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ORIGINAL ARTICLE

Prevalence of Craniofacial Anomalies - 14 Years of Experience in a Brazilian Referral Service

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ABSTRACT

Objective: To delineate the frequency of congenital craniofacial anomalies (CCAs) in a Brazilian reference center. **Material and Methods:** A cross-sectional, retrospective epidemiological study was conducted, updating information from the reference center. Data were extracted from the medical records of patients assisted between January 2009 and December 2022 at the Craniofacial Anomalies Rehabilitation Center (*Centro Pró-Sorriso*) in Alfenas, Brazil. Previous studies were used as a reference for the classification of CCAs. Data were analyzed using statistical software for absolute and relative frequency descriptive analysis. A 95% confidence interval was adopted. Study approved by ethics and research committee. **Results:** 817 records were analyzed, comprising 53.5% males and 46.5% females. Identified 954 congenital anomalies (CAs); of these, 86.9% of cleft lip and/or palate (CL/P), 16.0% of CAs without CL/P, and 2.8% of syndromes or sequences recognized in the absence of CL/P. The CAS most commonly associated with any CL/P were cardiovascular system anomalies (23%), and the most common CL/P was cleft palate (48.7%). **Conclusion:** Among the CAs, CL/P was the most prevalent, exhibiting a higher ratio in males. Following CL/P, ear anomalies were the most commonly observed; however, when associated with the presence of any CL/P, cardiovascular system anomalies were more numerous. Regarding the presence of syndromes and/or sequences, Goldenhar Syndrome was more prevalent in cases without an association with clefts.

Keywords: Congenital Abnormalities; Craniofacial Abnormalities; Cleft Lip; Cleft Palate; Epidemiology.

Introduction

Congenital anomalies (CAs) are developmental defects, structural, functional, behavioral, or metabolic alterations that compromise an individual's physical, intellectual, or social well-being [1]. The most prevalent CAs are nervous system anomalies (neural tube defects such as spina bifida, anencephaly, and encephalocele), cleft lip and/or palate (CL/P), musculoskeletal system anomalies, and cardiovascular anomalies [2,3].

The CA etiology remains unknown in 50 to 60% of cases. However, it is acknowledged that 20-25% have a multifactorial cause, 7-10% are associated with environmental factors, 7-8% are monogenic, and 6-7% are chromosomal [4]. Specific preventive measures for CAs can be implemented, including rubella vaccination, prenatal care, prevention of sexually transmitted infections (STIs), and supplementation with folic acid and other micronutrients. Additionally, the severity of CAs can be mitigated through early diagnosis [5].

Approximately 240,000 newborns worldwide die each year due to congenital diseases [6]. A previous study conducted in Central China revealed that between 1997 and 2019, the incidence of CAs was 122.5 per 10,000 births [7]. Most low-income countries do not have a structured prenatal screening and diagnosis system, which contributes to the increased incidence of births of babies with CAs [8]. Children with congenital craniofacial anomalies (CCAs) are at an elevated risk of various clinical alterations, including respiratory and feeding disorders, which may have enduring effects and potentially evolve into various complications over time [9].

Individuals with CCAs maintain a normal life expectancy. However, they frequently contend with alterations in speech, hearing, appearance, and psychological adjustments. These challenges may exacerbate over time without proper treatment and monitoring [10-12]. Considering the high prevalence and significant impact of craniofacial anomalies (CAs) on the quality of life of affected individuals, it is essential to understand their distribution in various contexts, particularly in Brazil, where comprehensive data are limited. This study aims to assess the frequency of CAs at a Brazilian referral center for craniofacial anomaly rehabilitation to inform improvements in public health policies and enhance prevention and early intervention strategies.

Material and Methods

Study Design and Ethical Clearance

A cross-sectional, retrospective epidemiological study was conducted, updating information from the reference center. The Research Ethics Committee approved the present study by protocol number 6,318,929.

Data Collection

Data were extracted from the medical records of patients assisted between January 2009 and December 2022 at the Craniofacial Anomalies Rehabilitation Center (*Centro Pró-Sorriso*) in Alfenas, Minas Gerais. Data collection was carried out from December 2022 to February 2023.

For the extraction of clinical data from the records, information was analyzed according to the type of CCAs (adapted from Vallino-Napoli et al. [13] and Jaruratanasirikul et al. [14], including: (1) cleft lip and/or palate (CL/P), defects resulting from incomplete development of the lip and/or palate; (2) syndromes or sequences recognized in the absence of cleft lip and/or palate (RSS); (3) single or multiple congenital anomalies without cleft lip and/or palate (SMCA); (4) congenital anomalies associated with cleft lip and/or palate (CACL/P) without a defined syndrome or sequence. The classification of orofacial clefts was divided into four groups concerning the incisive foramen [15], as follows: (1) isolated cleft lip (CL): complete or incomplete, unilateral or bilateral; (2) cleft lip and palate (CLP): transforaminal, unilateral or bilateral; (3) isolated cleft palate (CP): post-foraminal, complete or incomplete; (4) rare orofacial cleft (ROC). Clinical records were jointly

reviewed and analyzed by two examiners who had received prior training. The collected variables included: (1) gender; (2) presence or absence of orofacial cleft; (3) type of orofacial cleft; (4) frequency of congenital malformations; (5) presence of syndromes; (6) syndromes with the presence of orofacial clefts; and (7) frequency of malformations identified in association with orofacial clefts. Records with incomplete and/or incorrect information were excluded from the analysis.

Data Analysis

The clinical data collected from the records were used to construct a database, utilizing the Statistical Package for the Social Sciences, version 22.0 (IBM Corp., Armonk, NY, USA), for descriptive statistical analyses of frequency and percentile, as well as calculations of sex ratios and their respective confidence intervals (95%).

Results

A total of 817 records were analyzed, comprising 437 (53.5%) males and 380 (46.5%) females, ranging in age from 5 days to 83 years. Within this cohort, 954 CAs were identified. Concerning the frequency of CAs, 710 cases (86.9%) of CL/P, 131 (16.0%) of congenital anomalies without CL/P (SMCA), and 23 (2.8%) of syndromes or sequences recognized in the absence of CL/P (RSS) were observed. CL and CLP were more prevalent in males (1.42:1 and 1.73:1, respectively), while CP was more frequent in females (1.74:1). When all cases were considered together, the male-to-female ratio was 1.14 (Table 1).

Table 1. Distribution of specific types of non-syndromic cleft lip and/or palate, according to gender.

Specific Types	Total N (%)	Male N (%)	Female N (%)	Male: Female Ratio (CI 95%)
Isolated Cleft Lip	167 (23.5)	98 (58.7)	69 (41.3)	1.42 (1.14–1.77)
Cleft Lip and Palate	306 (43.1)	194 (63.4)	112 (36.6)	1.73 (1.46–2.05)
Isolated Cleft Palate	236 (33.2)	86 (36.4)	150 (63.6)	0.57 (0.47–0.69)
Rare Orofacial Cleft	1 (0.1)	1 (100.0)	0 (0.0)	
Total	710 (100.0)	379 (53.4)	331 (46.6)	1.14 (1.03–1.27)

In this study, 23 cases of RSS were identified. The most prevalent were Goldenhar Syndrome, with 7 cases; Treacher Collins Syndrome, with 4 cases; and Hereditary Ectodermal Dysplasia, with 4 cases. Table 2 describes the syndromes and sequences with CL/P found in this study, totaling 46 cases.

Table 2. Distribution of syndromic clefts.

Syndromes	Isolated Cleft Lip N (%)	Cleft Lip and Palate N (%)	Isolated Cleft Palate N (%)	Total N (%)
Pierre Robin Sequence	0 (0.0)	1 (10.0)	20 (58.8)	21 (45.6)
Van der Woude Syndrome	1 (50.0)	4 (40.0)	1 (2.9)	6 (13.0)
Patau Syndrome	0 (0.0)	3 (30.0)	0 (0.0)	3 (6.5)
Apert Syndrome	0 (0.0)	0 (0.0)	2 (5.8)	2 (4.3)
Treacher Collins Syndrome	1 (50.0)	0 (0.0)	1 (2.9)	2 (4.3)
Orofaciodigital Syndrome	0 (0.0)	0 (0.0)	2 (5.8)	2 (4.3)
Cornelia de Lange Syndrome	0 (0.0)	0 (0.0)	2 (5.8)	2 (4.3)
Aarskog Syndrome	0 (0.0)	1 (10.0)	1 (2.9)	2 (4.3)
Blepharophimosis Syndrome	0 (0.0)	0 (0.0)	1 (2.9)	1 (2.2)
Kabuki Syndrome	0 (0.0)	0 (0.0)	1 (2.9)	1 (2.2)
Wolf-Hirschhorn Syndrome	0 (0.0)	0 (0.0)	1 (2.9)	1 (2.2)
Moebius Syndrome	0 (0.0)	0 (0.0)	1 (2.9)	1 (2.2)
Down's Syndrome	0 (0.0)	1 (10.0)	0 (0.0)	1 (2.2)
Pallister-Killian Syndrome	0 (0.0)	0 (0.0)	1 (2.9)	1 (2.2)
Total	2 (4.3)	10 (21.7)	34 (73.9)	46 (100.0)

Ear anomalies were the most common alteration in the SMCA group (Table 3). In this group, five patients were identified with ear anomalies associated with maxillomandibular defects, three individuals with ear anomalies and musculoskeletal anomalies, three patients with a combination of ocular anomalies with musculoskeletal anomalies, two patients with anomalies of the nervous system and the ear, and two individuals with anomalies of the nervous system associated with ocular anomalies. The SMCA most related to the RSS were ear anomalies (13 cases), with 7 cases associated with Goldenhar syndrome, followed by maxillomandibular defects (6 cases) and musculoskeletal anomalies (6 cases).

Table 3. Frequency of single or multiple congenital malformations without cleft lip and/or palate.

Single or Multiple Anomalies	N [% (CI 95%)]
Ear anomalies	42 [32.1 (24.7–40.5)]
Eye anomalies	25 [19.1 (13.3–26.7)]
Musculoskeletal Anomalies	15 [11.4 (7.0–18.0)]
Facial hemangioma	11 [8.4 (4.7–14.4)]
Maxillomandibular Defects	11 [8.4 (4.7–14.4)]
Cardiovascular abnormalities	7 [5.3 (2.6–10.6)]
Nose anomalies	6 [4.5 (2.1–9.6)]
Nervous system anomalies	6 [4.5 (2.1–9.6)]
Tongue malformations	3 [2.3 (0.8–6.5)]
Growth anomalies	3 [2.3 (0.8–6.5)]
Limb/extremity anomalies	2 [1.5 (0.1–5.4)]
Total	131

CI 95%: 95% Confidence Interval.

Of the 710 cases of CL/P found in this study, 93 (13%) presented additional CAs, with some patients exhibiting more than one CA. The CA most commonly associated with any CL/P was cardiovascular system anomalies (26 cases, 23%), and the most common CL/P was CP (55 cases, 48.7%) (Table 4).

Table 4. Frequency of malformations associated with orofacial clefts.

Anomaly	CL	CLP	CP	ROC	Total
	N (%)	N (%)	N (%)	N (%)	N (%)
Cardiovascular system	1 (6.6)	8 (19.5)	16 (29.0)	1 (50.0)	26 (23.0)
Musculoskeletal system	2 (13.3)	7 (17.0)	9 (16.3)	0 (0.0)	18 (15.9)
Uvula anomalies	4 (26.6)	1 (2.4)	7 (12.7)	0 (0.0)	12 (10.6)
Nose anomalies	2 (13.3)	6 (14.6)	1 (1.8)	0 (0.0)	9 (8.0)
Extremity/limb changes	1 (6.6)	4 (9.7)	3 (5.4)	0 (0.0)	8 (7.1)
Facial hemangioma	2 (13.3)	3 (7.3)	2 (3.6)	0 (0.0)	7 (6.2)
Congenital clubfoot	1 (6.6)	3 (7.3)	3 (5.4)	0 (0.0)	7 (6.2)
Tongue malformations	0 (0.0)	2 (4.8)	4 (7.2)	0 (0.0)	6 (5.3)
Eye anomalies	0 (0.0)	3 (7.3)	2 (3.6)	1 (50.0)	6 (5.3)
Ear anomalies	2 (13.3)	1 (2.4)	2 (3.6)	0 (0.0)	5 (4.4)
Maxillomandibular Defects	0 (0.0)	1 (2.4)	4 (7.2)	0 (0.0)	5 (4.4)
Growth anomalies	0 (0.0)	1 (2.4)	2 (3.6)	0 (0.0)	3 (2.7)
Nervous system	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	1 (0.9)
Total	15 (13.3)	41 (36.3)	55 (48.7)	2 (1.7)	113 (100.0)

CL: Isolated Cleft Lip; CLP: Cleft Lip and Palate; CP: Isolated Cleft Palate; ROC: Rare Orofacial Cleft.

Discussion

This study constitutes an update of a previous investigation [12]. In line with prior findings, CL/P emerged as the most prevalent CAs. CL/P ranks among humans' most frequently identified congenital anomalies and stands as the predominant craniofacial congenital anomaly [16,17]. A study conducted in Saudi Arabia similarly reported an elevated prevalence of CL/P among patients with CCAs [18]. A similar survey in Iraq

noted a higher occurrence of CL/P in conjunction with a dysmorphic face [19]. Interestingly, in the Colombian population, a higher incidence of ear anomalies was observed [20]. In Brazil, the prevalence of orofacial clefts ranges between 0.19 and 1.54 per thousand live births [21,22].

Among the patients with CL/P, 53.5% were male, with a ratio of 1.14:1, mirroring previous findings [10-13,18,23]. Other studies also underscore a greater prevalence of CL/P in males [23-25]. Associations between gender and CL/P manifestation are diverse, with studies [24,26] proposing that genetic factors, including sex-related genes on the Y chromosome, and modifiable factors such as exposure to sex hormones contribute to the male predilection for CL/P. Furthermore, Daliri et al. [26] found that the risk of CAs in males is 1.25 times higher than in females.

CLP constituted the most prevalent form, accounting for 43.1% of cases, followed by CP (33.3%), CL (23.5%), and CLP with floor of the nose involvement (0.1%). CLP and CL were more frequently observed in males, while CP was more prevalent in females. Gender-specific variations in the prevalence of different types of clefts have been reported, with males exhibiting a greater predisposition to CLP and/or CL and females being more affected by CP [23,27-29]. The heightened incidence of CP in females may be linked to hormonal influences, X chromosome-linked patterns, and the fact that palate closure occurs a week later than in males, expanding the timeframe for potential failures during the formation process [30].

The association of orofacial clefts with other CAs or a syndromic pattern was identified in 13% of participants. Notably, CP was the most associated with other CAs (48.7%), aligning with other related studies [28,30-32], highlighting that the proportion of CP associated with additional anomalies surpasses that for CL and CLP [31]. The CAs most commonly associated with CL/P were anomalies of the cardiovascular and musculoskeletal systems, corroborating previous reports [2,3]. However, Paranaíba et al. [33] noted that tongue malformations, alterations of the nervous system, and limb/extremity malformations were the most frequently encountered in association with CL/P.

Among the syndromes and sequences identified in this study, the most prevalent were the Pierre Robin sequence, Goldenhar syndrome, and Van der Woude syndrome. These syndromes primarily relate to disorders involving craniofacial structures, which constitute the primary focus of the treatment center [34]. Pierre Robin sequence emerged as the most common in patients with CL/P. Additionally, CP was the most prevalent cleft in syndromic patients, mirroring findings from other studies [18,35]. The heightened incidence of the Pierre Robin sequence, particularly associated with CP, may stem from insufficient mandibular growth due to collagen deficiency and Meckel cartilage growth, leading to tongue retropositioning and hindering the fusion process of palatal shelves [36,37].

The manifestations resulting from CL/P can extend beyond the craniofacial complex, affecting other organic systems and leading to issues in the cardiovascular and respiratory systems, anemias, and mental health alterations during adulthood [25]. Moreover, children with orofacial clefts are predisposed to cognitive and learning disorders [25].

Among the most globally prevalent CAs are nervous system anomalies, facial anomalies (CL/P), and musculoskeletal, cardiovascular, urogenital, and digestive system anomalies [17,18,32]. Within the subset of patients with CL/P, the most frequent were ear anomalies (32.1%), ocular anomalies (19.1%), and musculoskeletal anomalies (11.5%), aligning with the findings of Paranaíba et al. [12].

Unfortunately, it was not feasible to assess the risk factors (maternal education, maternal and/or paternal age, previous abortions, family income, education, and others) associated with CAs due to the unavailability of this pertinent data in the medical records. We recommend initiating new studies investigating

potential risk factors linked to CAs in diverse populations to gain a deeper understanding of the etiology of these conditions. As a limitation, this study was conducted in a Brazilian reference center for craniofacial deformities, which may account for the heightened incidence of anomalies related to the face and skull (CL/P, ear anomalies, and ocular anomalies) compared to other body regions. Additionally, the population served in the unit predominantly hails from a small geographic area, mainly residents of the southern region of Minas Gerais. Therefore, conducting studies encompassing a broader range of the Brazilian territory is imperative.

Conclusion

Among the congenital anomalies, cleft lip and/or palate were the most prevalent, exhibiting a higher ratio in males for both cleft lip and palate and isolated cleft lip. Following oral clefts, ear anomalies were the most commonly observed, followed by ocular anomalies; however, cardiovascular system anomalies were more numerous when associated with any cleft lip and/or palate. Regarding the presence of syndromes and/or sequences, Goldenhar Syndrome was more prevalent in cases without an association with clefts. In contrast, the Pierre Robin sequence was more prevalent with cleft lip and/or palate. We suggest further investigating congenital craniofacial anomalies in other locations to outline local variables that may inform potential risk factors for these malformations.

Authors' Contributions

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All authors declare that they contributed to a critical review of intellectual content and approval of the final version to be published.

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Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

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