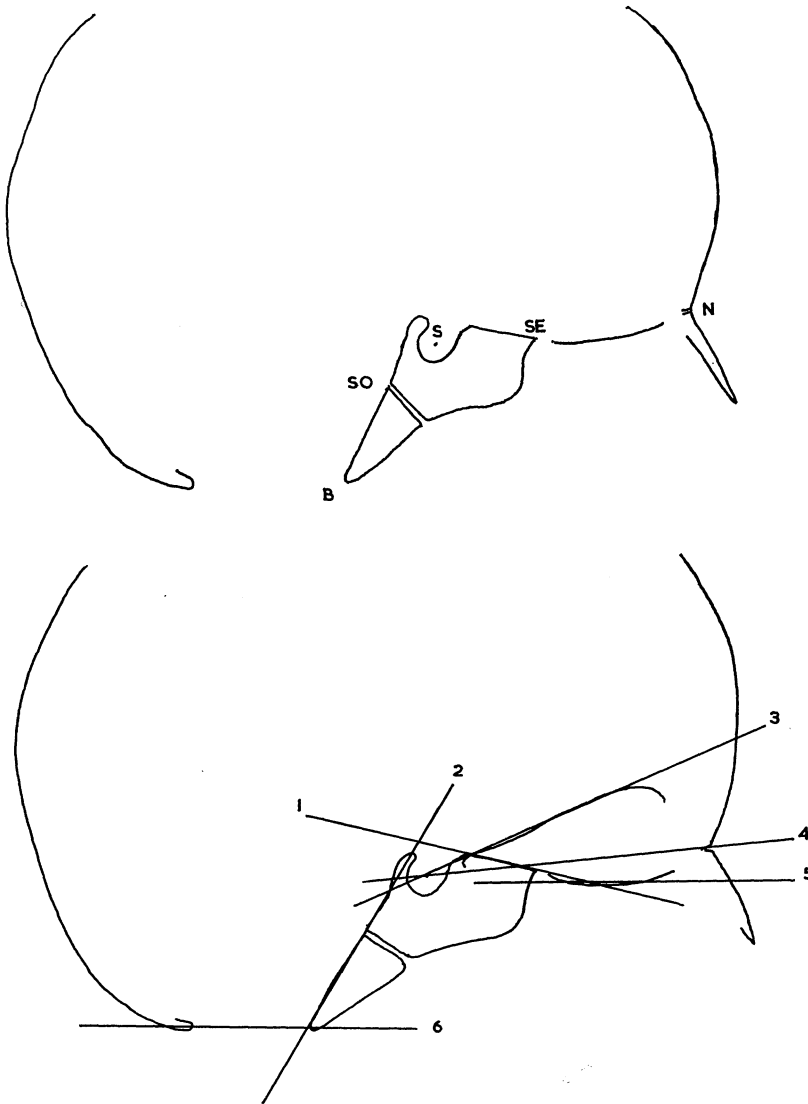


FIGURE 4. Diagram of the lateral view of the cranial base in the midline. Measurements were taken of the occipital bone (B-SO), and the combined length of the sphenoid bone (SO-S plus S-SE) and the ethmoid-nasal-frontal complex (SE-N). (B-basion, SO-spheno-occipital synchondrosis, S-sella turcica, SE-spheno-ethmoidal synchondrosis, N-nasion).

FIGURE 5. Angular relationships within the cranial base were indicated by measuring the angles formed by the intersection of clivus plane (2) with planum sphenoidale (1), orbital plane (3), SN plane (4), cribriform plane (5), and foramen magnum plane (6).

TABLE 2. Incidence of cervical vertebral anomalies by cleft-type.

	<i>N</i>	<i>Category</i>		
		<i>Severe</i>	<i>Moderate</i>	<i>Mild</i>
Lip Only.....	38	0	0	0
Palate Only.....	103	6	1	2
Lip and Palate				
Unilateral.....	134	1	3	0
Bilateral.....	67	0	0	1
Total Cleft.....	342	7	4	3
Noncleft.....	800	0	0	6

TABLE 3. Data for comparing occipital length, cranial base length, and the ratio between them for normal, lip and palate, palate only, Klippel-Feil syndrome, and moderate vertebral anomaly groups.

<i>Sample</i>	<i>Number</i>	<i>Mean Age</i> <i>(in years)</i>	<i>Occipital</i> <i>Length</i> <i>(SO-B)</i> <i>(in mm)</i>	<i>Remaining</i> <i>Cranial</i> <i>Base Length</i> <i>(N-SE-S-</i> <i>SO)</i> <i>(in mm)</i>	<i>Ratio</i>
Normal Children.....	80	9	28.1	85.4	1:3.0
Cleft Lip and Palate.....	34	8	27.8	83.6	1:3.0
Cleft Palate.....	37	8	26.2	81.1	1:3.1
Klippel-Feil Syndrome.....	8	9	23.7	82.6	1:3.5
Moderate Vertebral Anomalies.....	6	7½	23.5	80.0	1:3.4

cranial base was often unusual in these cases, but no consistent pattern of irregularity could be determined. The cranial vault appeared more distorted than the cranial base in most cases.

Discussion

One of the most severe anomalies of the cervical vertebrae is known as the Klippel-Feil syndrome. An extensive review of this condition has recently been published (8). The classic case presents an extremely short neck with limitation of movement and a low hairline. The cervical vertebrae are grossly abnormal, usually fused into an irregular column of bone. It is probable that the correct number of vertebrae are present but the fusion and abnormal morphology make it impossible to arrive at an accurate count.

Other anomalies are frequently associated with the Klippel-Feil syndrome and cleft palate has been noted among them. Fraser and Calnan (6), in their study of cleft lip and palate, noted four cases of Klippel-

Feil syndrome in a sample of 211 cases of cleft palate but found no cases of Klippel-Feil associated with cleft lip with or without cleft palate. Martin and Traube (11) presented three cases with cleft palate; Cohnsey (2) presented six cases, all with cleft palate. Ross (17) noted a high incidence of vertebral anomalies in individuals with clefts. It would appear, then, that severe vertebral anomalies of the Klippel-Feil type occurring in children with facial clefts are almost exclusively associated with clefts of the palate, and almost never with clefts of the lip. To explain this phenomenon requires an investigation of the embryology and teratology of the areas concerned.

It is currently accepted that there are narrow temporal limits within which most congenital anomalies are induced and that the limits vary with particular organ or tissue involved. Each organ has a 'critical' period of increased susceptibility to teratogenic agents, usually corresponding to the stage of rapid organization and differentiation of its cellular components. When two anomalies occur in the same individual, the organs frequently have a common 'critical' period; that is, the structures were affected by a single teratogenic agent when they were in a state of increased susceptibility to injury (22).

Initially, the somites that develop in the region of the future vertebral column and occipital area are identical (19). Vertebral rudiments can still be identified in the occipital region in the six-week embryo. Soon after, however, these segments are assimilated into the cranium and become the precursors of the basi-occipital bone.

If the severe vertebral anomalies arise early as mesenchymal defects, it might be expected that the occipital bone would also be involved. If, however, these anomalies occur later in embryonic life as fusion of originally separate elements, probably the occipital bone would not be involved since it would have become incorporated into the cranium. The findings in this study (a decrease in the size of the occipital bone) suggests an early development of severe vertebral anomalies. This has also been proposed by other investigators (7, 8, 16). Such is not necessarily the case for the less severe vertebral defects, which may occur later in embryonic life, or even in the post-natal period (1, 4, 18).

The 'critical' period for cleft lip has been shown to be earlier than for cleft palate (12, 14, 21) and the 'critical' period for severe vertebral anomalies appears to be even earlier than for cleft lip. Studies on animals (10, 13) have noted that vertebral anomalies occurred when embryos were treated several days before the time when clefts of the lip were usually produced. Thus the time factor cannot be implicated in the association of vertebral anomalies and cleft palate.

A functional developmental relationship which fits the observed data can be hypothesized between cervical vertebrae and facial structures.

In the eighth or ninth week of embryonic life the tongue lies between the vertically orientated palatal shelves. Shortly before the formation

of the secondary palate, the head is lifted from the pericardial region and the mandible and tongue drop, permitting the palatal shelves to meet and fuse in the midline. The lengthening of the neck is of particular importance to the change in head position. When the cervical vertebrae are grossly abnormal (as in Klippel-Feil syndrome) the neck remains short and the mandible may remain compressed against the chest, noted in a case reported by Noble and Frawley (15). Thus the tongue may continue to lie between the palatal shelves during the time when palatal closure would normally occur, and the result is a cleft palate. There would, of course, be no interference with the mechanism of normal primary palate (lip and alveolus) development. We have noted, incidentally, that individuals with the Klippel-Feil syndrome but with no cleft palate tend to have high palatal vaults; that observation supports the above hypothesis.

Vertebral anomalies classified here as being of moderate severity occur frequently in association with cleft lip and/or palate. No isolated mechanical factors are therefore apparent. This may be a case of a milder and more chronic teratogenic influence acting on a susceptible individual or it may be a case of some complex genetic mechanism.

If severe and moderate cervical anomalies occur more frequently in cleft individuals, mild defects would also be expected to show a higher incidence. Such was not the case. The cleft and noncleft groups had an almost identical incidence of mild defects. This may indicate that such vertebral anomalies develop after vertebral differentiation, perhaps even in the post-natal period.

Summary

A radiographic survey of 342 children with lip and palate clefts and 800 noncleft children revealed that severe congenital synostosis of the cervical vertebrae was frequently associated with isolated cleft palate. Moderate synostosis was associated with all types of cleft lip and palate, while mild anomalies occurred with about the same frequency as in the normal population. In the noncleft sample no severe or moderate anomalies were found. The hypothesis was advanced that failure in the development of the cervical vertebrae could interfere with normal palate formation.

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