ANDES PEDIATRICA
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Andes pediatr. 2023;94(1):37-44
DOI: 10.32641/andespediatr.v94i1.4179

ORIGINAL ARTICLE

Studies of sleep and therapeutic actions in children and adolescents with craniofacial anomalies

Estudios de sueño y conducta terapéutica en niños y adolescentes con alteraciones craneofaciales

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Received: December 21, 2021; Approved: July 4, 2022

What do we know about the subject matter of this study?

Sleep-disordered breathing is common in pediatric patients with craniofacial anomalies (CFA), so their specific diagnosis is essential to choose the appropriate approach and reducing multisystemic sequelae.

What does this study contribute to what is already known?

This group of patients presents a high prevalence of obstructive sleep apnea-hypopnea syndrome (OSAHS), with major severity in cleft lip and palate and craniosynostosis. The type of therapeutic decision was associated with OSAHS diagnosis and not with the type of CFA, being mainly surgical initially and dental subsequently.

Abstract

Objective: To describe the presence of obstructive sleep apnea syndrome (OSAS) in children with craniofacial anomalies (CFA), associate biodemographic characteristics and polygraph variables, and analyze the therapeutic management decided after the sleep study and the evaluation by a multidisciplinary team. **Patients and Method:** Retrospective study. Polygraphs were performed on patients aged between 1 month and 19 years with CFA. An initial and projected management was established categorized into ventilatory support, tracheostomy, surgery, dental, and medical treatment. Descriptive and inferential statistics were performed, evaluating the association between demographic and polygraph variables and therapeutic management. **Results:** 34 patients were included with a median age of 4.0 years (IQR 0.9 - 6.5). Diagnosis was 41.2% cleft lip and palate, 35.3% craniosynostosis, and 23.5% micrognathia. Polygraphs were altered in 70.6% of the cases; of these, 26.5% were diagnosed

Keywords:
Pneumonology;
Polygraphy;
Apnea;
Craniofacial Anomalies;
Therapeutic Behavior;
Obstructive Sleep Apnea Syndrome;
Craniosynostoses;
Cleft Lip and Palate;
Micrognathism

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How to cite this article: Andes pediatr. 2023;94(1):37-44. DOI: 10.32641/andespediatr.v94i1.4179

as mild, 5.9% moderate, and 38.2% severe OSAS. There was an association between minimum saturation and diagnosis of OSAS (p = 0.0036), and in the presence of OSAS with the initial management applied (p=0.0013). There was no significant relationship between the different types of CFA with the initial therapeutic management (p = 0.6565). Initial and projected managements, respectively: Ventilatory support (11.8% and 2.9%), tracheostomy (11.8% and 0%), surgery (35.2% and 26.5%), dental (20.6% and 53%), and medical treatment (20.6% and 17.6 %). **Conclusions**: 70% of the patients with CFA presented OSAS. The greatest severity was found in Cleft Lip and Palatine and Craniosynostosis. Therapeutic management was mainly oriented towards initial surgical and planned dental treatments based on the diagnosis of OSAS and not on the type of CFA.

Introduction

Craniofacial anomalies (CFA) are alterations of the craniofacial anatomy, caused by disorders in the formation or development of the different tissues. They are attributable to environmental or genetic causes generated during intrauterine life and vary as the individual grows, showing postnatal morphofunctional alterations due to a lack of skeletal or soft tissue or alterations in the fusion of facial processes[1]. We have focused on the first three categories of Whitaker's classification of CFA: I) Clefts, II) Synostosis, and III) Hypoplasia[2].

Obstructive sleep apnea-hypopnea syndrome (OSAHS) is the most common sleep disorder in children with CFA, with a prevalence that may vary according to the type of anatomical alteration and the method used for its diagnosis[3].

The most frequent CFA is cleft lip and palate, with an incidence of 1 in 1000 live births and 1 in 585 live births in Chile[4], and those affecting the soft palate are the most related to OSAHS. This alteration of the oropharyngeal musculature negatively affects the maintenance of airway patency, especially during sleep, resulting in a higher incidence of OSAHS[3,5]. Based on pediatric sleep questionnaires, a prevalence between 14-32% of OSAHS has been reported in this group of patients[6,7].

In the case of synostoses, they have an incidence of 1 in 2500 live births[3]. The risk of OSAHS is associated with midfacial hypoplasia and its consequent obstruction of the upper airway, however, additionally the increase in intracranial pressure, the affection to the respiratory center, and the higher frequency of Chiari malformation predispose to the presence of central apneas among which we can find the Apert, Crouzon, and Pfeiffer syndromes[4]. The prevalence of OSAHS in this group has been described as between 50-87%[8,9].

Hypoplasias, mainly those related to mandibular development such as micrognathia, can generate a marked secondary retrognathism, with the consequent collapse of the upper airway by retrusion of the muscular insertions[1,3,5,10,11]. The Pierre Robin sequence stands out, with an incidence of 1 in 8500 live births. Since the incidence of OSAHS in this group of patients is high (85-100%) and the signs are relatively subtle, screening for sleep-disordered breathing (SDB) is recommended in all these patients[3,12].

OSAHS can generate multisystemic repercussions, including neurocognitive, cardiovascular, and metabolic conditions, significantly impacting the quality of life[13]. Objective sleep studies, such as polysomnography and polygraphy, allow us to diagnose and determine its degree and contribute to the evaluation of specific therapeutic results[14,15]. In this group of patients, dealing with OSAHS constitutes a challenge for health teams, and should ideally be managed by multidisciplinary teams[3].

There are several treatments applied to the pediatric population with diagnosis of OSAHS associated or not with CFA, some of which are based on non-invasive medical treatments, such as Non-Invasive Ventilation (NIV) and nasal corticosteroids[16]. In contrast, other approaches are of greater complexity, such as surgical interventions ranging from adenotonsillectomy to mandibular osteodistraction in micrognathia, Pierre Robin sequences in mandibular hypoplasia, and midfacial advancement in craniosynostosis[15,17,18].

The objective of this work was to describe the presence of OSAHS in children with CFA to associate biodemographic characteristics and polygraphic variables, as well as to describe and analyze the therapeutic approach decided after the sleep study and the evaluation by a multidisciplinary team.

Patients and Method

Retrospective study. We included records of polygraphies performed on children and adolescents aged 1 month to 19 years, with a diagnosis of CFA and suspected OSAHS, in the Pediatrics Service of the *Hospital Dr. Guillermo Grant Benavente* in Concepción, Chile, between January 2013 and December 2019. Records of

those patients with previous airway surgeries were excluded, except for adenotonsillectomy. The suspicion of OSAHS was performed by interviewing the primary caregiver, asking about the presence of habitual snoring (snoring ≥ 3 days per week), apneas, or awakenings witnessed by the parents.

The polygraph results were analyzed by a team of specialists formed by a bronchopulmonary, otolaryngologist, maxillofacial surgeon, and a dentist, establishing a course of action. The initial therapeutic approach was defined as that applied immediately and then a projected approach, based on the clinical context, severity of the polygraphic result, and persistence of the patient's symptoms after the polygraphic results. The projected approach would be implemented in no less than 6 months from the application of the initial treatment.

The following approaches were implemented: 1) NIV: initiated in the hospital and continued at home, 2) Tracheostomy: associated or not with ventilatory support, 3) Surgical: mandibular osteodistraction, fronto-orbital advancement with bone distraction of the middle third of the face, 4) Dental: orthodontic treatment performed before orthognathic surgery, and 5) Medical treatment: nasal corticosteroids and/or anti-leukotrienes.

Polygraphy

The Alice Pdx® (Philips Respironics®) equipment was used which recorded the channels corresponding to nasal flow with nasal pressure transducer, oxygen saturation, heart rate, microphone, and thoracic and abdominal band and was installed by a professional trained in technical and methodological aspects of the examination. Those polygraphies with at least 4 hours of recording and with less than 20% of time of disconnections and/or artifacts were considered acceptable. Examinations that did not meet these conditions were excluded.

Variables

Demographic and clinical data were recorded, in addition to the following polygraphic variables: duration of the validated study in hours and minutes, the apnea/hypopnea index (AHI), mixed obstructive apnea/hypopnea index (MOAHI), mean oxygen saturation, and minimum oxygen saturation. In addition, the initial and projected therapeutic approaches of each patient included in the study were recorded. Also, the severity degree of OSAHS was determined and was categorized according to the AHI score. In patients up to 13 years of age, AHI < 1 was considered normal, mild AHI 1- 5, moderate AHI 5-10, and severe AHI > 10. In those participants older than 13 years, AHI < 5 was considered normal, mild AHI 5- 15, moderate > 15 -30, and severe > 30 according to the recommendations of the American Academy of Sleep Medicine[19].

Statistical Analysis

Normality analysis was performed for each of the variables using the Shapiro-Wilk test. Descriptive statistics were performed with the calculation of median and interquartile range for quantitative variables which were expressed as percentages and absolute values. The Kruskal-Wallis test was used to compare polygraphic variables between CFA categories. In addition, the correlation between the age of the participants and the polygraphic variables (AHI, MOAHI, and minimum and mean saturation) was determined by calculating Spearman's Rho coefficient. The association between minimum saturation and mean saturation with the presence of OSAHS was determined using the Mann-Whitney U test. Additionally, the Chi-Square test was used to analyze the relationships between minimum saturation values < 80%, CFA categories, and initial therapeutic approaches with the diagnosis of OSAHS. Finally, the association between the initial approach with the type of CFA and projected approaches was also determined. For these analyses, the following were considered as dependent variables: minimum saturation, minimum saturation < 80%, mean saturation, and initial and projected therapeutic approaches; and as independent variables the presence of OSAHS and diagnosis of CFA. Statistical analysis was performed in SPSS Statistics v23 software and a p-value < 0.05 was considered significant.

Ethical considerations

This study was performed according to the guidelines of the Declaration of Helsinki of the World Medical Association and was approved by the Scientific Ethical Committee of the Health Service of Concepción, Chile (No. 19-12-113). The data analyzed were entered into a spreadsheet without personal identification information and the file was password-protected.

Results

34 patients aged 4.0 years (IQR 0.9 - 6.5) were admitted to the study, 56% were female. All patients underwent 36 polygraphies, with diagnosis of CFA and suspected OSAHS, hospitalized in the pediatric service of the hospital. 2 patients were excluded due to previous tracheostomies. In relation to the diagnostic categories of the participants, cleft lip and palate account for 41.2%, craniosynostosis 35.3%, and micrognathia for 23.5%.

Regarding the overall results of the polygraphies, the total validated time was 7.3 hours (5.9-8.0). The

mean saturation was 96% (94-96.2), with 83% of minimum saturation (72.2-89.2). An AHI of 3.9 (1.7-14.9) and a MOAHI of 3 (1.6-13.7) were observed. Table 1 shows the overall results of the polygraphies performed, according to CFA categories.

Regarding the diagnostic conclusion of the polygraphies, 29.4% were normal (Figure 1). Of the altered polygraphies, 26.5% were diagnosed as mild, 5.9% as moderate, and 38.2% as severe OSAHS. There was no significant difference in minimum saturation or mean saturation between the CFA groups (p = 0.125 and p = 0.450, respectively).

Besides, the AHI and MOAHI did not show significant differences between the CFA categories (p = 0.301 and p = 0.382, respectively). However, in patients with cleft lip and palate, there were markedly higher values in AHI of 7.5 (1.8-30.3) and MOAHI of 4.7 (1.7-30.3).

Considering the total sample, the initial therapeutic approach most frequently applied was surgical management, accounting for 35.2%. In the case of cleft lip and palate patients, this approach corresponded to 42.9% of the cases, in Micrognathia to 25%, and in craniosynostosis to 33.3%. Regarding the projected approaches, the most frequently applied was dental treatment with 53% (Figure 2).

Statistically significant associations were found between minimum saturation and diagnosis of OSAHS (p = 0.0036), between minimum saturation values < 80% and presence of OSAHS (p<0.001), and in the presence of OSAHS with the initial approach applied (p = 0.0013). There was no relationship between mean saturation values and diagnosis of OSAHS (p = 0.183). Table 2 shows the correlations between the quantitative variables.

There was no significant relationship between the different types of CFA and the initial therapeutic approach (p = 0.6565) nor was there a statistical association between the type of CFA and the existence of OSAHS (p = 0.3949).

There was a significant association between initial and projected approaches (p = 0.003), with the relationship between initial surgical management and projected approaches as the most significant (p = 0.038).

Discussion

The frequency of OSAHS in the sample studied was 70.6%, with different degrees of alteration according to the defined criteria and without significant differences in the respiratory indices between the CFA groups evaluated. However, there was a greater alteration of these indexes in the cleft lip and palate and craniosynostosis categories, which could be explained by the greater degree of upper airway obstruction in this group of patients, mainly due to a small retropalatal area along with the deficient development of soft tissues derived from the pharyngeal arches and to the higher frequency of association with genetic syndromes[20-22].

Patients with cleft lip and palate presented the highest percentage of severe OSAHS, accounting for 50% of the cases. On the other hand, the micrognathia category presented the highest proportion of results within normal ranges and mild OSAHS (75%). This severity degree difference of OSAHS between these 2 categories of CFA has been attributed to the lesser structural compromise in the upper airway of patients with isolated mandibular hypoplasia compared with cleft lip and palate patients[5,11].

In relation to the correlation analysis of the polygraphic indices, a strong positive correlation between AHI and MOAHI stood out, showing a predominant obstructive pattern in the breathing of the sample. This explains the approach considered to de-

Table 1. Polygraph results according to CFA

Variables	Total (n = 34)	CLP (n = 14)	MG (n = 8)	CRS (n = 12)	p value[a]
Gender (F/M)	19/15	5/9	4/4	10/2	-
Age (years)	4 (0.9-6.5)	2 (0.2-5.2)	5 (3-10.4)	4.9 (2-12.5)	0.243
Total validated time (h)	7.3 (5.9-8.0)	6.7 (5.5-7.6)	7.1 (6.6-7.9)	7.8 (6-8.5)	0.303
Validated time (min)	441 (358.5-482.2)	402 (333.7-460.5)	429 (402-478.5)	468 (365.5-514.5)	0.299
Average saturation (%)	96 (94-96.2)	95.5 (92.5-97)	96 (96-96)	95 (91.7-97.5)	0.450
Minimum saturation (%)	83 (72.2-89.2)	74 (68-86)	88.5 (80.2-91.5)	85 (76.5-89.5)	0.125
AHI	3.9 (1.7-14.9)	7.5 (1.8-30.3)	2.7 (0.6-10.3)	4 (1.7-14.3)	0.301
OMAHI	3 (1.6-13.7)	4.7 (1.7- 30.3)	2.5 (0.6-10.3)	2.4 (1.7-11.5)	0.382

F: Female; M: Male; FLP: Cleft lip palate; MG: Micrognathia; CRS: Craniosynostosis; IAH: apnea hypopnea index; OMAHI: obstructive and mixed apnea hypopnea index. a Kruskal Wallis. A p value < 0.05 was considered significant. Quantitative variables were expressed in median and interquartile range.

Table 2. Correlations between polygraphic variables

Variables	Average saturation (%)	Minimum saturation (%)	AHI	OMAHI
Age (years)	Rho = 0.192 p = 0.235[a]	Rho = 0.529 p = < 0.001[a]	Rho = -0.219 p = 0.175[a]	Rho = -0.215 p = 0.183[a]
Average saturation (%)	- -	Rho = 0.498 p = 0.001[a]	Rho = -0.276 p = 0.084[a]	Rho = -0.232 p = 0.150[a]
Minimum saturation (%)	- -	- -	Rho = -0.625 p = < 0.001[a]	Rho = -0.588 p = < 0.001[a]
AHI	- -	- -	- -	Rho = 0.989 p = < 0.001[a]
OMAHI	- -	- -	- -	- -

AHI: Apnea hypopnea index; OMAHI: Obstructive and mixed apnea hypopnea index. [a]Spearman's rho. A p value < 0.05 was considered significant.

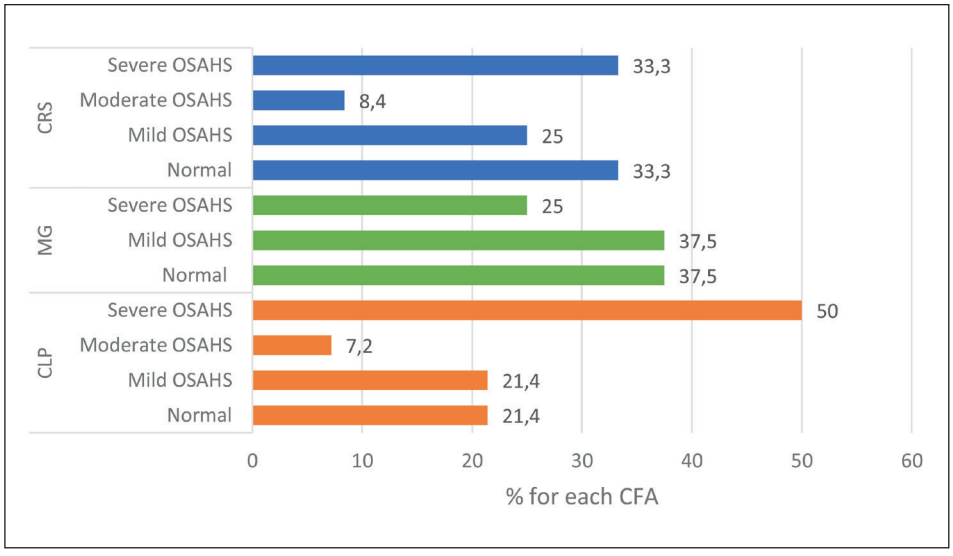

Figure 1. Diagnostic conclusion of polygraphs according to CFA categories. CFA: Craniofacial anomaly; CLP: Cleft lip- palate; MG: Micrognathia; CRS: Craniosynostosis; OSAHS: Obstructive sleep apnea hypopnea syndrome, Values were expressed in percentages in relation to each CFA.

cide the initial therapeutic management, which was exclusively aimed at decreasing the obstruction degree in the upper airway of these patients. In this sense, our study with polygraphy allowed us to identify the presence and degree of severity of OSAHS in the different types of CFA studied, being useful when prioritizing treatment strategies according to the needs of each patient. This fact is supported by the results of studies that have used sleep studies for the diagnosis of SDB in these pathologies[5,21].

In all patients with altered studies, specific therapeutic approaches were adopted aimed at reducing the alteration in the polygraphic variables and/or the severity degree of OSAHS in order to avoid potential multisystemic effects that have been documented in the pediatric population[13]. The initial approach mainly applied was surgical treatment with 35.2%, which is related to the fact that an important group of the sample was diagnosed with severe OSAHS (38.3%), requiring corrective surgeries of the maxillomandibular and/or Fronto-orbital structure to successfully reverse the degree of obstruction in these patients, most of whom corresponded to cleft lip and palate patients and with craniosynostosis, thus explaining this initial treatment approach.

In the cleft lip and palate group, almost one-third of the patients with severe OSAHS required tracheostomy as an initial procedure due to the high structural compromise of the upper airway in these patients, which is often difficult to reverse with more conservative methods. However, NIV was successfully used in some patients with severe OSAHS with diagnoses of

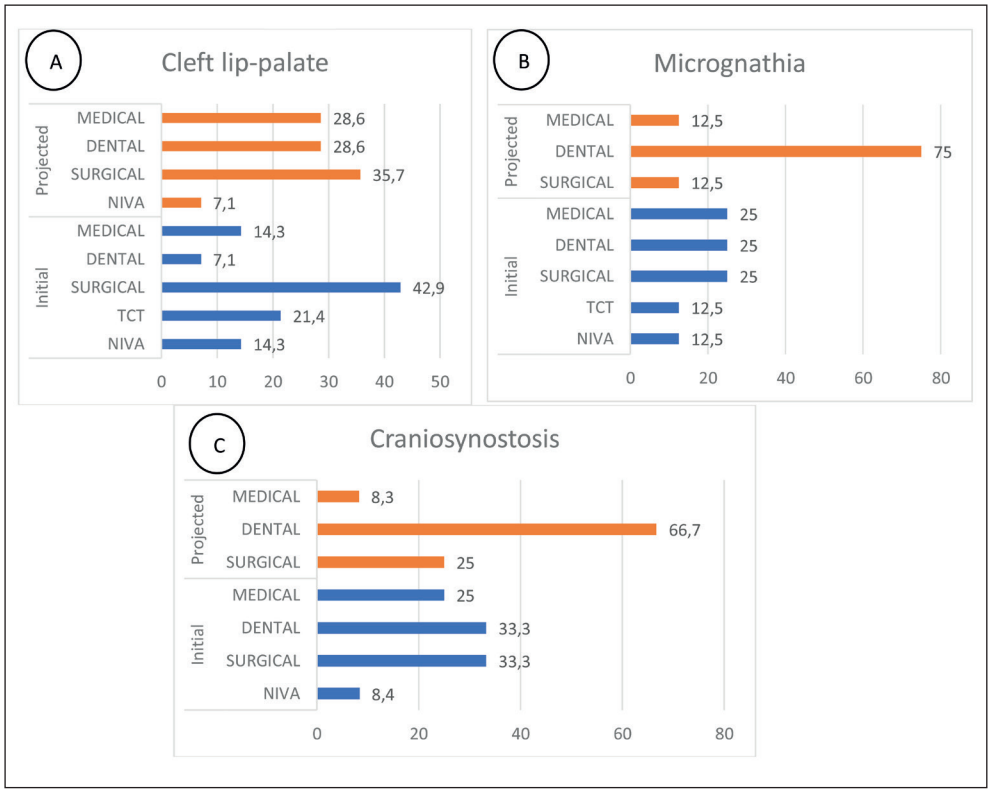

Figure 2. Initial and projected actions applied according to CFA: **A)** Cleft lip- palate, **B)** Micrognathia, **C)** Craniosynostosis. CFA: Craniofacial anomaly; NIVA: Non-invasive ventilatory assistance; TCT: Tracheostomy. Values were expressed in percentages with respect to each CFA category.

cleft lip and palate, micrognathia, and craniosynostosis since, given the severity of respiratory symptoms in this group, immediate treatment was required while surgical planning was being carried out by the team of specialists[23].

Initial medical and dental treatments were applied almost exclusively in patients with mild OSAHS or with normal grade polygraphy (92.9%); of these, half corresponded to the diagnosis of craniosynostosis. The decision of medical treatment as initial approach in these cases was based on the effectiveness of the use of nasal corticosteroids in improving respiratory indices in pediatric patients with mild OSAHS[16]. On the other hand, orthodontic treatment in these patients with craniosynostosis played an important role as initial approach since it helped to correct dental structures, thus facilitating the application of long-term treatments by the maxillofacial specialist. In addition, the severity degree of OSAHS did not make invasive interventions necessary.

We can affirm that, in general, the projected therapeutic approach of the patients was mostly dental management, with 75% in patients with micrognathia. This can be explained by the fact that a significant number of patients with mandibular hypoplasia underwent mandibular osteodistraction surgery as an initial procedure, requiring orthodontic treatment as projected approach to ensure an optimal surgical result in the medium and long term[24].

It is relevant to point out that no case considered tracheostomy as a projected approach given that good results have been demonstrated in reversing or improving the degree of OSAHS with the application of surgical and dental measures throughout childhood in this group of patients[25-27].

According to our analysis results, the statistically significant association between minimum saturation and the diagnosis of OSAHS may be useful when prioritizing the initiation of therapeutic approaches in pediatric patients with CFA, especially those with minimum saturation < 80% since, in these cases, this association was considerably higher.

Although there was a relationship between the presence of OSAHS and its severity with the initial approach applied, there was no significant association between the types of CFA and the initial therapeutic approach followed. From this analysis, we can say that the variable that determined in greater proportion the decision of a specific initial therapeutic approach, according to the clinical condition of each patient, was the diagnosis of OSAHS.

In general, the initial approaches were statistically associated with those projected, but when this analysis was carried out considering each initial approach separately, there was only a significant association in the case of surgical management as the initial approach.

This could be explained by the fact that most of our patients with CFA required this treatment as initial management, involving surgeries of important structures at maxillomandibular and upper airway levels, which determined as coadjuvant projected therapeutical approaches to ensure the correct evolution of these surgeries, thus contributing to reverse the symptoms and degree of severity of OSAHS in the sample studied.

Polysomnography is the test of choice for the diagnosis of SDB, however, its availability in our sphere is currently quite limited, so some international and expert recommendations recommend using polygraphy as an alternative test to improve diagnostic accessibility, as we did in our study[28].

This study has certain limitations that should be pointed out. Since it is a retrospective study, there was no follow-up of patients, not allowing us to analyze the subsequent effect of the applied approaches. In addition, the sampling method entails a lack of clinical information to better describe the sample studied and there was no history of genetic studies, only malformations associated with patients with syndromic CFA. Three different CFA groups were included in the sample since there is a scarce sample of patients with these pathologies. This study constitutes an attempt to characterize this population and is part of the need to progress in differentiating the therapeutic approaches applied in patients with CFA. However, future studies with better methodological quality should be conducted to verify the evaluation properties of polygraphy in the effectiveness of treatments applied in these patients.

Conclusions

70% of patients with CFA presented some type of OSAHS and 44% presented moderate to severe OSAHS. The greatest severity was observed in children and adolescents with cleft lip and palate and craniosynostosis. Therapeutic approaches were mainly oriented to initial surgical and dental treatments and the decision was associated with the diagnosis of OSAHS and not with the type of CFA. There is a need to actively and systematically study sleep in this at-risk group in order to be able to provide assertive therapeutic actions according to the needs of each patient.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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