BMC Oral Health

RESEARCH

Open Access

Prevalence of upper cervical vertebral anomalies in children with non-syndromic cleft lip and/or palate in comparison with children without cleft in Iranian population

Shabnam Ajami[1], Samaneh Dehghanpoor[2], Seyedeh Sara Tabibi[1] and Najmeh Movahhedian[3*]

Abstract

Background To evaluate the prevalence of upper cervical vertebral anomalies (CVA) in Iranian children with cleft lip and/or palate (CL/P) and compare it with children without a cleft.

Methods A case-control study on lateral cephalograms from Orthodontics Research Center, Shiraz University of Medical Sciences, Shiraz, Iran of 92 subjects (41 females and 51 males) with non-syndromic CL/P with a mean age of 13.54 ± 4.63 years, and 184 age- and sex-matched individuals (82 females and 102 males) with no craniofacial anomalies or skeletal malocclusion as the control group. Upper cervical vertebrae (C1-C3) were examined regarding the following CVA: (1) posterior arch deficiencies: spina bifida and dehiscence; (2) Fusion Anomalies (FAs): fusion and occipitalization; (3) accessory ossicles. Vertebral artery canal morphology was also evaluated.

Results The prevalence of CVA was significantly higher in the cleft group (62%) than in the control group (25%) ($P < 0.001$). FAs, fusion, accessory ossicle, and deviation of artery canal type 2 were the anomalies with significantly higher prevalence in the cleft group compared to the noncleft group (all $P < 0.05$). 11 individuals (11.9%) of the cleft group and five (2.7%) of the control group had more than one CVA. When considering the subgroups of the CL/P, the prevalence of CVA was significantly higher in almost all the CL/P subgroups compared to the control group (all $P < 0.05$).

Conclusions Upper CVA, especially fusion anomalies, were significantly more prevalent in children with non-syndromic CL/P compared to the children without cleft in an Iranian population. A female predilection for CVA was also noted in both the general population and the cleft group.

Keywords Cervical vertebrae anomaly, Cleft lip and palate, Posterior arch deficiency, Vertebral artery Canal, Vertebral fusion

*Correspondence:
Najmeh Movahhedian
movahedian@sums.ac.ir
[1]Orthodontic Research Center, School of Dentistry, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Student Research Committee, School of Dentistry, Shiraz University of Medical Sciences, Shiraz, Iran
[3]Department of Oral and Maxillofacial Radiology, School of Dentistry, Shiraz University of Medical Sciences, Corner of Mehr Ave., Qasrodasht St, Shiraz, Iran

Background

Cleft lip and/or palate (CL/P) is the most common congenital anomaly affecting the craniofacial region [1, 2]. Numerous studies have explored the association of CL/P with various other congenital anomalies [3, 4]. These malformations can involve many systems, including the musculoskeletal, cardiac, and central nervous systems [5]. Among these, the potential link between defects in the cervical vertebrae—particularly in the upper region—and CL/P has been a focus of investigation in several studies, yielding varying results [5–10]. Furthermore, research has highlighted a correlation between morphological variations in the upper cervical vertebrae, craniofacial structure, and occlusal morphology [11–15].

Cervical vertebral anomalies (CVA), which encompass both morphologic variations and pathological anomalies [16, 17], have been generally classified into two main categories [18]: Posterior arch deficiencies (PAD) and Fusion anomalies (FAs). PAD arises from partial fusion of the vertebral arches and is further subdivided into spina bifida and dehiscence [19]. FAs occur due to synostosis between different parts of two or more vertebral units or occipitalization, where the atlas fuses with the base of the skull [19].When symptomatic, fusion anomalies can lead to complications such as myelopathy, restricted neck movement, muscular weakness or atrophy, and neurological sensory deficits [20]. During surgery or anesthesia, occipitalization poses significant risks, including compression and distortion of the spinal cord and vertebrobasilar vascular system [21]. Patients with PAD show variable clinical features, ranging from an absence of significant symptoms to neck pain that may radiate to the arm. Additionally, head injuries can trigger or exacerbate these symptoms [22].

Understanding the distribution of CVA, particularly in the C1, C2, and C3 vertebrae, is essential due to their significant impact on spinal stability, range of motion, and potential neurological complications [23]. These anomalies are often identified incidentally during routine radiographic examinations, as they may remain asymptomatic until adolescence or early adulthood. Clinical symptoms, when present, can include restricted neck motion, skeletal deformities (e.g., scoliosis or torticollis), and nerve compression (e.g., pain, weakness, or sensory loss) [24]. Therefore, early detection and timely referral for specialized evaluation are crucial for effective management and improved outcomes.

In addition to common anomalies, there are other morphologic deviations in the cervical vertebrae, such as accessory ossicles and abnormalities in the vertebra artery canal. Accessory ossicles often result from ossification within ligaments, muscles, or connective tissues [19]. The diagnostic importance of accessory ossicles lies in their recognition as an anatomical variant, not a pathologic condition. In rare cases, accessory ossicles may cause dysphagia or affect atlantooccipital movements [25]. Furthermore, they have been implicated in contributing to atlantoaxial instability [26]. Deviations in vertebral artery canal morphology are frequently observed in the lateral articular process of the atlas [10, 19, 27]. The morphology of this canal ranges from a shallow groove to a complete bony ring known as the foramen arcuate [28]. The presence of a foramen arcuate can lead to clinical symptoms such as shoulder and neck pain, headache, and vertigo due to external compression on the vertebral artery [29].

Considering that individuals with CL/P often require multiple surgical procedures throughout their treatment, many of which involve extension and rotational movements of the head and neck, the presence of CVA, particularly severe ones, heightens the risk of spinal cord or vertebral artery injury [20]. Establishing a clear association between CVA and CL/P is, therefore, critical since it necessitates thorough evaluations and tailored patient care. Moreover, it could provide valuable insights into the underlying embryological processes contributing to these anomalies.

While a few studies have explored the relationship between certain congenital anomalies and CL/P in the Iranian population [30, 31], the prevalence of CVA in patients with CL/P has not yet been reported in this group. Recognizing the significance of this gap, the present study aims to evaluate the prevalence of upper CVA in individuals with CL/P compared to those without clefts. Additionally, it seeks to examine the relationship between various types of clefts and upper CVA within the Iranian population.

Methods

The Human Ethics Review Committee of the Faculty of Dentistry, Shiraz University of Medical Sciences, approved the present study's research protocol (IR.Sums.Dental.REC.1399.118).

The sample size was determined based on the prevalence rates of CVA reported by Dogan et al. [32], which were 64.5% for the cleft group and 40.9% for the control group. Given the type 1 error rate of $\alpha = 0.05$, a power value of 80%, and a group ratio of 2, the minimum required sample size was calculated to be 52 patients with clefts and 104 controls. Ultimately, we included a total of 92 individuals (41 females and 51 males) diagnosed with non-syndromic CL/P, with a mean age of 13.54 ± 4.63 years (age range: 8–21 years). For each subject in the cleft group, two randomly selected age- and sex-matched controls who did not have craniofacial anomalies, asymmetry, or sagittal/vertical skeletal discrepancies were included in the study. In other words, the control group

consisted of 184 age- (82 females and 102 males) with the same age range and mean age of the cleft group.

The lateral cephalograms for this study were conveniently selected from the archives of the Cleft Lip and Palate Clinic at the Orthodontic and Dental Research Center, School of Dentistry, Shiraz University of Medical Sciences, and the Department of Orthodontics and Dental Research Center, Mashhad University of Medical Sciences. All the radiographs were taken for orthodontic treatment purposes. At the time of imaging, all patients or their legal guardians signed written informed consent for the anonymous use of radiographic data in future research and publications.

To ensure standardization of the samples, only high-quality lateral cephalograms taken in the natural head position of individuals aged eight years or older were included in the study. participants with a history of head or neck trauma or systemic diseases affecting cervical vertebrae were excluded.

The cleft group was categorized into three main groups and their sub-groups: (1) Cleft lip with or without alveolus cleft (CL ± A); (2) Cleft lip and palate (CLP) including (a) unilateral cleft lip and palate (UCLP) and (b) bilateral cleft lip and palate (BCLP); 3. Isolated cleft palate (CP).

Abnormalities in the first three cervical vertebrae (C1, C2, and C3) were identified through direct visual assessment of the lateral cephalograms by an experienced oral and maxillofacial radiologist. These anomalies were further subdivided into three categories: PAD, FAs, and accessory ossicles:

1. PAD with two subgroups: (a) Spina bifida: characterized by incomplete ossification of the spinous process (Fig. 1a), and (b) Dehiscence: defined as partial development of any part of the vertebral unit [18]. (Fig. 1b)
2. FAs with two subgroups: (a) Fusion: identified as bony synostosis between two or more units at articular facets, neural arch, or transverse process [27] (Fig. 1c), and (b) Occipitalization: defined as an osseous union between the atlas (C1) and the base of the skull, either partially or completely [5]. (Fig. 1d)
3. Accessory ossicles: recognized as separate bony particles located near the cervical vertebrae [16, 19]. (Fig. 1e)

The morphology of the vertebral artery canal was also evaluated and classified based on the posterior margin of the lateral articular process of the atlas (C1) as follows: Type (1) An almost perpendicular posterior margin with no lipping; Type (2) Slight posterior lipping along this margin; Type (3) An extension toward the posterior arch without fusion; Type (4) Complete ring formation (foramen arcuate) caused by fusion with the lateral components of the posterior arch [16, 19]. (Fig. 2)

In case of uncertainty regarding the presence of an anomaly, the condition was considered as "no CVA." To evaluate intra-observer agreement, the examiner reevaluated 60 randomly selected radiographs after a two-week interval to confirm consistency in identifying CVA.

All statistical analyses were conducted using PASW SPSS software for Windows version 18.0 (SPSS Inc., Chicago, IL, USA). The occurrence of CVA was analyzed using Chi-square test, odds ratio (OR), and corresponding 95% confidence intervals (CI). The intraclass correlation coefficient (ICC) was used to evaluate the intra-examiner agreement. Additionally, Chi-square tests were used to examine associations between cleft subgroups and the different types of anomalies. A P of less than 0.05 was considered statistically significant.

Results

The intra-examiner reliability for evaluating CVA was highly acceptable, with an ICC value of 95.2%.

Regarding vertebral artery canal morphology, Type 2 morphology was more common in the cleft group (30.4%) than in the control group (15.7%), with a significant difference ($P = 0.005$). (Table 1)

The prevalence of upper CVA was significantly higher in the cleft group, with 62% ($n = 57$) of individuals with CL/P having at least one CVA, compared to 25% ($n = 46$) in the control group ($P < 0.001$). The odds of having CVA were 4.9 times higher in the cleft group than in the controls. Among the specific anomalies, FAs, fusion, and

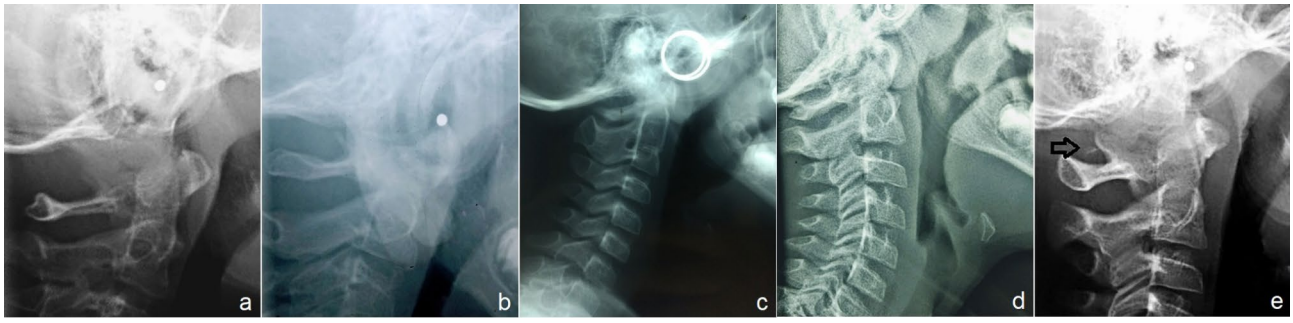

Fig. 1 Radiographic images showing cervical vertebral anomalies: (**a**) spina bifida, (**b**) dehiscence, (**c**) fusion, (**d**) occipitalization, and (**e**) accessory ossicle

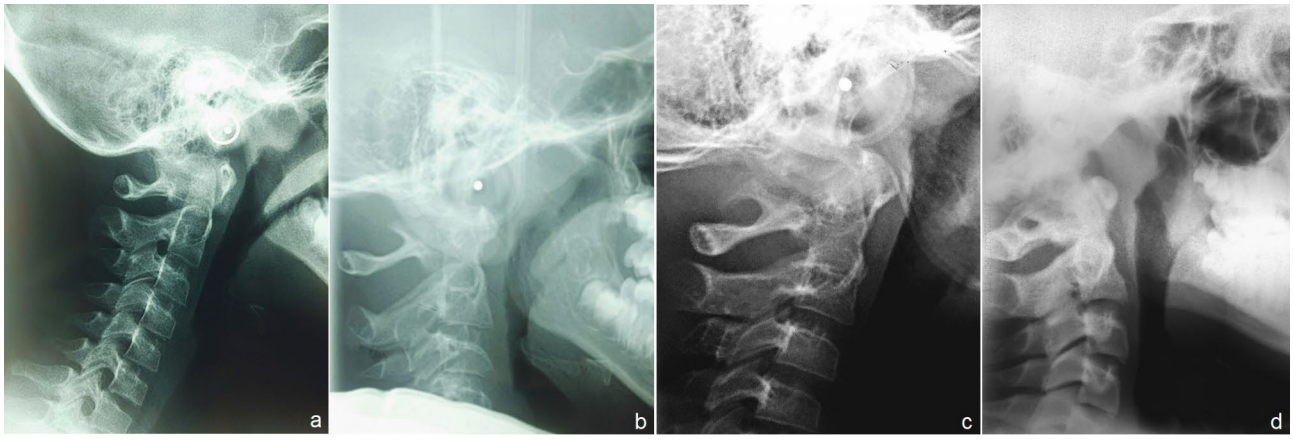

Fig. 2 The classification of cervical vertebral canal morphologies: (**a**) Type 1: nearly perpendicular posterior margin without lipping, (**b**) Type 2: slight posterior lipping, (**c**) Type 3: extension toward the posterior arch without fusion, and (**d**) Type 4: complete ring formation (foramen arcuate)

Table 1 Distribution of different types of vertebral artery morphology in subjects with cleft and the control group

		Cleft group (*n* = 92)	Control group (*n* = 184)	OR (95% CI)	*P*-value*
Vertebral Artery Canal	**Type 1**	57 (62.0%)	129 (70.1%)	0.7 (0.4–1.3)	0.173
	Type 2	28 (30.4%)	29 (15.7%)	2.5 (1.4-5.0)	0.005
	Type 3	2 (2.2%)	6 (3.3%)	0.7 (0.1–3.3)	0.723
	Type 4	5 (5.4%)	20 (10.9%)	0.5 (0.2–1.4)	0.138

Abbreviations: N: number; %: Percent; OR: Odds Ratio; CI: Confidence Interval 95%

* Chi-square test was used to analysis

Table 2 Distribution of subjects with cervical vertebral anomalies in the cleft and control groups

Cervical vertebral anomaly type	Cleft group (*n* = 92)	Control group (*n* = 184)	OR (95% CI)	*P*-value*
PAD	16 (17.4%)	18 (9.8%)	2 (1.0–5.0)	0.070
Dehiscence	4 (4.4%)	5 (2.7%)	1.7 (0.4–10)	0.47
Spina bifida	12 (13.0%)	13 (7.1%)	2 (0.9-5.0)	0.103
FAs	37 (40.2%)	27 (14.7%)	5 (2.0–10.0)	< 0.001
Occipitalization	9 (9.8%)	9 (4.9%)	2.5 (0.8–10.0)	0.121
Fusion	28 (30.4%)	18 (9.8%)	5 (2.5–10.0)	< 0.001
Accessory ossicle	4 (4.3%)	1 (0.5%)	10 (0.0–1.0)	0.025
Total	57 (62%)	46 (25%)	4.9 (2.8–8.4)	< 0.001

Abbreviations: OR: Odds Ratio; CI: Confidence Interval 95%; PAD: Posterior arch deficiency including Dehiscence and Spina bifida; FAs: Fusion anomalies including Occipitalization and Fusion

* Chi-square test was used to analysis

accessory ossicles were significantly more prevalent in the cleft group, with P of < 0.001, < 0.001, and 0.025, respectively. (Table 2)

A subset analysis revealed that 11.9% of individuals in the cleft group (10 CLP and 1 CP) exhibited more than one CVA, compared to 2.7% (5 individuals) in the control group. All these cases exhibited the coexistence of fusion with another CVA subtype.

Analysis of CVA prevalence across cleft subcategories revealed significantly higher rates in most cleft subgroups compared to the control group (all $P < 0.05$). Odds ratios indicated that individuals in cleft subgroups were between 3.8 times (BCLP) and 6 times (UCLP) more likely to have CVA compared to controls. However, no significant differences in CVA prevalence were observed between cleft subgroups. Due to the limited number of cases in the CL ± A subgroup, the statistical indices for this group were not computable (Table 3).

When each CVA subtypes were compared between the cleft subgroups and the control group, FAs were consistently more prevalent in the cleft subgroups (all $P < 0.05$). Fusion was significantly more common in BCLP, UCLP, and CLP groups compared to controls ($P = 0.0028$, $P = 0.0001$, and $P < 0.0001$, respectively). Occipitalization and PAD were notably higher in the CP and CLP groups

Table 3 Comparison of distributions of cervical vertebral anomaly types between each subcategory of cleft and the control group

Cervical vertebral anomalies	Control(*n* = 184)	CLP(*n* = 79)		CLP(*n* = 79)	CP(*n* = 11)
		BCLP(*n* = 34)	UCLP(*n* = 45)		
PAD	18 (9.8%)	6 (17.6%)	9 (20%)	15 (19%)	1 (9.1%)
OR (95% CI)		1.98 (0.72–5.41)	2.31(0.96–5.54)	2.16(1.03–4.55)	0.92(0.11–7.63)
P-value	-	0.1849	0.0621	0.0421	0.9401
Dehiscence	5 (2.7%)	2 (5.9%)	2 (4.4%)	4 (5.1%)	0
OR (95% CI)	1	2.24 (0.42–12.03)	1.67(0.31–8.87)	1.91(0.50–7.31)	1.42(0.07–27.27)
P-value	-	0.3481	0.5503	0.3449	0.8165
Spina bifida	13 (7.1%)	4 (11.8%)	7 (15.6%)	11 (13.9%)	1 (9.1%)
OR (95% CI)	1	1.75(0.54–5.74)	2.42(0.91–6.48)	2.13(0.91–4.98)	1.32(0.16–11.09)
P-value	-	0.3531	0.0779	0.0819	0.8010
FAs	27 (14.7%)	12 (35.3%)	19 (42.2%)	31 (39.2%)	6 (54.5%)
OR (95% CI)	1	3.17(1.41–7.15)	4.25(2.07–8.72)	3.76(2.04–6.90)	6.98(1.99–24.48)
P-value	-	0.0054	0.0001	< 0.0001	0.0024
Occipitalization	9 (4.9%)	2 (5.9%)	4 (8.9%)	6 (7.6%)	3 (27.3%)
OR (95% CI)	1	1.22(0.25–5.89)	1.90(0.56–6.46)	1.60(0.55–4.65)	7.29(1.65–32.24)
P-value	-	0.8086	0.3060	0.3898	0.0088
Fusion	18 (9.8%)	10 (29.4%)	15 (33.3%)	25 (31.6%)	3 (27.3%)
OR (95% CI)	1	3.84(1.59–9.30)	4.61(2.10-10.14)	4.27(2.16–8.42)	3.46(0.84–14.21)
P-value	-	0.0028	0.0001	< 0.0001	0.0853
Accessory ossicle	1 (0.5%)	1 (2.9%)	2 (4.4%)	3 (3.8%)	0
OR (95% CI)	1	5.55(0.34–90.88)	8.51(0.75–96.04)	7.22(0.74–70.55)	5.32(0.21-137.95)
P-value	-	0.2299	0.0833	0.0890	0.3143
Total	46 (25%)	19(55.9% (	30 (66.7%)	49 (62%)	7 (63.6%)
OR (95% CI)	1	3.80(1.79–8.08)	6.00(2.97–12.13)	4.90(2.79–8.61)	5.25(1.47–18.75)
P-value*	-	0.0005	< 0.0001	< 0.0001	0.0107

Abbreviations: OR: Odds Ratio; CI: Confidence Interval 95%; CLP: Cleft lip and Palate; BCLP: Bilateral Cleft lip and Palate; UCLP: Unilateral Cleft Lip and Palate; CP: Isolated Cleft Palate; PAD: Posterior arch deficiency; FAs: Fusion anomalies including Occipitalization and Fusion

Since the control group was the reference group of comparison, the odds ratio was 1, and the P-value was incomputable

*Chi-square test was used to analysis

Table 4 Distribution of the subjects with cervical vertebral anomalies based on gender in the general population

Cervical vertebral anomaly type	F (*n* = 123)	M (*n* = 153)	OR (95% CI)	*P*-value*
PAD	17 (13.8%)	17 (11.1%)	1.2 (0.6–2.6)	0.496
Dehiscence	4 (3.2%)	5 (3.3%)	0.9 (0.2–3.7)	0.994
Spina bifida	13 (10.5%)	12 (7.8%)	1.3 (0.6–3.1)	0.433
FAs	38 (30.9%)	26(17%)	2.2 (1.2–3.8)	0.007
Occipitalization	11 (8.9%)	7 (4.6%)	2.0 (0.7–5.4)	0.151
Fusion	27 (21.9%)	19 (12.4%)	1.9 (1.0-3.7)	0.037
Accessory ossicle	3 (2.4%)	2 (1.3%)	1.8 (0.3–11.4)	0.490
Total	58(47.15%)	45 (29.4%)	2.1 (1.3–3.5)	0.002

Abbreviations: OR: Odds Ratio; CI: Confidence Interval 95%; PAD: Posterior arch deficiency including Dehiscence and Spina bifida; FAs: Fusion anomalies including Occipitalization and Fusion

* Chi-square test was used to analysis

compared to controls, with P of 0.0088 and 0.0421, respectively (Table 3).

When analyzing the relationship between CVA prevalence and sex, females generally demonstrated a significantly higher prevalence of CVA, FAs, and fusion compared to males ($P = 0.002$, 0.007, and 0.037, respectively). Females were found to be 2.1 times more likely to have CVA than males (OR = 2.1, 95% CI = 1.3–3.5) (Table 4).

Specifically, within the cleft group, CVA prevalence was significantly higher in females (78%) compared to males (27.2%) ($P = 0.005$). No significant gender difference in CVA prevalence was observed in the control group ($P = 0.061$). Subgroup analysis of CVA types showed no significant differences in prevalence between genders, except for FAs in the control group, which were significantly more common in females ($P = 0.041$) (Table 5).

Table 5 Distribution of the subjects with cervical vertebral anomalies based on gender in case and control groups

Cervical vertebral anomaly type	Cleft group		*P*-value*	Control group		*P*-value*
	F	M		F	M	
	(*n* = 41)	(*n* = 51)		(*n* = 82)	(*n* = 102)	
PAD	9 (21.9%)	7 (13.7%)	0.304	8 (9.7%)	10 (9.8%)	0.991
Dehiscence	2 (4.9%)	2 (3.9%)	0.823	2 (2.4%)	3 (2.9%)	0.835
Spina bifida	7 (17.1%)	5 (9.8%)	0.309	6 (7.3%)	7 (6.9%)	0.905
FAs	21 (51.2%)	16 (31.4%)	0.055	17 (20.7%)	10 (9.8%)	0.041
Occipitalization	5 (12.2%)	4 (7.8%)	0.488	6 (7.3%)	3 (2.9%)	0.185
Fusion	16 (39%)	12 (23.5%)	0.111	11 (13.4%)	7 (6.9%)	0.143
Accessory ossicle	2 (4.9%)	2 (3.9%)	0.823	1 (1.2%)	0 (0%)	0.418
Total	32 (78%)	25 (27.2%)	0.005	26 (31.7%)	20 (19.6%)	0.061

Abbreviations; OR: Odds Ratio; CI: Confidence Interval 95%; PAD: Posterior arch deficiency; FAs: Fusion anomalies

* Chi-square test was used to analysis

Discussion

The present study investigated the association between the occurrence of upper CVA in Iranian children with non-syndromic CL/P and those without CL/P using lateral cephalograms. Early diagnosis of CVA is essential for identifying potential comorbidities and assessing the risk of future neurological complications. For instance, fusion of the first and second cervical vertebrae (C1 and C2) often manifests with symptoms during the first decade of life, whereas fusion of the second and third cervical vertebrae (C2 and C3) exhibits neurological symptoms in the third decade [33]. Therefore, evaluating cervical vertebral morphology plays a critical role in early intervention and management.

Three-dimensional imaging, such as cone beam computed tomography, enables precise assessment of craniofacial structures in multiple orthogonal planes [15] and overcomes limitations like overlapping of structures, which can lead to false-positive diagnoses of vertebral fusions [34, 35]. However, its superior precision comes at the cost of increased radiation exposure, restricting its routine use. Consequently, lateral cephalograms remain a practical choice for routine orthodontic evaluations due to their lower radiation exposure and accessibility.

The assessment was limited to the first three cervical vertebrae due to the constraints of the imaging field, head position, and the protective thyroid collar used during lateral cephalograms.

Upper CVA cannot be definitively confirmed until complete skeletal development, with recent studies suggesting that the pediatric cervical spine reaches its final proportions and physiologic characteristics by 8–10 years of age [36, 37]. Consequently, the present study focused on patients aged 8 years or older.

Since the relation between class II and class III skeletal malocclusions and upper CVA has been reported in prior research [12, 38], only individuals with neutral occlusion, normal craniofacial morphology, and no skeletal discrepancies were included in this study as the control group. This ensured that any observed differences were attributable to the presence or absence of cleft conditions rather than craniofacial or skeletal discrepancies. The association between CLP and CVA is well-documented in the literature [8–10]. The development of cervical vertebrae, particularly the vertebral bodies, as well as the basilar part of the occipital bone in the cranial base, is determined by the notochord. The para-axial mesoderm, formed from notochordal inductions, is responsible for developing the vertebral arches and remaining parts of the occipital bone [39, 40]. Consequently, deviations in notochordal development can potentially affect the surrounding bone tissue of the vertebral column and the posterior cranial base [13]. On the other hand, craniofacial structures are formed through the migration of neural crest cells to the mandible, maxilla, and nasofrontal area [39]. Any deviation in the quantity or timing of these migrating cells can result in developmental anomalies in the craniofacial region [11]. During early embryogenesis, an intricate and still poorly understood signaling exists between the notochord and neural crest cells. This interaction, involving the notochord, para-axial mesoderm, neural tube, and neural crest, underpins the developmental link between the cervical vertebral column, cranial base, and craniofacial structures (11, 13, 14).

Moreover, a functional developmental connection between cervical vertebral formation and normal palate development has been noticed. Morphological anomalies in the cervical vertebrae can lead to neck shortening, which may result in compression of the mandible against the chest. This compression can restrict the descent of the tongue, thereby interfering with the normal closure of the palatal shelves [6, 10]. As a final point, some studies proposed that the association between spinal malformations and craniofacial defects may be explained by the involvement of similar gene sets in the patterning and growth of these two regions [13].

According to the results of the present study, 62% of individuals with CL/P exhibited CVA. This prevalence

is notably higher than the values reported in most previous studies, which range from 13.3 to 37.7% [8, 10, 18, 33, 34]. However, it aligns closely with the frequency of 64.5% reported by Dogan et al. in a Turkish population [32]. These differences in reported frequencies may be attributed to differences in methodologies, inclusion and exclusion criteria, or ethnic variations among study populations. Additionally, this study found that the prevalence of CVA in the CL/P group (62%) was significantly higher than in the control group (25%) ($P<0.001$). This finding is in agreement with previous research [5, 6, 8–10, 18, 41–44], and supports the hypothesis that CVA is closely associated with CL/P.

In this study, fusion of the cervical vertebrae was the most common anomaly within the CL/P, irrespective of cleft type, and also in the control group. This finding is consistent with the results of previous studies by Lima et al. [9], Ugar et al. [8], Karsten et al. [10], and Dogan et al. [32]. However, it contrasts with the findings of Sandham et al. [18] and Rajion et al. [42], who reported PAD as the most common CVA in both cleft and non-cleft groups.

When comparing the CL/P and control groups regarding the prevalence of different types of CVA, it was found that FAs, fusion, and accessory ossicles were significantly more prevalent in the CL/P group. Additionally, vertebral artery canal variation type 2 was more frequent in the CL/P group. Similarly, Karsten et al. [10] reported a significantly higher prevalence of FAs in individuals with clefts compared to controls, although their study group also included patients with soft palate cleft, bifid uvula, and submucosal cleft. Notably, Karsten et al. [10] also reported a higher prevalence of PAD, a finding not observed in the present study. In another study by Dogan et al. [32], both FAs and PAD were found to be more prevalent in the cleft group compared to the control group. However, their research focused exclusively on patients with CLP, excluding other types of clefts. Conversely, Lima et al. [9] did not observe significant differences in the prevalence of PAD and FAS in the first four cervical vertebrae (C1-C4) between cleft and non-cleft individuals. Regarding morphological variations in the vertebral artery canal, Karsten et al. [10] reported no statistically significant differences between cleft and non-cleft groups. However, their study did not include a classification system for vertebral artery canal variations. Disparities in the findings across these studies may be attributed to differences in sample selection criteria, cleft type inclusion, and research methodologies.

The findings of the present study indicated no significant difference in the frequency of CVA among the various subcategories of CL/P. This result is consistent with the findings of Lima et al. [9]. Horswell et al. [5] also reported comparable results, with the exception of soft palate and submucous clefts, which exhibited a significantly higher incidence of CVA compared to other cleft types. In contrast, the study by Uğar et al. [8] revealed a significantly higher prevalence of CVA, PAD, and fusion anomalies in the CP group compared to the UCLP and BCLP groups. Additionally, Karsten et al. [10] found that patients with CLP exhibited a notably increased incidence of CVA and FAs compared to those with isolated CL or CP.

In the comparative analysis of CVA prevalence across cleft subcategories and the control group, the present study revealed that the occurrence of FAs and fusion was significantly higher in almost all cleft subcategories, except for fusion in the CP group. Similarly, Ugar et al. [8] reported a significantly greater prevalence of FAs in the CP and BCLP groups compared to the control group; however, this difference was not observed in the UCLP group. Karsten et al. [10] also demonstrated that individuals with CLP had a significantly higher incidence of fusion than those without clefts. Conversely, Sandham et al. [18] reported no statistically significant differences in FAs across any cleft type, including CL, CP, UCLP, and BCLP, when compared to the control group. Our findings indicated that occipitalization was significantly more prevalent in the CP group than in the control group, corroborating the results reported by Hensinger et al. [45] and Bodon et al. [46]. Moreover, as noted by Dogan et al. [32], the incidence of occipitalization and spina bifida was higher among individuals in individuals with CLP than in those without clefts. In the present study, PAD prevalence was significantly higher in the CLP subgroup compared to the non-cleft group ($P=0.042$), a result consistent with Dogan et al. [32]. In contrast, Karsten et al. [10] reported a higher incidence of PAD in the CP group relative to controls, while Sandham et al. [18] found an increased prevalence of PAD in individuals with CP and UCLP compared to those without cleft conditions.

The differences observed between UCLP and BCLP cases, as shown in Table 3, may be attributed to the inherent asymmetry in UCLP cases. Ustdal et al. [47] demonstrated that individuals with non-syndromic UCLP often exhibit significant midface asymmetry due to the unilateral nature of the defect, which can influence craniofacial morphology and related structures. In contrast, BCLP cases typically display a more symmetric involvement of craniofacial structures, albeit with varying degrees of severity, which may account for the differences noted in our study. In our analysis, the higher prevalence of certain CVAs (e.g., FAs and PAD) in the UCLP subgroup compared to the BCLP subgroup could partially reflect the asymmetric developmental patterns associated with unilateral clefts. Such asymmetry may lead to compensatory growth adaptations or imbalances in cervical vertebral development. Additionally, the unilateral defect in UCLP may affect not only the craniofacial morphology

but also associated musculoskeletal structures, thereby contributing to these differences.

The data analysis in the present study revealed a notable female predominance in the prevalence of CVA within both the overall sample ($P = 0.002$) and the CL/P group ($P = 0.005$). Upon examining the subcategories of CVA, a similar female predisposition was observed for FAs ($P = 0.007$) and fusion ($P = 0.037$) across the total sample. Conversely, no gender predisposition was identified for PAD (including dehiscence and spina bifida) or accessory ossicles. These findings align with the results reported by Karsten et al. [10], who also noted a significantly higher prevalence of CVA in females compared to males. In contrast, their study suggested that PAD, FAs, and vertebral artery canal variations are not gender-specific. Ugar et al. [8] demonstrated a female predominance for PAD in the CP group and for fusion in the UCLP group, whereas Lima et al. [9] concluded that CVA prevalence does not differ significantly by gender.

Some factors may limit the generalizability of the findings in this study. Firstly, the reliance on two-dimensional radiography may obscure subtle morphological variations. Additionally, our evaluation was restricted to the first three cervical vertebrae; expanding the analysis to include additional vertebral levels could influence the prevalence of cervical vertebral anomalies (CVA). In the future, conducting prospective long-term multicenter studies would enable larger patient samples and a more detailed analysis of their clinical features. Additionally, comprehensive genetic studies are essential to uncover the unknown genetic connections between cleft lip and/or palate (CL/P) and morphological deviations of the upper cervical vertebrae. Additionally, as proposed by Kamei et al. [48], advancements in artificial intelligence, such as the development of an AI-based algorithm for assessing skeletal age and detecting cervical vertebral anomalies in patients with cleft lip and palate, highlight the potential for integrating innovative technologies into this field to enhance diagnostic accuracy and clinical decision-making.

Conclusions

Anomalies of the upper cervical vertebrae were found to be significantly more prevalent in children with non-syndromic CL/P compared to those without cleft in the Iranian population. In addition, a notable female predilection for CVA was observed in both the general population and the CL/P group. The high frequency of CVA highlights the importance of routinely evaluating the upper cervical vertebra to detect anomalies and ensure timely referral to specialists for appropriate management when necessary.

Abbreviations

CL/P	Cleft lip and/or palate
CVA	Cervical vertebral anomalies
PAD	Posterior arch deficiencies
FAs	Fusion anomalies
CL ± A	Cleft lip with or without cleft alveolus
CLP	Cleft lip and palate
UCLP	Unilateral cleft lip and palate
BCLP	Bilateral cleft lip and palate
CP	Isolated cleft palate
C1	Atlas
OR	Odds ratio
CI	Confidence intervals
ICC	Intraclass correlation coefficient

Acknowledgements

This article is based on the thesis by Samaneh Dehghanpour. The authors express gratitude to the vice-chancellery of Shiraz University of Medical Sciences for their support (Grant#21183) and to Dr. Mehrdad Vossoughi from the Dental Research Development Center for the statistical analysis. We also appreciate the guidance of Liselotte Sonnesen from the Faculty of Health Sciences at the University of Copenhagen regarding the study design and thank Dr. Amir reza Bazooband for assisting with the figures.

Author contributions

S. A. and N. M. designed the study, N.M. evaluated the images, all authors analyzed and interpreted the patient data, N.M. and S.T prepared the figures. All authors read and approved the final manuscript.

Funding

Vice-chancellery of Shiraz University of Medical Sciences.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This cross-sectional study has been performed following the Declaration of Helsinki and was approved by the Human Ethics Review Committee of the Faculty of Dentistry, Shiraz University of Medical Sciences, approved the present study's research protocol (IR.Sums.Dental.REC.1399.118). All the patients or their legal guardians signed written informed consent at the imaging time for anonymous use of their radiographic data in future research/publications.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 16 October 2024 / Accepted: 13 March 2025
Published online: 19 April 2025

References

1. Al-Mendalawi MD. Incidence of cleft lip and palate in Iran. A meta-analysis. Saudi Med J. 2011;32(11):1208.
2. Movahhedian N, Vossoughi M, Hajati-Sisakht M. A cone-beam computed tomographic study of alveolar bone morphology in patients with unilateral cleft lip and palate. Cleft Palate-Craniofacial J. 2020;57(3):273–81.
3. Milerad J, Larson O, Hagberg C, Ideberg M. Associated malformations in infants with cleft lip and palate: a prospective, population-based study. Pediatrics. 1997;100(2):180–6.
4. Hermann N, Kreiborg S, Darvann TA, Jensen B, Dahl E, Bolund S. Craniofacial morphology and growth comparisons in children with robin sequence, isolated cleft palate, and unilateral complete cleft lip and palate. Cleft palate-craniofacial J. 2003;40(4):373–96.

5. Horswell BB. The incidence and relationship of cervical spine anomalies in patients with cleft lip and/or palate. J Oral Maxillofac Surg. 1991;49(7):693–7.
6. Ross R, Lindsay W. The cervical vertebrae as a factor in the etiology of cleft palate. Cleft Palate J. 1965;2(3):273–81.
7. Šmahel Z, Škvařilová B. Length of the cervical spine as a factor in the etiology of cleft palate. Cleft palate-craniofacial J. 1993;30(3):274–8.
8. Uğar DA, Semb G. The prevalence of anomalies of the upper cervical vertebrae in subjects with cleft lip, cleft palate, or both. Cleft palate-craniofacial J. 2001;38(5):498–503.
9. Lima MC, Franco EJ, Janson G, Carvalho IMM, Santos CF, Capelozza ALA. Prevalence of upper cervical vertebrae anomalies in patients with cleft lip and/or palate and noncleft patients. Cleft palate-craniofacial J. 2009;46(5):481–6.
10. Karsten A, Sideri M, Spyropoulos M. Morphologic anomalies of upper cervical vertebrae in Swedish children born with nonsyndromic cleft lip and/or palate compared to Swedish children without cleft. Cleft palate-craniofacial J. 2019;56(6):751–8.
11. Sonnesen L, Kjær I. Cervical vertebral body fusions in patients with skeletal deep bite. Eur J Orthod. 2007;29(5):464–70.
12. Sonnesen L, Kjær I. Cervical column morphology in patients with skeletal class III malocclusion and mandibular overjet. Am J Orthod Dentofac Orthop. 2007;132(4):427. e7-. e12.
13. Sonnesen L, Kjær I. Anomalies of the cervical vertebrae in patients with skeletal class II malocclusion and horizontal maxillary overjet. Am J Orthod Dentofac Orthop. 2008;133(2):188. e15-. e20.
14. Sonnesen L. Associations between the cervical vertebral column and craniofacial morphology. Int J Dent. 2010;2010(1):295728.
15. Sonnesen L, Jensen KE, Petersson AR, Petri N, Berg S, Svanholt P. Cervical vertebral column morphology in patients with obstructive sleep Apnoea assessed using lateral cephalograms and cone beam CT. A comparative study. Dentomaxillofacial Radiol. 2013;42(6):20130060.
16. Farman AG, Escobar V. Radiographic appearance of the cervical vertebrae in normal and abnormal development. Br J Oral Surg. 1982;20(4):264–74.
17. Kattan KR, Pais MJ. Some borderlands of the cervical spine: part I: the normal (and nearly normal) that May appear pathologic. Skeletal Radiol. 1982;8:1–6.
18. Sandham A. Cervical vertebral anomalies in cleft lip and palate. Cleft Palate J. 1986;23(3):206–14.
19. Farman A, Nortje C, Joubert JV. Radiographic profile of the first cervical vertebra. J Anat. 1979;128(Pt 3):595.
20. Samson RS, Varghese E, Kumbargere SN, Chandrappa PR. Fused cervical vertebrae: a coincidental finding in a lateral cephalogram taken for orthodontic diagnostic purposes. Case Rep. 2016;2016:bcr2016217566.
21. Gholve PA, Hosalkar HS, Ricchetti ET, Pollock AN, Dormans JP, Drummond DS. Occipitalization of the atlas in children: morphologic classification, associations, and clinical relevance. JBJS. 2007;89(3):571–8.
22. Elmalky MM, Elsayed S, Arealis G, Mehdian H. Congenital C1 arch deficiency: grand round presentation. Eur Spine J. 2013;22:1223–6.
23. Klimo P Jr, Rao G, Brockmeyer D. Congenital anomalies of the cervical spine. Neurosurg Clin North Am. 2007;18(3):463–78.
24. Alhazmi DM, Shi W, Allareddy V, Anamali S, Allareddy TV, Rengasamy Venugopalan S. A cone beam computed tomographic analysis of cervical vertebral nonsegmentation. Oral Surg Oral Med Oral Pathol Oral Radiol. 2024;137(1):67–72.
25. Naji MF, Bhat R. The typical appearance of the inferior accessory ossicle of the anterior arch of the atlas. Surg Radiol Anat. 2009;31:69–71.
26. Ali FE, Al-Bustan MA, Al-Busairi WA, Al-Mulla FA, Esbaita EY. Cervical spine abnormalities associated with down syndrome. Int Orthop. 2006;30:284–9.
27. Koletsis DD, Halazonetis DJ. Cervical vertebrae anomalies in orthodontic patients: a growth-based superimpositional approach. Eur J Orthod. 2010;32(1):36–42.
28. Dahiphale V, Bahetee B. The retro-articular vertebral artery ring of the atlas and its significance. J Anat Soc INDIA. 2009;58(2):149–51.
29. Hasani M, Shahidi S, Hasani M, Pourhoseini AH. Cone beam CT study of the foramen of Huschke: prevalence, and characteristics. Curr Med Imaging. 2018;14(1):99–102.
30. Rajabian MH, Sherkat M. An epidemiologic study of oral clefts in Iran: analysis of 1669 cases. Cleft palate-craniofacial J. 2000;37(2):191–6.
31. Yazdee AK, Saedi B, Sazegar AA, Mehdipour P. Epidemiological aspects of cleft lip and palate in Iran. Acta Medica Iranica. 2011;49(1):54–8.
32. Dogan E, Ergican GO, Dogan S. Evaluation of the cervical vertebral anomalies in patients with cleft lip and palate in Aegean region of Turkey. J Pak Med Assoc. 2021;71(1).
33. Kharbanda OP, Qureshi T, Kandasamy D. Prevalence of cervical vertebrae anomalies in patients with cleft lip and palate. Australasian Orthodontic J. 2019;35(1):46–52.
34. de Rezende Barbosa GL, Pimenta LA, Tyndall DA, Allareddy TV, Sousa Melo SL. Three-dimensional assessment of cervical vertebrae anomalies in patients with cleft lip and palate. Cleft Palate-Craniofacial J. 2021;58(9):1102–9.
35. Dias RCdC, Marzano Rodrigues MN, Trindade-Suedam IK, Trindade SHK. Tomographic evaluation of the upper cervical spine in patients with cleft lip and palate and class III malocclusion. Cleft Palate Craniofac J. 2024;61(11):1894–900.
36. Lustrin ES, Karakas SP, Ortiz AO, Cinnamon J, Castillo M, Vaheesan K, et al. Pediatric cervical spine: normal anatomy, variants, and trauma. Radiographics. 2003;23(3):539–60.
37. McAllister AS, Nagaraj U, Radhakrishnan R. Emergent imaging of pediatric cervical spine trauma. Radiographics. 2019;39(4):1126–42.
38. Arntsen T, Sonnesen L. Cervical vertebral column morphology related to craniofacial morphology and head posture in preorthodontic children with class II malocclusion and horizontal maxillary overjet. Am J Orthod Dentofac Orthop. 2011;140(1):e1–7.
39. Kjaer I. Prenatal traces of aberrant neurofacial growth. Acta Odontol Scand. 1998;56(6):326–30.
40. Jasemi A, Sonnesen L. Tooth agenesis and craniofacial morphology in pre-orthodontic children with and without morphological deviations in the upper cervical spine. World J Stomatology. 2016;5(1):15–21.
41. Hoenig J, Schoener W. Radiological survey of the cervical spine in cleft lip and palate. Dentomaxillofacial Radiol. 1992;21(1):36–9.
42. Rajion ZA, Townsend GC, Netherway DJ, Anderson PJ, Yusof A, Hughes T et al. A three-dimensional computed tomographic analysis of the cervical spine in unoperated infants with cleft lip and palate. The cleft palate-craniofacial journal. 2006;43(5):513–8.
43. Datana S, Bhalla A, Kumar P, Roy SK, Londhe S. Comparative evaluation of prevalence of upper cervical vertebrae anomalies in cleft lip/palate patients: a retrospective study. Int J Clin Pediatr Dentistry. 2014;7(3):168.
44. Srivastava M, Aggarwal A, Batra P, Datana S, Kumar P, Macrcusson KA. Association of cervical vertrebra anomalies with cleft lip and palate. J Cleft Lip Palate Craniofac Anomalies. 2014;1(1):43–7.
45. HENSINGER RN. Congenital anomalies of the cervical spine. Clin Orthop Relat Res (1976–2007). 1991;264:16–38.
46. Bodon G, Glasz T, Olerud C. Anatomical changes in occipitalization: is there an increased risk during the standard posterior approach? Eur Spine J. 2013;22:512–6.
47. Üstdal BT, Evlice B, Duyan Yüksel H. Midface asymmetry in non-syndromic unilateral cleft lip-palate: a retrospective Cbct analysis. Eur Oral Res. 2024;58(2):83–7.
48. Kamei G, Batra P, Singh AK, Arora G, Kaushik S. Development of an artificial Intelligence-Based algorithm for the assessment of skeletal age and detection of cervical vertebral anomalies in patients with cleft lip and palate. Cleft Palate Craniofac J. 2024:10556656241299890.

Publisher's note