Prevalence of cervical vertebrae anomalies in patients with cleft lip and palate

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Objective: To investigate the prevalence of cervical vertebral anomalies (CVA) in a group of patients presenting with cleft lip and palate (CLP) and to compare with a non-cleft population.

Material and methods: The sample comprised of 150 lateral cephalograms of non-syndromic patients with CLP and 150 non-cleft age-matched controls. The age range of both groups covered 6 to 20 years. An expert radiologist blinded to the cleft status evaluated the cephalograms for CVA and categorised them into normal, fusion, dehiscence and multiple cervical anomalies. The cleft group was subdivided according to the types of cleft (UCLP/ BCLP/ CPO) and gender (male/female). The CVA prevalence was compared between the cleft and non-cleft patients.

Results: The prevalence of CVA was 37.7% and 20.7% in cleft and non-cleft patients, respectively. The difference was statistically significant with a p-value <0.01. Of the types of clefts, a left UCLP had the highest prevalence of CVA (47.2%), with fusion (35.8%) most commonly seen. On comparing CLP with CPO, no significant variation was observed between the types of anomalies.

Conclusions: A high prevalence of CVA was observed in cleft patients compared with non-cleft subjects. The prevalence of CVA was similar between males and females. The practitioner should carefully evaluate the lateral cephalogram of CLP patients for CVA, which otherwise may remain undetected and lead to neurological symptoms later in life.

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Introduction

The lateral cephalogram is an essential diagnostic record routinely advised in orthodontic practice. Although the cervical vertebral maturation index is used to predict the growth status of patients,1 anatomical deviations in the morphology of the upper cervical spine may remain unrecognised. A lateral cephalogram offers significant diagnostic value in recording aberrations in the morphology of the cervical spine. Cervical vertebral anomalies can present with myelopathy, cause limitation in neck movement, muscular atrophy, and regional sensory loss.2 Early diagnosis of cervical vertebral anomalies (CVA) is critical in determining the risk of associated diseases at the time of presentation in young patients and the occurrence of secondary neurological symptoms later in life.

CVA develop during early intrauterine life due to a combination of genetic and environmental factors. Malformation of the notochord, the poor performance of retinoids, decreased local blood supply to the spine and an alteration in gene expression, especially members of Hox and Pax family genes, are some of the proposed reasons for interrupted development and fusion of the cervical vertebrae.3 Cervical vertebrae development and the approximation of the developing palatine shelves arising from the maxillary process of either side occur early in intrauterine life, with a closure of the shelves occurring around eight to nine weeks. The CVA and the development of the cleft
CERVICAL VERTEBRAL ANOMALIES IN CLP PATIENTS

Cervical vertebral anomalies (CVA) seem to be interrelated. A short neck with vertebral synostosis or other changes limiting head extension of the foetus interfere with the anterior and descending development of the glosso-mandibular complex. Consequently, there may be inadequate space above the tongue, which is required to allow horizontal approximation of the palatal shelves towards the midline, the failure of which may result in incomplete closure of the palate.4

Fusion of the cervical vertebrae is also prevalent in conditions such as Klippel-Feil syndrome,5 Goldenhar syndrome,6 Pfeiffer syndrome,6 Crouzon syndrome7 and Apert syndrome.8 Fusion of the cervical vertebrae can be a cause for precordialgia, a condition of cervicogenic angina due to the union of the C3-C4 vertebrae.9

The prevalence of CVA and its association with cleft lip and palate patients has been previously reported (Table I) to range from 13–38.7% in cleft subjects and 0.8–12.6% in non-cleft subjects. The method of evaluation in all studies was a careful visual examination of lateral cephalograms and the hand tracing of cervical vertebrae on acetate paper. A non-radiologist researcher recorded the cervical anomalies. An expert radiologist was not involved in the detection of abnormal/normal morphology of the cervical vertebrae in the previously-published studies.

Cleft palate only (CPO), and cleft lip and palate (CLP) are considered distinct categories because of their unique aetiology and genetic differences. Though a higher prevalence of CVA in cleft patients has been reported, the literature lacks information on the association, if any, specific to the presence of CVA between CPO and CLP. The current study aimed to determine the prevalence of CVA in cleft subjects compared with an age-matched non-cleft group. The study also expected to reveal any differences in the prevalence of CVA between the CPO and CLP groups.

Material and methods

The current retrospective study was performed on lateral cephalograms available from the archives of the postgraduate department of orthodontics and cleft lip and palate clinic. The cephalograms were obtained grouped, checked for diagnostic quality and assessed for the presence of CVA. All cephalograms were obtained on a digital panoramic machine (Villa Sistemi Medicali) using STRATO 2000 D software.

A review of the literature10 showed approximately 20% of cleft cases and 6% of non-cleft cases had CVAs detected in their lateral cephalograms. Assuming the same picture is true in the study population,
a sample of 134 patients, each from cleft and non-cleft backgrounds, was calculated to detect a possible difference in the prevalence of CVA, with 90% power in a two-sided test with 5% alpha error.

Accordingly, cephalograms were selected of a sample of 150 cleft cases and 150 non-cleft orthodontic patients. The lower age limit of six years was selected because malformations or anomalies of the upper cervical vertebrae cannot be confirmed at a younger age.11

Four out of 150 lateral cephalograms in the cleft group were excluded due to inadequate diagnostic quality. An expert radiologist (DK), blinded to the cleft status, examined all of the cephalograms for the presence of CVA. Each cephalogram was categorised as normal, or with the presence of a cervical vertebrae anomaly (CVA). Further, each cephalogram with an identified CVA was evaluated in detail for the presence of dehiscence (Currarino criteria – Figure 1) or fusion, or for the presence of multiple cervical anomalies (Figure 2).

Data were compiled on an Excel spreadsheet for statistical analyses. All analyses were conducted using Stata software, version 14.2. The prevalence of CVA was calculated as a percentage at a 95% confidence interval in both groups. The Chi-Square test assessed the significance of the difference in the prevalence of cervical anomalies between the cleft and non-cleft groups. The odds ratio for a cervical anomaly associated with the cleft group was calculated at 95% confidence interval.

The prevalence of CVA between the two types of cleft groups, namely cleft palate only (CPO) and cleft lip and palate (CLP), between the gender groups and laterality groups were also compared using the Chi-Square test. A p-value of <0.05 was considered to be statistically significant.

Results

The prevalence of CVA was 37.7% (95% CI: 29.8% – 46.1%) in the cleft group and 20.7% (95% CI: 14.5% – 28.0%) in the non-cleft group. The difference in the prevalence of CVA between the two groups was statistically significant (p = 0.001). The odds of CVA in a cleft case were 2.3 times (95% CI: 1.3 – 3.89) more compared with the chances of CVA in a non-cleft case. Fusion was the most common type of anomaly observed in both groups, accounting for 81.8% (45/55) of the anomalies in the cleft group and 54.8% (17/31) in the non-cleft group. Overall, the pattern of the anomalies between the two groups was statistically different (p < 0.001). When the differences

Figure 1. Classification of posterior arch defects of the atlas based on Currarino criteria.26
were examined with respect to each type of anomaly, a significant difference was observed between the cleft and non-cleft groups for fusion only (Table II).

Of the cleft cases, there was no significant difference in the prevalence of CVA or the distribution of anomaly types between males and females (38.1% versus 37.1%); between CLP and CPO (38.4% versus 30.8%); and between the type of clefts. The average age of all sub-groups of anomaly type appeared to be similar (Table III).

Discussion
The association between two or more anomalies linked to a common embryologic factor is frequently reported in studies related to craniofacial dysmorphia. Based on this observation, a relationship between the CLP and CVA was hypothesised. Ross and Lindsay studied the association and questioned inappropriate cervical development in CLP aetiology. Developmental abnormalities of the cervical spine vary widely, are often sporadic, and may be isolated or part of a multi-organ-systemic syndrome anomaly. Many anomalies are asymptomatic and go undetected, but several types may result in biomechanical instability or compress neurologic structures, thus placing a patient at risk of neurologic injury or chronic pain from the deformity. Identifying the lesions with significant clinical implications is essential, not only for treatment of the malformation but because there may be an association with other spinal and non-spinal diseases related to development.

Klimo et al. and Soni et al. described many congenital upper CVA. These included malformation of the occipital condyles and the occipitalisation of the atlas, characterised by fusion of the occiput to the atlas. Interestingly, many patients do not present with symptoms requiring medical attention until later in life. Of the different types of malocclusion (Angle Class I, Class II and Class III), no significant difference in the distribution of CVAs has been observed, nor gender dimorphism. Farman et al. evaluated lateral cephalograms of 220 normal adolescent orthodontic patients and patients with craniofacial dysostosis and oculodento-osseous dysplasia. Variation was observed in the morphology of the upper cervical vertebrae, which exhibited posterior arch dehiscence in eight individuals. Three patients had accessory ossicles above the posterior arch of the atlas, and two showed evidence of fusion of the second and third cervical vertebrae.

Yoshihara et al. incidentally encountered an anomaly of the cervical vertebrae during an orthodontic examination of an eight-year-old boy who presented with a cleft lip and palate. The patient was diagnosed with Klippel-Feil syndrome by an orthopaedic
specialist to whom referral was made for a detailed examination. Mild cases of CVA may not present with significant clinical symptoms but may develop neurological symptoms secondary to degenerative disc disease of the adjacent mobile segments, spinal instability from hypermobility or after trauma, or spinal stenosis in the later decades of life. Fusion of the first and second cervical vertebra (C1 and C2) tends to produce symptoms in the first decade of life, while fusion of the second and third cervical vertebra (C2 and C3) exhibits neurological symptoms in the third decade. Most symptoms, regardless of the location of the lesion, appear before 30 years of age.

Meibodi et al.\textsuperscript{16} showed that 73.3\% of Class III patients exhibited fusion of cervical vertebrae compared with 32.6\% of Class I patients. Sun and Li\textsuperscript{17} found that males and females with cleft lip and palate had lower skeletal maturity than their unaffected peers and a delayed pubertal growth peak. Patients with CVA are at a higher risk of developing obstructive sleep apnoea.\textsuperscript{18} CVA may narrow the spinal canal so that hyperextension of the neck during endotracheal intubation or while positioning the patient’s head for palatoplasty may injure the spinal cord. Pharyngeal flap surgery may not be advisable in adult patients with cleft palate.\textsuperscript{19} A lateral cephalogram offers an excellent diagnostic tool to exclude CVA.

The present study using lateral cephalograms confirms a high prevalence of CVA in cleft patients (37.7\%) within the North Indian population. The prevalence is significantly higher compared with that reported by Srivastava et al.\textsuperscript{20} and Datana et al.\textsuperscript{10} A higher prevalence could be the outcome of an accurate recording by an expert radiologist in the present study while the earlier studies did not specify the involvement of a trained person. In addition, the quality of the radiographic image could influence the accuracy of the diagnosis. The expert radiologist employed in this study used digital images on a high resolution medical grade monitor and image processing tools to differentiate normal and anomalous vertebrae. Although objective data are lacking on the influence of non-digital versus digital images in accurately recording the CVA, accurate recording could be the reason for the higher prevalence of CVA detected in non-cleft cases compared with previous reported studies.

The present study reports a fusion of cervical vertebrae as the most common anomaly within the cleft/non-

| Table II. Comparison of cervical vertebrae anomalies in cleft and non-cleft patients. |
|-----------------------------------|---------------|---------------|-----|-------------------|
| Distribution of anomalies (N = 146) | Cases (N = 150) | P | Odds ratio (95\% CI) |
| No cervical anomaly | 91 (62.3\%) | 119 (79.3\%) | < 0.001 | 1.00 |
| Dehiscence | 8 (5.5\%) | 6 (4.0\%) | 1.7 (0.58 - 5.20) |
| Fusion | 45 (30.8\%) | 17 (11.3\%) | 3.5 (1.86 - 6.44) |
| Multiple cervical anomalies | 2 (1.4\%) | 8 (5.3\%) | 0.3 (0.07 - 1.58) |
| Total anomaly prevalence | 55 (37.7\%) | 31 (20.7\%) | 0.001 | 2.3 (1.38 - 3.89) |

| Table III. Comparison of cervical vertebrae anomalies in patients with CLP and CPO. |
|-----------------------------------|-------------------|-------------------|-----|
| Characteristic | Nil (N = 91) | Dehiscence (N = 8) | Fusion (N = 45) | Multiple (N = 2) | Anomalies | P |
| Sex | | | | | 32 (38.1\%) | 0.90 |
| M (N = 84) | 52 (61.9\%) | 5 (5.9\%) | 27 (32.1\%) | 0 (0.0\%) | |
| F (N = 62) | 39 (62.9\%) | 3 (4.8\%) | 18 (29.0\%) | 2 (3.2\%) | |
| Type of cleft | | | | | 51 (38.4\%) | 0.59 |
| CLP (N = 133) | 82 (61.5\%) | 8 (6.0\%) | 41 (30.8\%) | 0 (0.0\%) | |
| CPO (N = 13) | 9 (69.2\%) | 0 (0.0\%) | 4 (30.8\%) | 0 (0.0\%) | 4 (30.8\%) |
| Left UCLP (N = 53) | 28 (52.8\%) | 5 (9.4\%) | 19 (35.8\%) | 1 (1.9\%) | 25 (47.2\%) |
| Right UCLP (N = 30) | 18 (60.0\%) | 2 (6.7\%) | 9 (30.0\%) | 1 (3.3\%) | 12 (40.0\%) |
| BCLP (N = 50) | 36 (72.0\%) | 1 (2.0\%) | 13 (26.0\%) | 0 (0.0\%) | 14 (28.0\%) | 0.22 |
| CPO (N = 13) | 9 (69.2\%) | 0 (0.0\%) | 4 (30.8\%) | 0 (0.0\%) | 4 (30.8\%) |
| Age | | | | | 13.3 ± 5.80 | 0.36 |
| Mean ± SD | 14.2 ± 4.89 | 12.2 ± 3.45 | 13.8 ± 6.27 | 16.0 ± 2.83 | 0.64 |
CERVICAL VERTEBRAL ANOMALIES IN CLP PATIENTS

cleft groups, irrespective of cleft type. However, previous studies\textsuperscript{10,20} reported a higher prevalence of fusion in the UCLP group. The prevalence of CVA within the cleft and non-cleft groups shows considerable global variation. The prevalence of CVA in the cleft group varied from 13 to 39\% while it varied from 0.8 to 31\% in non-cleft cases. The present study reports a prevalence of 37.7\% in the cleft group and 20.7\% in the non-cleft group. The present study also noted a higher prevalence of fusion within the cleft/non-cleft group, in contrast with the Sandham\textsuperscript{11} report in which dehiscence occurred significantly more often in the CP group (16\%) compared with controls. A study by Horswell\textsuperscript{21} indicated that patients with a soft palate and submucous cleft within the cleft type had a higher prevalence of CVA. The study by Üğar and Semb\textsuperscript{22} revealed a higher prevalence of CVA in the CPO group. The findings of the present study support those of Lima et al.,\textsuperscript{23} which did not show a significant variation of CVA between the different cleft types. The present study also revealed no gender predilection, in agreement with Üğar and Semb\textsuperscript{22} and Lima et al.\textsuperscript{23}

It is improbable that the association between cleft and CVA varies between populations. Therefore, the wide variations observed in the prevalence of CVA in cleft patients could be due more to procedural differences than actual differences.

In the present study, lateral cephalograms were relied upon for the detection of CVA. Even so, a high proportion of cleft and non-cleft cases were observed showing CVA. If a more sensitive imaging technique such as CBCT and MDCT is used, the prevalence may well be different.\textsuperscript{24} However, such techniques are associated with exposure to radiation and come with specific indications. The finding of a CVA in a lateral cephalogram should be interpreted with caution and identified cases appropriately referred to a neurologist/orthopaedic specialist or for counselling and alternative management.

The long-term sequelae of a cleft associated CVA are a subject requiring further investigation. The orthodontic management of patients with clefts and CVA likely does not differ from that of other patients, but a diagnosis of CVA allows a better understanding of the cleft development process. Early diagnosis of fusion is critical in determining the risk of other associated diseases at presentation and secondary neurological symptoms in the future. CVA, which may have remained obscure, can be revealed incidentally via radiological examinations performed for orthodontic reasons.

Limitations and future perspectives

In future, prospective multicentre studies with larger sample sizes could further clarify the relationship between CVA and cleft lip and/or palate. Furthermore, the advancement of technology using 3D reconstruction from cone beam computed tomography images with reduced radiation will enable a more accurate assessment of the cervical spine area.

Conclusion

The present study highlights the substantial prevalence of CVA within orthodontic patients (cleft/non-cleft), which, for the welfare of patients, should not be ignored. Identified orthodontic cleft patients may need a timely referral to appropriate specialists for counselling and management.

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Conflict of interest

No conflict of interest

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