Sleep-Disordered Breathing in Children with Cleft Palate

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Sleep-Disordered Breathing in Children with Cleft Palate

PhD thesis presented by

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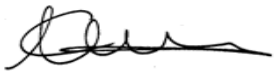

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Abbreviations

ADHD	Attention-deficit/hyperactivity disorder
AHI	Apnea-hypopnea index
AASM	American Academy of Sleep Medicine
BMI	Body Mass Index
CDC	Centers for Disease Control
CI	Confidence interval
CL/P	Cleft lip and/or palate
CP	Cleft palate
EC	Early childhood
GI	Global Index
HS	Habitual snoring
MED	Middle ear disease
NE	Nasal emission
OR	Odds ratio
OSA	Obstructive sleep apnea
PLMS	Periodic limb movements
PSG	Polysomnography
PSQ	Pediatric Sleep Questionnaire
QoL	Quality of life
RLS	Restless leg syndrome
SD	Standard deviation
SDB	Sleep-disordered breathing
SRBD	Sleep-related breathing disturbance
SRMD	Sleep-related movement disorders
TST	Total sleep time
VPI	Velopharyngeal insufficiency

Summary

Introduction: One in 700 newborns in the United States is born with cleft palate every year. It is estimated that the prevalence of sleep-disordered breathing symptoms in children with cleft palate, compared with children without craniofacial anomalies, is about three-fold higher. Recurrent and persistent episodes of upper airway obstruction during sleep in typically developing children has been associated with health and neurodevelopmental morbidities, including behavioral problems, learning difficulties, poor school performance, low quality of life and depressive symptoms. Behavioral problems are common in children with orofacial clefts. However, to date only one study has investigated the impact of Sleep-Disordered Breathing in this pediatric population, and no study has assessed other sleep disorders such as sleep-related movement disorders and the impact on daytime functioning in pediatric cleft populations, who may be a particularly susceptible cohort not only for Sleep-Disordered Breathing, but also for Sleep-related movement disorders due to functional difficulties. In addition, children with repaired cleft palate are also at high risk for middle ear disease and speech problems, two medical conditions routinely assessed in this pediatric population. The common risk factors, peak incidence, and close pathophysiology between middle ear disease, habitual snoring, the cardinal symptom of Sleep-Disordered Breathing, and speech problems have prompted some authors to suggest that these conditions may be related in general pediatric populations. Nevertheless, the association between these three common medical problems, that might impact positively on early diagnosis of Sleep-Disordered Breathing, has not been investigated in children with cleft palate.

Objectives: The aims of this study were: 1. To assess the frequency of Sleep-Disordered Breathing in preschool and school age children with cleft palate and to investigate whether Sleep-Disordered Breathing, and its severity play a role in neurobehavioral outcomes/quality of life in the study population, 2. To investigate the frequency and characteristics of habitual snoring, middle ear disease and speech problems in the same pediatric population, and to assess the association between these three medical conditions, 3. To investigate for the first time the frequency of Sleep-related movement disorders and growing pains symptoms in young children with non-syndromic cleft palate, and to determine differences in daytime (internalizing and externalizing symptoms) and bedtime behavior between Sleep-related movement disorders and growing pains in this patient populations.

Methods: Parents of children between 2.0 and 7.9 with different non-syndromic cleft palate anomalies (isolated cleft palate, cleft lip and/or palate, and Pierre Robin sequence) completed the Pediatric Sleep Questionnaire, a middle ear disease questionnaire, and the Conners' Early Childhood Scale. Symptomatic children were referred for a nocturnal polysomnography. Audiograms and speech assessment were also conducted.

Results: Ninety-five children were enrolled, 15% of children screened positive for Sleep-Disordered Breathing or reported habitual snoring and 84.6% were identified with sleep apnea. Ninety-eight per cent reported middle ear disease, 17.1% speech problems, 14.1% screened positive for periodic limb movements, 8.5% reported restless legs syndrome symptoms and 9.9% growing pains.

Positive screening for Sleep-Disordered Breathing was associated with an elevated frequency of behavioral problems (elevated T-scores for anxiety and physical symptoms, and significant differences in mean T-scores for inattention/hyperactivity, social functioning/atypical behavior, social functioning, and mood), and lower quality of life scores for emotional and family well-being. Children with moderate/severe apnea compared to those with mild apnea showed differences in mean T-score for externalizing behavioral problems (aggressive and defiant temper), and lower family quality of life scores.

Habitual snoring and early episodes of middle ear disease were more likely to be reported for children with isolated cleft palate when compared to those with cleft lip and palate. While children with cleft lip and palate had a higher frequency of middle ear disease with effusion compared to those with Robin sequence. The odds ratio for habitual snoring in children with ≥ 1 episode of otitis media in the last year was 7.37 (95% confidence interval 1.55–35.15, p=0.012). Moreover, there was a trend for children with speech problems reported by parents to have habitual snoring.

Children who screened positive for periodic limb movements and restless legs syndrome were more likely to report sleepiness and long sleep latency compared to those who did not endorse the respective sleep problems. However, these differences were not statistically significant between children with and without growing pains. Children who reported periodic limb movements had a higher T-score for emotional and somatic symptoms. Sleepiness was associated to an increased frequency of externalizing, psychiatric and somatic problems. While children with long sleep latency reported more emotional and somatic symptoms, and those with reduced sleep duration more

internalizing difficulties.

Conclusions: In children with cleft palate the presence of Sleep-Disordered Breathing and moderate/severe sleep apnea was associated with behavioral problems and lower family well-being. Anatomical factors play a role in the frequency of upper airway symptoms in children with cleft palate. A recent history of at least one episode of middle ear disease was associated with an increased frequency of habitual snoring. Parents of young children with cleft palate reported frequently periodic limb movements, restless leg syndrome and growing pains. Daytime/bedtime behavior varies depending on the presence of sleep-related movement disorders. Sleepiness and sleep variables might play a role on behavioral problems in children with cleft and Sleep-related movement disorders symptoms.

Resum

Introducció: Un de cada 700 nounats als Estats Units neix amb fissura palatina cada any. S'estima que la prevalença dels símptomes respiratoris durant el son en nens amb paladar fes, en comparació amb nens sense anomalies craniofacials, és aproximadament tres vegades superior. Episodis recurrents i persistents d'obstrucció de la via aèrea superior durant el son en población pediátrica general s'han associat amb problemes de salut i comorbiditats del neurodesenvolupament com ara problemes de comportament, dificultats d'aprenentatge, baix rendiment escolar, pitjor qualitat de vida i símptomes depressius. Els problemes de comportament són comuns en nens amb fissura palatina. Fins ara només un estudi ha investigat l'impacte dels trastorns respiratoris durant el son en aquesta població pediàtrica. I no hi ha cap estudi que hagi avaluat altres trastorns del son, com ara trastorns del moviment relacionats amb el son i l'impacte en el funcionament diürn, tot i tractar-se d'una població particularment susceptible a causa de les dificultats funcionals que presenta. D'altra banda, els nens amb fissura palatina tenen un risc elevat de presentar patología de l'oïda mitja i problemes del llenguatge, dues condicions mèdiques avaluades de forma rutinaria en aquesta població pediàtrica. La patología de l'oïda mitja, els símptomes respiratoris obstructius i els trastorns del llenguatge tenen factors en comú com ara factors de risc i mecanismes fisiofisiopatològics. No obstant, l'associació entre aquestes tres patologies, que podria afavorir el diagnòstic precoç dels trastorns respiratoris durant el son, no s'ha investigat fins ara en nens amb fissura palatina.

Objectius: Els objectius d'aquest estudi eren: 1. Avaluar la freqüència dels trastorns respiratoris durant el son en nens en edat preescolar i escolar amb fissura palatina i investigar el paper de la presència i la severitat dels trastorns respiratoris durant el son en els problemes neuro-conductual i de qualitat de vida en la població de l'estudi, 2. Investigar la freqüència i les característiques del ronc habitual, de la patología de l'oïda mitja i els problemes del llenguatge en una mateixa població pediàtrica, i avaluar l'associació entre aquestes tres condicions mèdiques, 3. Investigar per primera vegada la freqüència dels trastorns del moviment relacionats amb el son i els dolors de creixement en nens de curta edat amb fissura palatina congènita no-sindròmica, i determinar les diferències en el comportament diürn (internalització i externalització) i nocturn, previ a l'inici del son, entre els diferents tipus de trastorns del moviment relacionats amb el son i els dolors de creixement en la población d'estudi.

Mètodes: Pares/mares de nens d'entre 2,0 i 7,9 amb diferents anomalies congènites del paladar no-sindròmiques (paladar fes aïllat, llavi leporí i paladar fes, i seqüència de Pierre Robin) van completar el Qüestionari de Son Pediàtric, un qüestionari sobre la patologia de l'oïda mitja i l'Escala de la infantesa primarenca de Conners. Els nens simptomàtics van ser derivats per fer a una polisomnografia nocturna. També es van dur a terme audiogrames i l'avaluació de la parla.

Resultats: Un total de 95 van ser reclutats, dels quals el 15% dels nens presentar un cribratge positiu pels trastorns respiratoris durant la son o ronc de forma habitual i el 84,6% van ser diagnòsticats d'apnea del son. El 98% van presentar antecedents de patología de l'oïda mitja, el 17,1% problemes del llenguatge, el 14,1% van presentar un cribratge positiu pels moviments periòdics de cames, el 8,5% síndrome de cames neguitoses i el 9,9% dolors creixement.

La presència d'un cribratge positiu pels trastorns respiratoris durant el son es va associar amb una freqüència elevada de problemes de comportament (puntuacions elevades per ansietat i símptomes físics, i diferències significatives en les puntuacions mitjanes per problemes d'atenció/hiperactivitat, funcionament social/conducta atípica i l'estat d'ànim), i una pitjor puntuació per qualitat de vida a nivell emocional i familiar. Els nens amb apnea moderada/severa, en comparació amb aquells amb apnea lleu, van mostrar diferències significatives en la puntuació mitjana per problemes conductuals d'externalització (temperament agressiu i desafiant), i pitjor puntuació en la qualitat de vida en el àmbit familiar.

Els nens amb fissura palatina aïllada van reportar amb més freqüència ronc de forma habitual i episodios d'otitis mitja durant els primers mesos de vida en comparació amb aquells nens amb llavi leporí i paladar fes. Per altra banda, els nens amb llavi leporí i paladar fes tenien una major freqüència d'otitis mitja serosa en comparació amb aquells amb seqüència de Pierre Robin. La ràtio de risc de presentar ronc habitual en nens amb ≥ d'un episodi d'otitis mitja en l'últim any va ser de 7,37 (interval de confiança del 95% 1,55-35,15, p=0,012). Finalment, els nens amb problemes del llenguatge reportat pels pares van mostrar també una tendència a presentar ronc habitual.

Els nens amb cribratge positiu pels moviments periòdics de les cames i síndrome de les cames neguitoses presentaren amb més freqüència somnolència diürna i una latència de son allargada en comparació amb aquells que no van presentar aquests problemes. No es van objetivar diferències significatives en aquestes dues variables de son en nens amb i sense dolors de creixement. La presència de moviments periòdics de cames es

va associar a un augment en la puntuació per símptomes emocionals i somàtics. Els problemes conductuals d'externalització van ser més freqüents en nens amb somnolència diürna, així com els problemes psiquiàtrics i somàtics. Per altra banda, els nens amb latència de son allargada van reportar més símptomes emocionals i somàtics, i aquells amb un temps de son reduït més problemes conductuals d'internalització.

Conclusions: En nens amb fissura palatina, la presència de trastorns respiratoris durant el son i/o apnea moderada/severa es va associar amb problemes de comportament i pitjor qualitat de vida, especialmente en l'àmbit familiar. D'acord amb els resultats d'aquest estudi els factors anatòmics tenen un paper en la freqüència dels símptomes relacionats amb la via aèrea superior en nens amb paladar fes. Per altra banda, l'antecedent d'un episodi d'otitis mitja en l'últim any es va associar amb un increment en la incidència del ronc. Tant la presència de moviments periòdics de cames, com de cames neguitoses o dolors de creixement van ser reportats amb freqüència pels pares/mares de nens amb paladar fes, variant els problemes del comportament diürn/nocturn en relació amb el tipus de trastorn. La presència de somnolència diurna, així com alteracions en variables de son podrien intervindre en els problemes conductuals en nens amb fissura palatina i trastorns del moviment relacionats amb el son.

1. BACKGROUND

1.1. Definition

A cleft is an opening or a fissure of the lip or of the roof of oral cavity which is not normally open as a result of developmental anomalies during gestation. Orofacial clefts include a heterogeneous group of birth defects including cleft lip, isolated cleft palate and cleft lip and palate. Cleft lip (CL) consists in an opening from the lateral side of the upper lip to the philtrum and the alveolus. When the CL extends to the palatine suture it is considered a cleft lip and palate (CL/P), but sometimes the opening of the roof of oral cavity appears alone and is defined as isolated cleft palate (CP). Severity of clefts can vary widely. The mild form of CP is considered in those cases located in the uvula, while the severest form affects the soft palate. A complete CP involves the uvula, soft and hard palate.

1.2. Cleft lip and/or palate: Epidemiology, classification, and embryology

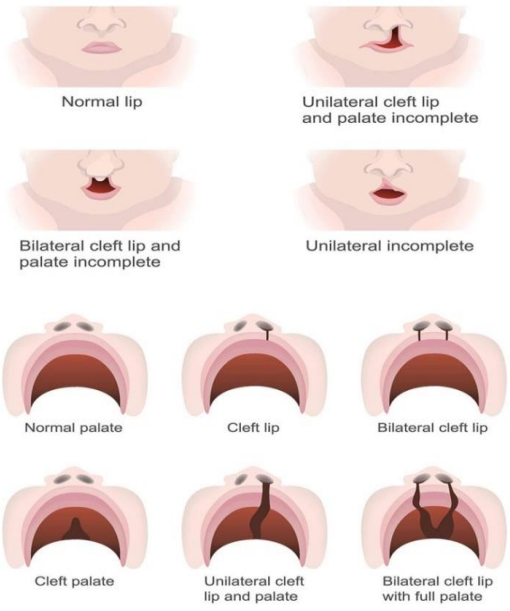
Craniofacial anomalies are highly prevalent congenital malformations, exceeded only by cardiovascular malformations. Approximately one in 700 children born in the United States has CL/P.[1] The incidence of CL/P varies between genders and different ethnic populations. Isolated cleft palate occurs more commonly in females (1/2000), approximate 2:1 ratio compared to males, likely due to the delay in the fusion of the palatal shelves in female embryos.[2] Asian populations (China, Japan) have the highest incidence (3.6/1000) of orofacial cleft, Sub-Saharans, Africans, and African Americans the lowest (0.2-1.7/1000), and Caucasians and Native Americans an intermediate incidence (0.9-2.7/1000).[3–5] Moreover, prevalence of this craniofacial anomaly varies among different geographical areas. In fact in Europe, Northern countries have higher incidence, in particular Finland with the highest incidence of CP in the world (2.6-8.1/1000), while Southern countries of Europe, such Portugal (0.8/1000), have lower.[1,6–8] According to the EUROCAT epidemiological study published in 2007 orofacial clefts can be divided into four groups: non-syndromic CL/P, non-syndromic isolated cleft palate, syndromic CL/P, and syndromic isolated cleft palate.[6] The non-syndromic clefts

represent approximately 71% with the remaining 29% of cases associated with other malformations (musculoskeletal, central nervous and cardiac systems), chromosomal aberrations and syndromes.[6] The most common orofacial cleft is cleft lip and palate (46%), followed by isolated cleft palate (33%). Unilateral clefts are more common than bilateral with a ratio of 4:1, and occur more frequently on the left side.[5] See **Figure 1**.

Pierre Robin sequence was described in 1923 by a French stomatologist.[9] This craniofacial anomaly, characterized by mandibular hypoplasia, glossoptosis, airway obstruction and in 80–90 % of cases cleft palate, is not considered a syndrome. The incidence of Pierre Robin sequence varies from 1/8500 to 1/30,000 newborns.[10]

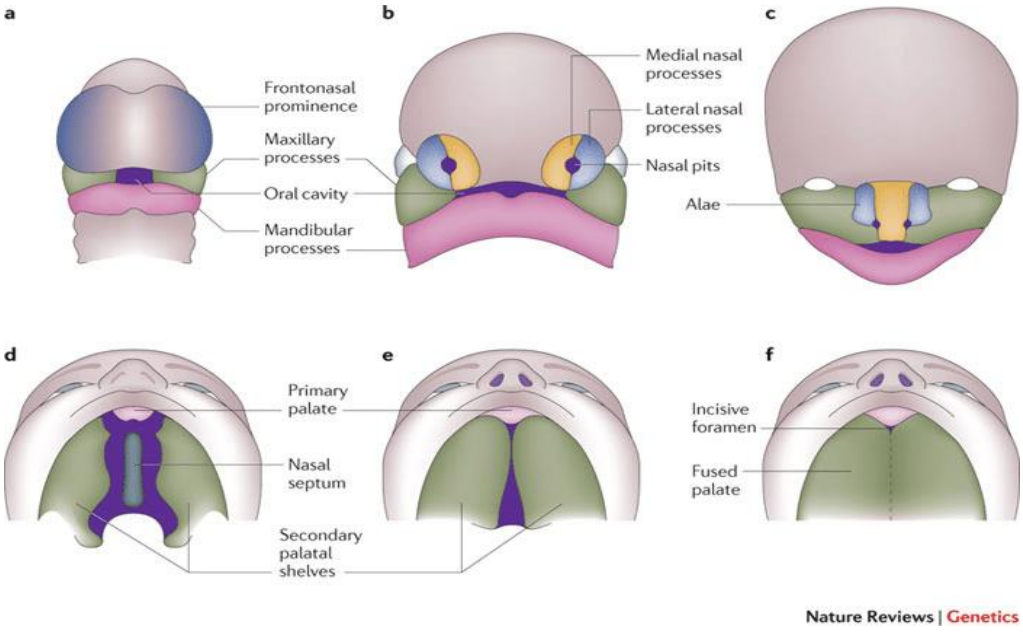
Regarding to the embryological development, cleft lip and/or palate results from a failure of fusion of the medial nasal prominence (from the fronto-nasal prominence) to contact or to maintain contact with the lateral nasal and maxillary processes that occurs between the 6th and 9th weeks of embryologic development. See **Figure 2**. The variety of fusion patterns between the two prominences results in heterogeneous degree of orofacial cleft as it is shown in **Figure 1**.

Figure 1 Types of cleft lip and/or palate



The pathophysiological mechanism of these craniofacial anomalies is still unknown. However, accumulating evidence suggests that genetic or unmodifiable factors (gender, ethnicity, positive family history or advanced age of parents), and environmental or modifiable factors are involved in the genesis of orofacial clefts. Intrauterine exposure during the periconceptional period and the first trimester of gestation to alcohol, phenytoin, and other anticonvulsants, retinoic acid, maternal tobacco smoking as well as nutrition deficiencies and hyperglycemia have been associated with an increased risk of cleft palate in the offspring. Moreover, while specific genes have been identified associated to syndromic cleft palates and to Pierre Robin sequence, it has been hypothesized that multiple genes are involved in non-syndromic cleft lip and palate.[11,12] Some of the main genes involved in non-syndromic cleft palate embryology are summarized in **table 1**. In addition, genes related to folate and homocysteine metabolism are also essential in cell proliferation, cell death, migration and differentiation and they have been investigated for their potential association with cleft palate.

Figure 2 Development of lip and palate in humans



Dixon MJ, Marazita ML, Beaty TH and Murray JC Cleft lip and palate: understanding genetic and environmental influences. Nature Reviews Genetics, (2011): 12(3), 167-178.)[13]

The disruption of the development of both facial and airway structures impacts in several important upper airway functions such as breathing, feeding, hearing, speech, and even growth and other developmental functions. Therefore, early surgical management of CL/P is mandatory to closure the velopharyngeal port and minimizes speech and eating difficulties. Repair of the cleft palate is usually undertaken between 6 and 14 months of age but may be delayed until 4 years of age. The timing and surgery repair varies depending on three factors: type of cleft palate, comorbidities associated with the orofacial cleft and the surgical team. However, concern about palatal operations has been raised due to the increased risk of upper airway obstruction.

Table 1 Genes involved in cleft palate embryology

Gene	Locus	Function	Studies
CDH1 Cadherin	16q22.1	Cell-adhesion: Participates in the epithelial-mesenchymal transition, allowing the palatal fusion	Letra 2009[14]
CRISPLD2	16q24.1	Cell-adhesion: Involved in cellular migration	Chiquet 2007[15] Swindell 2015[16]
JAG2	14q32.33	Cell-adhesion: Participates in the signaling mechanism during the palatal development for the correct adhesion of the palatal selves	Casey 2006[17]
IRF6	1q32.2	Cell-adhesion: Participates also in the signaling mechanism during the oral epithelial differentiation	Richardson 2009[18]
FOXE1	9q22.33	Cell-adhesion: It is a transcription factor, which are required for proper palatal formation	Venza 2011[19]
TGFA	2p13.3	Cell-adhesion: Probably involved in the fusion of the palatal shelves at the level of the medial edge	Lidral 1998[20] Letra 2012[21]
TCOF1	5q32-q33.1	Cell proliferation: Participates in the formation of the neural crests	Dixon 2006[22]
MSX1	4p16.2	Cell proliferation: Plays a critical role in the epithelial-mesenchimal interaction during the formation of craniofacial bones	Satokama and Maas, 1994[23]
TBX22	Xq21.1	Cell proliferation: Involved in the mesenchymal proliferation and elevation of palatal shelves	Marçano 2004[24] Stanier and Moore 2004[25]
PAX7	1p36.13	Cell proliferation: Participates in the formation of the neural crests.	Monsoro-Burq 2015[26]
GRHL3	1p36.11	Cell proliferation: Intervenes in the processes of closure of the neural tube and craniofacial development	Peyrard-Janvid 2014[27]
ROCK1	18q11.1	Cell migration: Regulates stress fiber, focal adhesion and modulates cytoskeleton organization	Philips 2012[28]
FLNB	3p14.3	Involved in cytoskeleton-dependent cell proliferation, differentiation, and cell migration.	Hu 2014[29,30]

1.3. Sleep-disordered breathing in general pediatric populations

Since the first report by Guilleminault in 1976 of several cases of pediatric obstructive sleep apnea (OSA),[31] knowledge about prevalence, mode of presentation, and negative outcomes associated with untreated OSA has notably improved in general pediatric population.

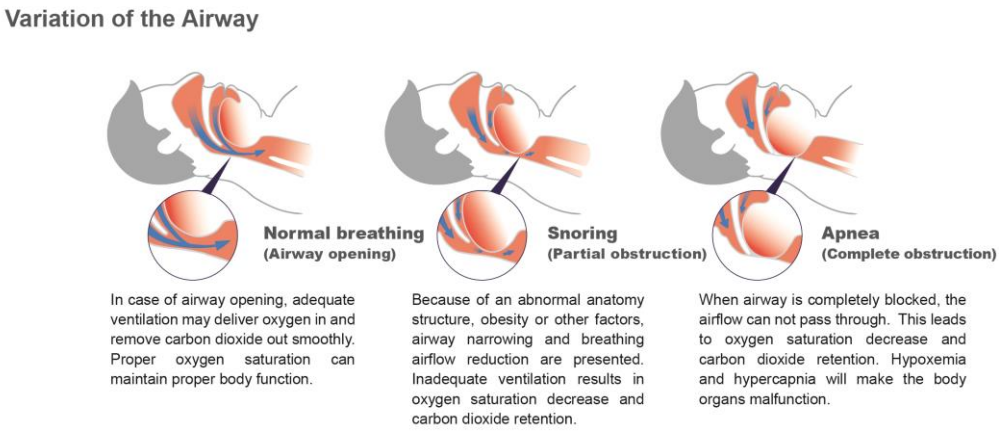
Sleep-disordered breathing (SDB) is a common medical condition in young children that encompasses a range of breathing disorders during sleep, from habitual snoring at one end of the spectrum to OSA at the other **(Table 2).** The latter is characterized by recurrent episodes of upper airway obstruction during sleep that causes, intermittent hypoxemia, disruption of normal ventilation and multiple arousals that results to significant medical and neurobehavioral morbidity. In general pediatric populations, it is estimated that approximately 11% have habitual snoring reporting by parents and about 4% have OSA based on polysomnography.[32–37] However, the prevalence of pediatric SDB could vary widely depending on the severity and the diagnostic method employed.[32,34,38–40]

Table 2 Definition of obstructive sleep-disordered breathing and its clinical entities

Obstructive sleep-disordered breathing (SDB) A syndrome of upper airway dysfunction during sleep characterized by snoring and/or increased respiratory effort that result from increased upper airway resistance and pharyngeal collapsibility
Obstructive SDB clinical entities
I. **Primary snoring**, the mildest and most prevalent manifestation, which is defined as habitual snoring for more than 3 nights per week without apnoeas, hypopnoeas, frequent arousals or gas exchange abnormalities.
II. **Upper airway resistance syndrome (UARS)** comprises snoring, increased work of breathing and frequent arousals, without recognizable obstructive events or gas exchange abnormalities.
III. **Obstructive hypoventilation** is characterized by snoring plus elevated end-expiratory carbon dioxide partial pressure in the absence of recognizable obstructive events.
IV. **OSA syndrome** manifests with recurrent events of partial or complete upper airway obstruction (hypopnoeas, obstructive or mixed apnoeas) with disruption of normal oxygenation, ventilation, and sleep pattern.

In a typically developing population, SDB occurs in all ages, but is especially prevalent in preschool and young school children between 2 and 6 years of age when adenotonsillar hyperplasia, considered the main risk factor, is most common.[41] Upper airway obstruction has been correlated not only with an increase of soft tissue structures, but also to a narrow anatomical airway, especially in older children. Positive family history of snoring is common in pediatric SDB. Other risk factors related to SDB are: allergies or recurrent upper airway infections such bronchitis or otitis media, gastroesophageal reflux, obesity and overweight, hypothyroidism, neuromuscular disease and craniofacial malformations.[41–47] All these anatomical and/or functional factors results in a narrow or dysfunctional upper airway that leads to increased upper airway collapsibility, decreased upper airway patency and respiratory drive **(Figure 3).**

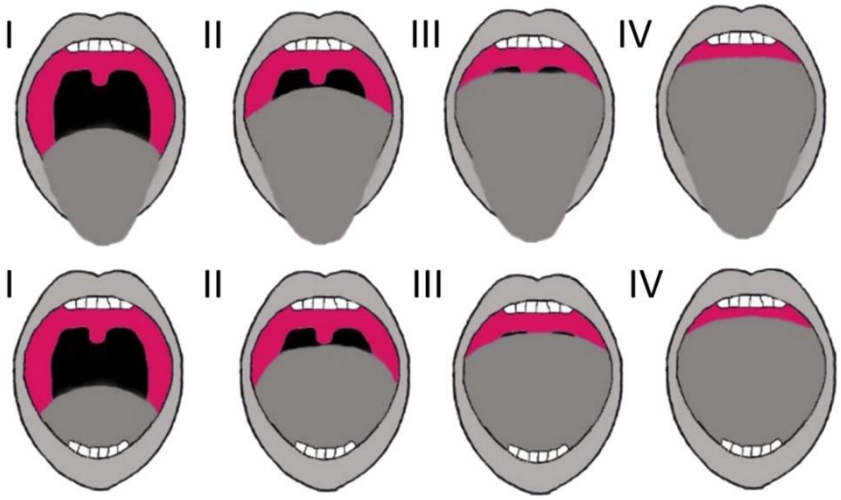
Figure 3 Variation of upper airway on normal breathing, snoring and OSA



According to the Task Force on the diagnosis and management of obstructive SDB in children aged 2-18 years of the European Respiratory Society published in 2016 recognition of a child at risk for SDB has been summarized in the following four points (at least one or more should be positive):[48]

- Symptoms of upper airway obstruction, frequently reported by parents, such as habitual and loud snoring, witnessed sleep apnea, mouth breathing, restless sleep, nighttime awakenings, sweating or abnormal sleeping positions.
- Physical examination: tongue size, palatal, uvula and lip integrity, tonsils size (Mallampati and Friedman classification **Figure 4**),[49] lateral facial profile (retrusive chin or mandibular hypoplasia), type of breathing (nasal or mouth, hyponasality), occlusion, obesity, allergic rhinitis, neuromuscular disorders, craniofacial malformations, and syndromes. It should be noted that many children with SDB have a normal physical examination.
- Prematurity or family history of SDB
- Objective findings of SDB: lateral neck radiography, flexible nasopharyngoscopy, cephalometry, upper airway MRI or CT. However, radiological evaluation is not routinely used on SDB assessment in clinic.

Figure 4 Diagram of modified Mallampati (upper row) and Friedman tongue position (lower row) grades



In 2007 Gozal et al proposed to differentiate two types of OSA: 1. Type I for a child with an OSA associated with marked lymphadenoid hypertrophy without obesity, 2. Type II for a overweight or obese child with OSA, associated with mild lymphadenoid

hyperplasia.[50] This second phenotype is similar to adults. Clinical differences between pediatric Type I and II of OSA are shown in **table 3**.

Table 3. Types I and II for pediatric OSA

Clinical Presentation of Pediatric OSA types I and II.

SIMILARLY FREQUENT SYMPTOMS AND FINDINGS SNORING DIFFICULTY BREATHING DURING SLEEP WITH SNORTING EPISODES RESTLESS SLEEP AND FREQUENT AWAKENINGS EXCESSIVE SWEATING NIGHT TERRORS ENURESIS BREATHING PAUSES REPORTED BY PARENTS MOUTH BREATHING AND LIMITED NASAL AIRFLOW CHRONIC RHINORRHEA FREQUENT VISITS TO PRIMARY CARE PHYSICIAN FOR RESPIRATORY-RELATED SYMPTOMS RETROGNATHIA PULMONARY HYPERTENSION AND COR PULMONALE		
	Type I	**Type II**
Excessive daytime sleepiness	+	++++
Weight gain	–	++
Hyperactive behavior	++++	– or +
Truncal obesity	– or +	+++
Enlarged neck circumference	– or +	+++
Enlarged Tonsils/Adenoids	++++	++
Depression and low self-esteem	+	+++
Shyness and social withdrawal	+	+++
Left ventricular hypertrophy	++	++++
Systemic hypertension	+	++++
Recurrent ear infections	+++	– or +
Insulin Resistance	–	++++
Dyslipidemia	+	++++
Elevated C-Reactive Protein	++	++++
Elevated Liver Enzymes	–	++

– : absent

- + infrequent to ++++ - very frequent

Nocturnal polysomnography (PSG) or polygraphy is considered the gold standard to objective diagnosis and severity assessment of OSA and it is recommended prior to adenotonsillectomy.[48]

1.4. Sleep-disordered breathing in children with cleft palate

Craniofacial anomalies such as CL/P have been associated with an increased risk of SDB compared to general pediatric populations. To date, the limited literature about the prevalence of SDB symptoms in this pediatric population suggests that the frequency of obstructive symptoms varies from 21% up to 37%, which represents between two and

almost four-fold increase compared to children without craniofacial anomalies.[43,51–53] The summary of published research studies about the prevalence of SDB in children with CL/P and Pierre Robin (PR) sequence is shown in **table 4**. The retrospective study of Muntz, published in 2008, included 539 medical records of children with cleft palate over three years and found that 22% reported SDB symptoms.[54] MacLean, in a prospective study, assessed for the first time the frequency of SDB symptoms in 248 infants and preschoolers with cleft palate using a standardized questionnaire, the pediatric sleep questionnaire (PSQ).[55,56] Results of this study showed that 31% of children screened positive for SDB.[56] Robison et al in a retrospective research investigated 459 children aged from 0 to 18 years with CP and 48 children with PR sequence for the presence of snoring and/or apneas. This study identified obstructive sleep symptoms in 37.5% of children with CP and in 73% of children with PR sequence.[53] The studies of Silvestre and Moraleda-Cibrián, both published in 2014, have several points in common: large sample sizes, the same screening tool for SDB (the PSQ), same age range of the study population, and they were not retrospective studies.[43,57] The incidence of positive screening for SDB – about 15% - was a little bit lower in the study of Silvestre compared to previous studies.[57] Moraleda-Cibrián and colleagues in a large cohort of children with craniofacial malformations that included a diagnosis of different orofacial clefts found that 21% of children with CL/P, 23% with CP and 43% with PR sequence screened positive for SDB.[43]

The frequency objectively-measured OSA based on symptomatic pediatric populations with orofacial clefts is considerably high. See **table 4**. MacLean et al published the first study that investigated the frequency of OSA in this pediatric population.[58] This retrospective review of PSG data found that 87% of children with CP were found to have OSA and 28% of these had severe OSA. A few years later the retrospective studies of Robison and Moraleda-Cibrián et al showed similar results (83% in children with non-syndromic cleft palate: 89% for CP, 81% for CL/P and 86% in PR sequence

respectively).[53,59] The recent retrospective study of Khayat et al found a lower frequency of OSA (48%) in a review of PSG data of infants with PR sequence likely due to the small sample size and the younger age of the study population.[60]

Table 4 Summary of studies about the prevalence of SDB and OSA in children with isolated cleft palate, cleft lip and palate or Pierre Robin sequence

Author	Year	Type of study	Age	N	Methods	Results
MacLean[58]	2008	Retrospective	Children	62	PSG	PSG consistent for OSA: 87%
Muntz[54]	2008	Retrospective	Children	539	Medical history	Symptoms suggestive of SDB: 22%
MacLean[56]	2009	Prospective	0-5 years	248	Questionnaire	Positive symptoms for SDB: 31.4%
Robison[53]	2011	Retrospective	0-18 years	459 + 48 Pierre Robin sequence	Medical history + PSG	Snoring and/or apneas: 37.5% PSG positive for OSA: 83.1% PR sequence: symptoms of SDB 72.9%, OSA 33.3%
Silvestre[57]	2014	Prospective	2-18 years	867	Questionnaire PSQ	Incidence of positive screening for SDB was 14.7%
Moraleda-Cibrián[43]	2014	Cross-sectional	2-18 years	575	Questionnaire PSQ	Positive screening for SDB 21% of children with CLP, 23% with CP and 43% of children with PR sequence
Moraleda-Cibrián[59]	2015	Retrospective	2-18 years	151	PSG	PSG positive for OSA: 89% CP, 81% CLP and 86% PR sequence
Khayat[60]	2017	Retrospective	Infants	46	PSG	PSG positive for OSA 47.8%

SDB Sleep disordered breathing, OSA obstructive sleep apnea, PR Pierre Robin sequence, PSG Polysomnography, PSQ Pediatric Sleep Questionnaire.

Although overnight PSG remains the diagnostic gold standard test it is not always easily accessible especially in children with cleft palate and other craniofacial malformations due to elevated cost, other medical concerns and that they are infrequently referred to a sleep clinic. Therefore, assessment of SDB based on validated screen questionnaires such as the PSQ is not uncommon in this pediatric population. The PSQ was validated to screen for SDB in otherwise healthy pediatric populations aged 2-18 years and it has

been widely used in research.[43,55,56,61] It includes a 22-item sleep-related breathing disturbance (SRBD) scale that contains questions regarding obstructive sleep symptoms such as habitual snoring, apnea or nocturnal breathing. A threshold score ≥0.33, which is a positive response to at least 33% of answered questions, showed a sensitivity of 78% and a specificity of 72% and is used as the cut-off point to identify children at high risk for SDB.[55]

While adenotonsillar hypertrophy is considered the main cause of SDB in general pediatric populations, the mechanisms involved in the pathophysiology of obstructive sleep symptoms in children with cleft palate are more complex, and likely multifactorial. They include obstructive factors, anatomical factors related to the reduced dimensions of the upper airway, and functional factors such neuromuscular dysfunction related to the craniofacial anomaly. In addition to the enlarged lymphoid tissue of the upper airway typical of childhood due to recurrent infections, other obstructive factors such macroglossia in children with PR sequence also play a role in the frequency of SDB symptoms in children with non-syndromic cleft palate. Other important risk factor for SDB in this pediatric population are surgical procedures to repair the craniofacial anomaly and to improve velopharyngeal insufficiency (palatoplasty,[62–65] pharyngeal flap (PF),[62,65–68] and sphincter pharyngoplasty (SP)[69,70]). In general, post-surgery incidence of OSA is higher compared to pre-operative results because they induce a reduction of upper airway diameter. For instance, the pharyngeal flap surgery confers an increased risk for OSA, greater in prospective studies than in retrospective, that varies from 20 to 96%.[62,65–68] Moreover, surgical procedures to correct velopharyngeal insufficiency were also associated to an increased frequency of OSA even higher than palotoplasty.[62,69,70] Therefore, it appears that surgical procedures, specifically PF and SP, should be taken into account as a risk factor for OSA. However, it should be pointed out that post-surgical frequency of OSA varies widely likely due to the limited information available and to other risk factors involved such specific characteristics of the craniofacial anomaly. In fact, a

study of MacLean undertaken in 50 infants with CL/P found an elevated risk for SDB and obstructive events even before the palate repair was performed.[71] Moreover, a study conducted in children with cleft palate suggested that dimensions of the upper airway in children with cleft are more similar to typically developing children with obstructive sleep apnea than to controls, even when no significant differences in apnea-hypopnea index (AHI) were found among both groups. [72] Studies in children with PR sequence have found a frequency of SDB symptoms about 2 and 3.5-fold higher compared to children with non-syndromic cleft palate suggesting that micrognathia induces a greater reduction of upper airway dimensions.[43,53,60] Finally, neuromuscular factors are also involved in the presence of SDB in this pediatric population. Changes in innervation, morphology, and insertion of the muscles of the oropharynx related to the presence of the cleft results in upper airway instability and velopharyngeal insufficiency.[73,74] Therefore, a better anatomical and functional assessment of SDB previous to surgical procedures in children with orofacial clefts is important due to the heterogenicity of this pediatric population and the multiple risk factors involved in upper airway obstruction compared to children without craniofacial malformations.

1.5. Otitis media in pediatric populations

Otitis media is a common medical condition in young children and the most frequent diagnosis in primary care offices. By one year of age, about 40% of children will have suffered at least one episode of otitis media and up to 85% by three years of age.[42,75] Non-modifiable risk factors for otitis media are: age younger than five years, male gender, Caucasian, prior or recent ear or other upper airway infection, positive family history of ear infection, prematurity, low birth weight and craniofacial anomalies.[75,76] However, environmental factors, considered potentially modifiable factors, are also involved in ear infection susceptibility such as: exposure to tobacco or pollution, allergies, lack of breastfeeding or gastroesophageal reflux.[77–81] Diagnosis of acute otitis media is

based on pneumatic otoscopy examination. Treatment includes antibiotics that allow the resolution of the episode in the vast majority of cases as well as tympanocentesis for those cases with severe symptoms and without improvement despite multiple antibiotic treatments. Moreover, it is not infrequent that children with otitis media suffer ≥ 3 acute episodes in one year considered recurrent acute otitis media. When the middle ear disease lasts three months and is accompanied with effusion it is considered chronic otitis media. Long-term consequences of recurrent and chronic otitis media include: hearing impairment, delay speech development, learning and behavioral problems and decreased quality of life.[82,83] Consequently, myringotomy with tymptanostomy tube insertion is not an uncommon treatment in children with chronic or recurrent otitis media.

1.6. Otitis media and sleep-disordered breathing in general pediatric populations

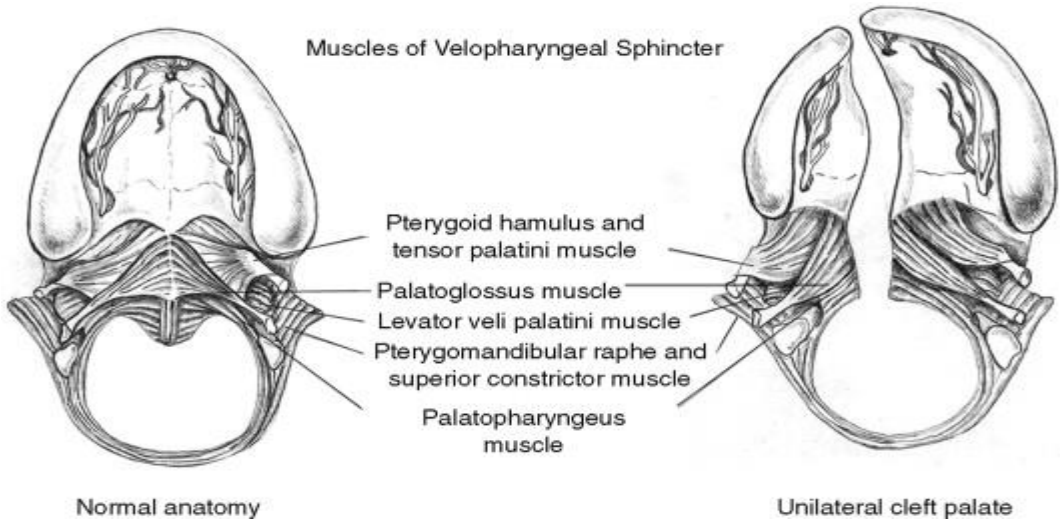
The close pathophysiology between recurrent or chronic otitis media and SDB, common risk factors and peak incidence prompted some researchers to consider that these two conditions may be related in general pediatric populations. Gozal surveyed over 16,000 parents of children aged 5-7 years from the Jefferson County Public schools and found that 11.3% reported habitual snoring, defined as snoring at least 3 nights per week, and of these, 44.8% had positive history of recurrent otitis media.[42] Investigation of the same pediatric population found a positive association between habitual snoring and recurrent otitis media or tympanostomy tube insertion. Odds ratio for recurrent otitis media among snoring children was 1.95 (confidence interval (CI): 1.8-2.2), and 2.19 (CI: 2.0-2.4) for tymptanostomy tube insertion compared to non-snoring children.[42] Similar results were obtained by the research group of Tauman et al in Israel. This case-control study included 457 surveys of children and investigated the increased risk for snoring in children who underwent tympanostomy tube insertion (OR=3.4, CI: 1.6-7.2) and adenotonsillectomy (OR=4.4, CI: 1.7-11.2).[84] Later, Robison et al showed that the prevalence of eustachian tube insertion was higher in patients diagnosed of OSA

compared to general pediatric populations (32% vs. 4-7%).[85] Moreover, a Canadian study demonstrated that performing adenoidectomy or adenotonsillectomy at the time of initial insertion of tympanostomy tubes substantially reduced the likelihood additional hospitalizations and operations related to otitis media among children of two years of age or older.[86]

1.7. Otitis media and speech problems in children with cleft palate

Children with cleft anomalies are at high risk for middle ear disease from recurrent acute otitis media to otitis media with effusion and hearing loss. In a case-control longitudinal study of 22 children with cleft lip and palate and 20 children without cleft, aged from 1 to 5 years, Flynn et al found a higher prevalence of otitis media with effusion in children with cleft compared to controls (74.7% vs. 19.4%, $p<0.001$) and independent of age.[87] Moreover, the frequency of hearing loss was also more elevated and pronounced in the cleft group (cleft 89.7% and 35.71 dB vs. non- cleft 70.0% and 26.41dB).[87] Palatal muscle dysfunction, before and after surgery, is considered the main cause of the high incidence of otitis media in children with cleft palate (**Figure 5**). The levator palatini muscle elevates the soft palate and excludes the nasopharynx from the oropharynx during speech and swallowing. In children with cleft palate, the levator muscle orientation changes, being longitudinal, and therefore, parallel to the cleft margin. Similarly, the tensor palatini muscle orientation is more longitudinal in children with cleft resulting in an inadequate opening of the eustachian tube. Although, when the child grows the Eustachian tube becomes stronger due to an improvement of the cartilaginous support, children with cleft require frequently myringotomy and tube placement during the early developmental period. Therefore, while the presence of cleft has been linked to a high risk for middle ear disease and SDB symptoms, the association between these two pathologies has not previously been studied in this pediatric population.

Figure 5 Anatomy of the cleft palate. (A) Normal anatomy; note the sling formed by the two sides of the levator palatini muscle. (B) Cleft palate; the levator muscle is oriented longitudinally, somewhat parallel with the cleft margin.



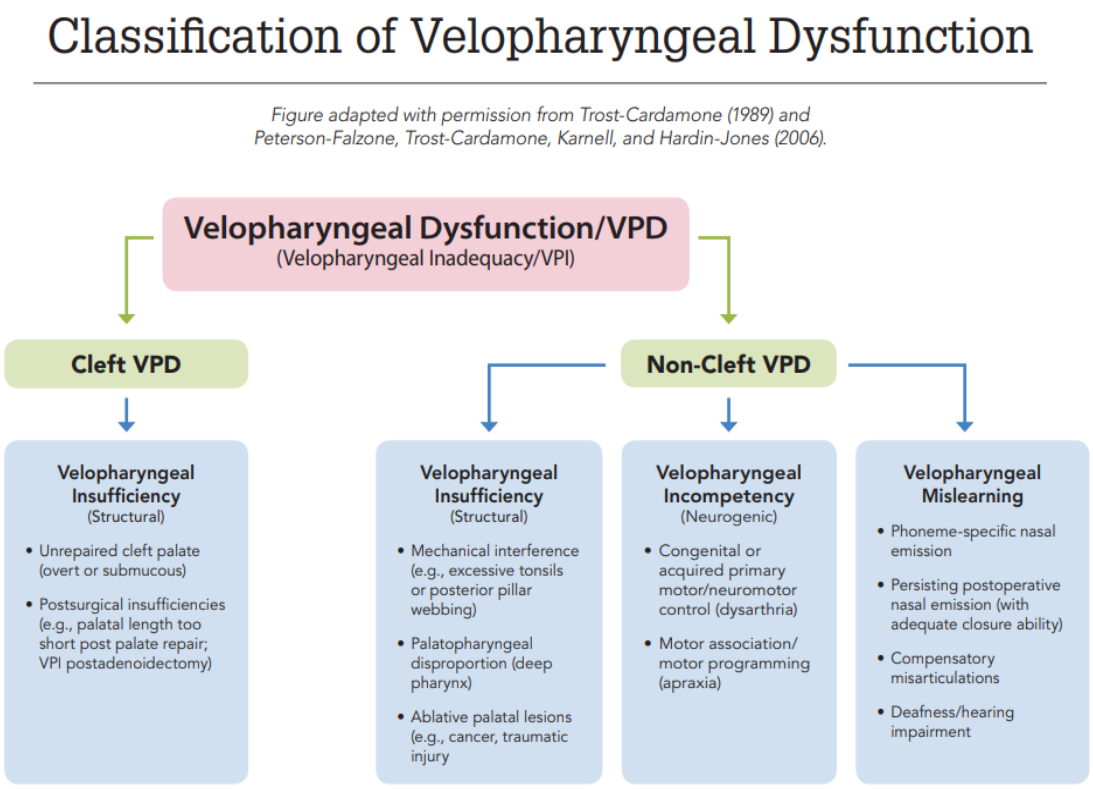
Lalwani AK. Current diagnosis and treatment otolaryngology. Neck and Head surgery, 3rd Edition.

Speech and breathing are two functions of the upper airway that share not only anatomical structures, but also a common embryonic development. Davidson, in a study from an evolutionary perspective, postulated that anatomical changes of the larynx in relation to the development of speech might contribute to upper airway obstruction at night due to changes of soft tissue anatomy and cranial base angulation.[88]

Speech difficulties and language delay are common in children born with orofacial cleft.[89–91] During normal speech production, the velopharyngeal wall act as a bidirectional valve, closing off the nose from the mouth: to prevent airflow and acoustic energy from going into the nose during the production of oral sounds, to allow nasal respiration and to prevent that food and liquid enter the nose.[92] In 1987 Loney and Bloem proposed, for the first time, the adoption of a standardized nomenclature to define velopharyngeal dysfunction. The term of velopharyngeal insufficiency (VPI) was defined as any malfunctioning that results in imperfect closure of the velopharyngeal apparatus and includes both velopharyngeal incompetent and velopharyngeal inadequate.[93] Later, Trost-Cardamone and other authors agreed with those recommendations proposed a

taxonomy classification for velopharyngeal disorders based on etiology.[94,95] See **Figure 6**.

Figure 6. Classification of velopharyngeal dysfunction



In children with cleft palate VPI is considered the main cause of speech difficulties. During speech assessment, VPI results in leakage of air into the nasal cavity and therefore, specific speech resonance patterns such as excessive nasality or hypernasality, the cardinal sign of VPI, audible/visible nasal emission and weak pressure consonants. Interestingly, De Serres et al investigated - for the first time in pediatric populations with cleft - speech outcomes and obstructive sleep symptoms. They found that hyponasality and snoring were frequently reported.[96] Subsequently, Moraleda-Cibrián et al in a study of 487 children with craniofacial malformations showed that 35% had hypernasality, 11% hyponasality, 19% consistent visible nasal emission (NE) and 2% audible NE or nasal turbulence during speech assessment.[91] As expected, children

with VPI were more likely to have hypernasality compared to those with competent or borderline competent velopharyngeal mechanism (73% vs. 27%, p = 0.0001) and children with consistent NE or audible/nasal turbulence were more likely to have VPI than children with other NE patterns (97% or 100% vs. 18%, p = 0.0001). Moreover, 75% of children with hyponasality had reduced or absent NE, compared to only 6% with hypernasality or 7% with normal nasality (p = 0.0001). Finally, in a logistic regression the adjusted OR for SDB in those children with hyponasality was 2.10 (95% CI: 1.21-3.61, p = 0.008) and for those with reduced or absent nasal emission was 1.75 (95% CI: 1.06-2.88, p = 0.028).[91] Therefore, a routine and accurate speech assessment of children with cleft could be a useful clinical tool not only to identify VPI status, but also to suspect obstructive sleep symptoms in this pediatric population and in children with other craniofacial malformations.

1.8. Other sleep disorders in pediatric populations

Despite the increased risk for both SDB and behavioural problems observed in children with cleft palate, the frequency of other sleep disorders is infrequently investigated in this pediatric population. Sleep-related movement disorders (SRMD) encompass a wide range of stereotypical and non-purposeful movements that occur during wake-sleep or sleep-wake transitions or during sleep. Restless legs syndrome (RLS) is an urge to move one or both legs associated with leg discomfort that is worse at night or rest and relieved with movement.[97] Restless legs syndrome is a clinical diagnosis. Previous studies in different pediatric populations without craniofacial malformations found that the frequency of RLS varied from 1 to 6%.[98–101] The pediatric 'REST' study that included over 10,000 subjects in the United States and the United Kingdom using the RLS consensus criteria[102] showed a prevalence of RLS of 2% among preadolescents and adolescents.[103] About one quarter of subjects reported moderate-severe symptoms, without predominance between genders. The periodic limb movements (PLMS) consist of brief and periodic jerks occurring at 20-40 seconds intervals. Periodic limb movements

disorder (PLMD) is considered in those cases with ≥5 PLMS per hour of sleep associated with significant sleep disturbance.[104] The PLMS and PLMD require overnight PSG which is a labor intensive, expensive, and not easily employed in pediatric populations outside of academic centers and with other medical conditions. To address this problem Chervin et al published the PLMS scale included in the Pediatric Sleep Questionnaire. A six-items scale to screen PLMS, RLS and growing pains in pediatric populations with a reasonable validity and reliability that could be useful for research studies.[105] The range of frequency of PLMS in general pediatric populations varies from 5% to 26% according to PSG data and from 8 to 12% according to survey studies.[98,103,106–108] Several large population studies have shown an association between RLS and PLMS.[109,110] While the pathophysiology of RLS and PLMS is still unclear emerging evidence of common risk factors for RLS and PLMS such as dopaminergic system dysfunction, low iron stores and genetic susceptibility have been proposed. [98,111]

In contrast to RLS, the definition of growing pains is not unified. Symptoms of growing pains are typically bilateral and occur in children aged between 3-12 years of age, typically by the end of the day, persist at least 3 months, are not accompanied by movement limitation, and physical examination and laboratory tests are negative. Studies of the last two decades have suggested that RLS and growing pains are frequently overlapping, and largely familial [112,113]. Picchietti in a cross-sectional study found that growing pains were more common in children with RLS than in children without (80.6% vs. 63.2%, $p<0.001$), and over half (54.5%) of children with RLS have been reported to experience growing pains.[101,103] Interestingly, a study of twins demonstrated that about 18% of twins with concordant growing pains met criteria for RLS vs. only 2% of twins with discordant growing pains ($p = 0.01$).[114] However, the frequency and association between SRMD and growing pains has not been investigated in children with cleft palate.

1.9. Comorbidities associated with sleep-disordered breathing and other sleep disorders in general pediatric populations and in cleft populations

Inflammation is an essential immune response of the body to fight against infections or injury processes, and to maintain tissue homeostasis. In the past decade, evidence has demonstrated the association between intermittent hypoxia or sleep fragmentation and an increase of peripheral biomarkers of inflammation, such as C-reactive protein, cytokines, chemokines, and prostaglandins. Activation of these peripheral pathways promotes several systematic inflammatory responses or cascades involved in end-organ endothelial dysfunction, neurobehavioral disturbance and cardiovascular dysregulation.[115–122]

The role of sleep in cognitive and behavioural development has been widely recognized in school age children and adolescents. However, little is known in children under school age or in specific pediatric populations such as children with craniofacial malformations. Neurobehavioral dysfunction associated with sleep-disordered breathing, restless legs, periodic limb movements, sleep deprivation and other sleep disorders encompasses a range from inattention/hyperactivity deficit disorder (ADHD), to learning and memory difficulties, daytime sleepiness and aggressive behavior.[61,118,120,123–126] The main pathophysiological mechanisms involved in these processes, investigated mainly in laboratory studies in mice exposure to intermittent hypoxia, included: activation of inflammatory pathways[127] and an excess free radicals that results in oxidative stress and cell apoptosis in hippocampus and cortex regions.[128–130] Interestingly, not all children with sleep disorders present cognitive dysfunction, suggesting that other factors may play a role in this association such as genetic factors or obesity.[115,131,132] Apolipoprotein E (ApoE) is a lipoprotein synthesized in the brain and involved in cholesterol transport and deposition. It is though that ApoE could be a key factor in neurodegerative processses.[133] In fact, children with OSA and ApoEε4 allele have shown a higher cognitive susceptibility compared to children with OSA and normal cognition. In addition, adipose tissue

produces and secretes a host of chemokines, also called adipokines, which results in metabolism dysfunction and stimulates also pro-inflammatory responses.[131,134]

Scholastic under-achievement and behavioral problems are frequent in children with repaired cleft palate compared to controls. According to parents and teachers one third of children with CL/P report learning difficulties by the end of the primary school.[135] A review of medical charts and educational records found that about 46% of the children with clefts showed learning disabilities, with the highest rate among males with CP (79%) and lowest among males with CL/P (37%).[136] In a more recent population-based study, children with non-syndromic clefts were more than three times likely to have received special education services compared to controls.[137] Lower reading skills, word recognition and reading comprehension were common in young children aged 6-7 years with cleft compared to non-cleft peers with continued low scores in reading comprehension in those with CP.[138,139] Reasons for the learning difficulties are likely multifactorial in this pediatric population. Reading difficulties and behavioral problems could play a role in scholastic under-achievement. Moreover as we have shown previously, an increased risk for behavioral difficulties due to untreated OSA, sleep disturbance or deficiency has been widely recognized in pediatric populations without craniofacial anomalies.[61,116,140] Nevertheless, up to now only one study has investigated the impact of neurocognition in infants with cleft and OSA.[52] The issue is important since SDB could be considered a modifiable risk factor for under scholastic achievement and daytime behavioral problems especially in pediatric populations with a high risk for obstructive sleep symptoms such as children with cleft.

In the last few decades evidence for an association between pediatric OSA and cardiovascular dysfunction has also increased.[141–143] Intermittent hypoxia and repeated cortical arousal, considered the triggers for cardiovascular morbidity, increase negative intrathroracic pressure, produce an activation of the sympathetic system, pro-inflammatory processes and oxidative stress that induce a disruption of the endothelium.

The metabolic syndrome includes a clustering of hypertension, insulin resistance, dyslipidemia and obesity. The frequency of metabolic syndrome in adolescents is estimated about 4-10% and appears to predict cardiovascular risk profile in adults.[144,145] Up to now obesity was considered one of the main risk factors for metabolic syndrome. However similar to obesity, OSA has been identified as an important risk factor for metabolic syndrome.[146,147] Redline, in a study of 270 adolescents, demonstrated after adjusting for age, race, sex, and preterm status, that children with SDB had a six-fold increase in the odds ratio of metabolic syndrome compared with those without OSA.[148] Unsurprisingly, similar to adults when obesity and OSA coincide in children the risk for metabolic syndrome is even higher (a significant association between fasting insulin levels and AHI, arousal index, and desaturation time).[149] The issue is important due to a longitudinal study in a pediatric population has demonstrated that many components of the metabolic syndrome become more prevalent between 10 and 19 years of age.[150] Moreover, emerging data support an association between visceral adipose tissue dysfunction and OSA.[134,151,152] Among the several adipokines, elevated leptin levels has been reported in pediatric patients with OSA independent of the BMI.[134] The infiltration by macrophages of adipocytes has been postulated as pathophysiological mechanism involved on insulin resistance.[152]

Somatic growth impairment was also initially described as a comorbidity associated to pediatric OSA, with an estimated frequency ≤5%.[147] Several pathophysiological mechanisms have been postulated to cause poor growth in pediatric populations with OSA: 1. Increased energy expenditure due to an increased work of breathing during sleep, 2. Swallowing difficulties and diminished appetite, 3. Stress and catabolism, and 4. Decreased levels of insulin-like growth factor-I and growth factor release secondary to sleep architecture disturbance.[147,153,154] Interestingly, several studies have demonstrated that while treatment of OSA with tonsillectomy and/or adenoidectomy increase heigh and weight in those children with somatic growth impairment, it appears

that obesity associated with OSA does not improve after surgical treatment of OSA in obese nor in morbidly obese children either.[155–157]

In addition, psychological distress and depressive mood are also common particularly in adolescents and pre-adolescents with OSA.[158] While some studies have shown an association between BMI and mood disorders,[159,160] Crabtree in a study population of 85 children with suspected SDB aged 8 to 12 years found that snoring was associated with a high risk for depressive symptoms, particularly anhedonia, independently of the AHI and BMI.[158]

Quality of life (QoL) is considered one of the most relevant health outcomes measures in medicine. The health-related QoL, based on the World Health Organization, is characterized by a multidimensional perspective of patient health focusing on well-being from the impact of disease and/or treatment on different aspects of life.[161] Instruments used in childhood to assess the QoL can be divided into generic and disease-specific measures. Generic instruments can be more advantageous because they can be used in a population with a specific disease and allow comparison of the results with the general population using the same instrument. Several studies have investigated the impact of OSA on QoL in children and adolescents without craniofacial malformations. While some cross-sectional and longitudinal studies have found weak correlations or no association between the presence and severity of OSA and QoL,[162,163] two points are important to take into account. First, it appears that the presence of overweight /obesity in children and adolescent with OSA without craniofacial anomalies was associated with a significant decrease in QoL scores.[164] Second, long-term follow-up and prospective studies of children reveal an improvement of sleep-related QoL and behavior post-adenotonsillectomy compared to before the surgery.[165,166] Research studies about the impact of orofacial anomalies such as CL/P on health-related QoL and caregiver well-being has been also increased. It appears that the impact on QoL was higher for adolescents with orofacial clefts than in primary schoolers, and for caregivers and

siblings of preschoolers.[167–170] However, little is known about the impact of SDB on QoL in this pediatric population.[52]

2. HYPOTHESIS

Hypothesis

Null hypothesis (H_0): We hypothesize that no differences in the frequency of Sleep-Disordered Breathing symptoms and Obstructive Sleep Apnea will be found in young children with repaired non-syndromic orofacial clefts compared to previous studies in general pediatric populations. In the same way, we hypothesize that no differences in the frequency of behavioral problems and quality of life will be found in children with cleft with and without Sleep-Disordered Breathing.

Alternative hypothesis (H_1): We hypothesize that the frequency of Sleep-Disordered Breathing symptoms and Obstructive Sleep Apnea will be higher in children with repaired non-syndromic orofacial clefts compared to previous studies in general pediatric populations. Similarly, children with cleft palate and Sleep-Disordered Breathing will report a higher frequency of behavioral problems and lower quality of life scores compared to those children with cleft palate but without Sleep-Disordered Breathing.

3. OBJECTIVES

This PhD research study includes six objectives and three articles.

Primary Aims

Aim 1 To determine the frequency of positive screening for Sleep-Disordered Breathing and Obstructive Sleep Apnea in young children with repaired non-syndromic cleft palate anomalies.

Aim 2 To assess whether the presence of Sleep-Disordered Breathing and severity of Obstructive Sleep Apnea impacts on behavior and quality of life in the same pediatric population.

Secondary Aims

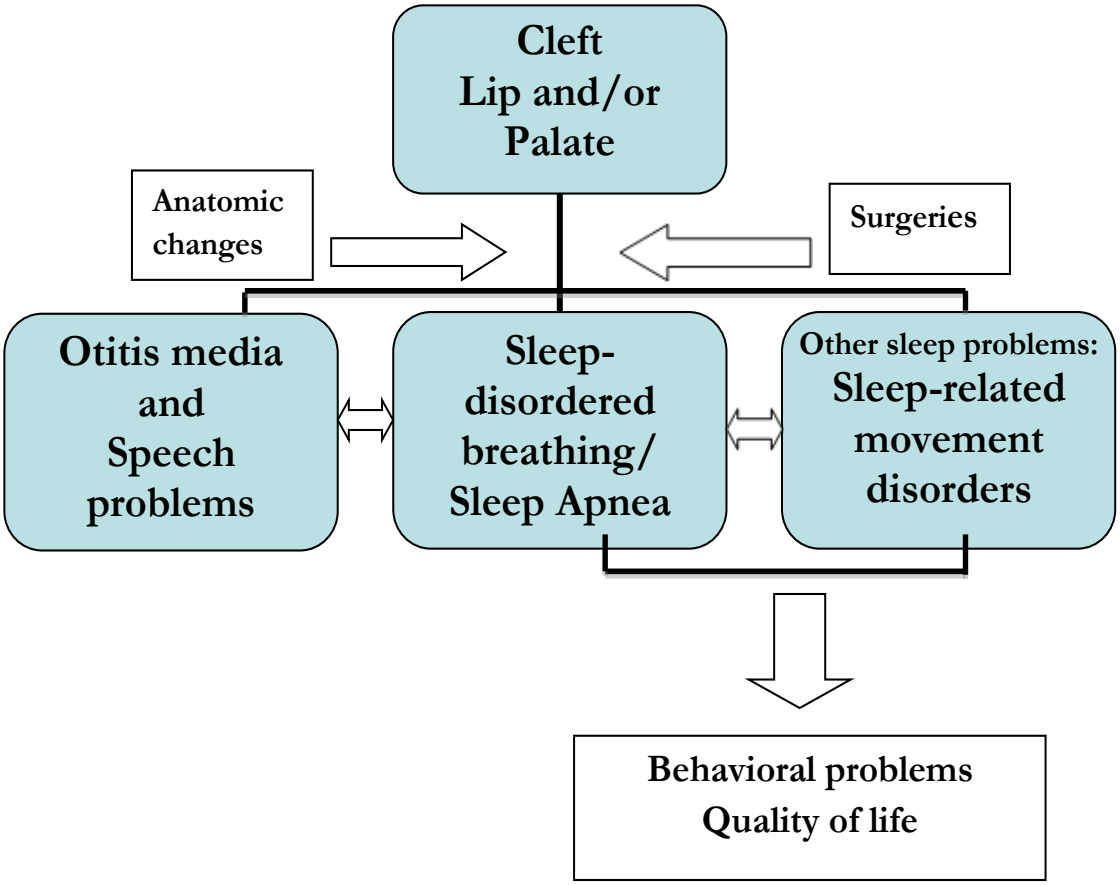
Aim 3 To investigate the frequency of habitual snoring, the cardinal symptom of Sleep-Disordered Breathing, and other upper airway symptoms such as otitis media and speech difficulties in children with orofacial clefts.

Aim 4 To assess the association between otitis media, speech problems, and habitual snoring in the same pediatric population.

Aim 5 To investigate the frequency of other sleep disorders such as sleep-related movement disorders (periodic limb movements and restless legs syndrome) and growing pains symptoms in young children with orofacial cleft.

Aim 6 To determine whether periodic limb movements, restless legs syndrome and/or growing pains play a role in daytime (internalizing and externalizing symptoms) and bedtime behavior in this patient population.

Figure 7. Summary of the main objectives of the present study



4. RESULTS

4.1. ARTICLE 1

Impact of Sleep-Disordered Breathing on Behavior and Quality of Life in Children aged 2 to 7 years with Non-syndromic Cleft Lip and/or Palate

- **Authors: Moraleda-Cibrián M,** Edwards SP, Kasten SJ, Warschausky SA, Buchman SR, Monasterio-Ponsa C, O'Brien LM
- **Citation**: Pediatr Pulmonol. 2021 Oct;56(10):3358-3365.
- **Objectives**:
  Aim 1 To determine the frequency of positive screening for Sleep-Disordered Breathing and Obstructive Sleep Apnea in young children with repaired non-syndromic cleft palate anomalies.
  Aim 2 To assess whether the presence of Sleep-Disordered Breathing and severity of Obstructive Sleep Apnea impacts on behavior and quality of life in the same pediatric population
- **Impact factor:** 3.039
- **Quartile:** Q1
- **Field**: Pediatrics, Perinatology and Child Health

Resum

Impacte dels Trastorns Respiratoris del Son en el Comportament i la Qualitat de Vida en nens de 2 a 7 anys amb llavi leporí i/o paladar fes no-síndròmic

Introducció: Els nens amb fissura palatina tenen un risc elevat de presentar Trastorns Respiratoris del Son. No obstant, la información disponible sobre l'impacte dels Trastorns Respiratoris del Son és molt limitada en aquesta población pediàtrica. L'objetiu d'aquest estudi era investigar la freqüència dels Trastorns Respiratoris del Son en nens de curta edat amb llavi leporí i/o paladar fes no-sindròmic, així com el seu paper en el comportament i la qualitat de vida en la población d'estudi.

Mètodes: Estudi trasversal de 95 nens de 2,0 a 7,9 anys amb diferents tipus de fissura palatina no-sindròmica. El pares van completar un qüestionari sobre el son (Qüestionari Pediatric de Son), un sobre comportament (Escala de la infantesa primarenca de Conner), i un qüestionari genèric sobre la qualitat de vida (qüestionari KINDL). Els nens simptomàtics van ser derivats a la Unitat de Son per la realització d'una polisomnografia nocturna.

Resultats: En general, el 14,7% dels nens (49,5% de sexe masculí) van presentar un cribratge positiu pels trastorns respiratoris del son. Es va realizar una polisomnografía nocturna en el 27,4% de la población d'estudi que va permetre identificar la presencia d'apnea obstructiva del son en el 84,6% del casos (índex d'apnea-hipòpnea [AHI] ≥1), dels quals un 27,2% de severitat moderada-severa. El cribratge positiu pels trastorns respiratoris del son es va associar amb puntuacions elevades (≥ 65) per ansietat i símptomes físics. A més diferències significatives en les puntuacions mitjanes per inatenció/hiperactivitat (64,2 ± 15,7 vs. 53,9 ± 11,4, p=0,02), funcionament social/conducta atípica (60,6 ± 11,7 vs. 51,9 ± 7,3, p=0,004 i 59,5 ± 10,9 vs. 51,2 ± 8,0, p = 0,01) i estat d'ànim (57,5 ± 8,2 vs. 50,7 ± 8,2, p=0,03). Els nens amb fissura palatina i trastorns respiratoris del son també van presentar puntuacions més baixes en qualitat de vida en l'àmbit emocional i familiar respecte els nens sense trastorns respiratoris del son (80,7 ± 13,4 vs. 90,0 ± 8,7, p= .01, 66,7 ± 15,8 vs. 76,9 ± 11,9, p=0,04). Per altre banda, els nens amb una apnea del son moderada-severa, en comparació amb ells amb apnea lleu, van mostrar diferències signifiacatives en la puntuació mitjana per comportament agressiu (65,2 ± 12,1 vs. 52,3 ± 11,3, p=0,04), temperament desafiant (62,8 ± 9,2 vs. 51,6 ± 10,2, p=0,03) i la qualitat de vida en l'àmbit familiar (59,4 ± 15,2 vs. 77,1 ± 9,6, p=0,006).

Conclusions: En nens amb fissura palatina de menys de 8 anys la presència de símptomes obstructius respiratoris durant el son o apnea moderada/severa es va associar amb problemas de comportament (internalització / externalització) i baixa qualitat de vida especialmente en l'àmbit familiar.

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Impact of sleep-disordered breathing on behavior and quality of life in children aged 2 to 7 years with non-syndromic cleft lip and/or palate

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Abstract

Introduction: Children with cleft are at high risk for sleep-disordered breathing (SDB). However, little is known about the impact of SDB in this pediatric population. The aim of this study was to investigate whether SDB play a role in behavior and quality of life (QoL) in young children with cleft.

Methods: Cross-sectional study of 95 children aged 2.0–7.9 years with cleft palate. Parents completed a sleep (Pediatric Sleep questionnaire), a behavior (Conners' Early Childhood scale), and a generic health-related QoL (KINDL questionnaire) assessment. Symptomatic children were referred for a polysomnography (PSG).

Results: Overall, 14.7% of children (49.5% boys) screened positive for SDB and 27.4% had a PSG, which identified 84.6% with sleep apnea (apnea-hypopnea index [AHI] ≥1) and 27.2% with AHI ≥5. Positive screening for SDB was associated with elevated T-scores for anxiety and physical symptoms, significant differences in mean T-scores for inattention/hyperactivity (64.2 ± 15.7 vs. 53.9 ± 11.4, $p = .02$), social functioning/atypical behaviour, social functioning (60.6 ± 11.7 vs. 51.9 ± 7.3, $p = .004$ and 59.5 ± 10.9 vs. 51.2 ± 8.0, $p = .01$) and mood (57.5 ± 8.2 vs. 50.7 ± 8.2, $p = .03$). Lower QoL scores for emotional and family well-being were also reported in children with SDB (80.7 ± 13.4 vs. 90.0 ± 8.7, $p = .01$, 66.7 ± 15.8 vs. 76.9 ± 11.9, $p = .04$). Children with AHI ≥5 compared to those with AHI ≥1 and <5 showed significant differences in mean T-score for aggressive behaviour (65.2 ± 12.1 vs. 52.3 ± 11.3, $p = .04$), defiant temper (62.8 ± 9.2 vs. 51.6 ± 10.2, $p = .03$) and lower family QoL scores (59.4 ± 15.2 vs. 77.1 ± 9.6, $p = .006$).

Conclusions: In children with cleft palate the presence of SDB symptoms and moderate/severe sleep apnea was associated with behavioral (internalizing/externalizing) problems and lower family well-being.

KEYWORDS

behavioral research, congenital malformations, quality of life, sleep disordered breathing, sleep medicine

1 | INTRODUCTION

Sleep-disordered breathing (SDB) is a syndrome characterized by upper airway dysfunction during sleep that includes a constellation of breathing disorders ranging from snoring at one end of the spectrum to obstructive sleep apnea (OSA) the severest form. In preschool and young school aged children the prevalence of SDB is estimated to be approximately 11% and end estimates of OSA prevalence of up to 4%.[1] Recurrent and persistent episodes of upper airway obstruction during sleep in typically developing children has been associated with health and neurodevelopmental morbidities, including behavioral problems, learning difficulties, poor school performance, low quality of life (QoL) and depressive symptoms.[2–5]

Cleft lip and/or palate (CL/P) is the most common congenital craniofacial anomaly. Children with CL/P have an increased risk for breathing disorders.[6–10] To date, the limited literature about the prevalence of SDB in this pediatric population suggests that the frequency of obstructive symptoms varies from 21% up to 34%, which represents an approximate three-fold increase compared to children without craniofacial anomalies.[6,7,9,10] In symptomatic children with heterogeneous craniofacial anomalies the frequency of objectively-measured OSA has been reported to be 70%–81%.[11]

An increased prevalence of scholastic under-achievement and problematic behaviors has been frequently reported in children with CL/P compared to controls. Studies have shown that early reading skills were lower in children with CL/P compared to non-cleft peers.[12,13] A Dutch study also suggested that one-third of children with CL/P had learning difficulties.[14] Behavioral, emotional and other health problems may compromise academic performance in early childhood. In school age children with CL/P 18%–35% have been reported to display greater frequency of internalizing behavior problems such as social inhibition.[15] In addition, an increase in externalizing behaviors has been reported in females with CL/P over 13 years of age.[15]

In the last decade there has been an increase in the number of studies reporting the impact of CL/P on health-related QoL and caregiver well-being, the former is now considered one of the most relevant health outcomes in medicine.[16–19] The aim of the proposed study was to assess the frequency of sleep-related breathing disorders in young children with cleft palate and to investigate whether SBD and severity of sleep apnea play a role in neurobehavioral outcomes/QoL in preschool and school age children with cleft palate.

2 | METHODS

2.1 | Study design and participants

Children with different non-syndromic cleft palate anomalies attending at the Craniofacial Anomalies Program of the C.S. Mott Children's Hospital, University of Michigan, were invited to participate in this cross-sectional study. This study was approved by the Institutional Review Board at the University of Michigan (ID HUM00054515). Families were approached by a study team member (MM) and parents signed an informed consent during the clinical appointment. Study aims were not described in detail during the recruitment process to avoid biased survey responses. Inclusion criteria were age between 2.0 and 7.9 years old and confirmed diagnosis of non-syndromic repaired unilateral or bilateral isolated cleft palate, cleft lip and cleft palate, or Pierre Robin sequence with cleft palate. Children with syndromic cleft palate, diagnosed with developmental delay and/or neurological disorders or who had a surgical procedure in the previous 3 months were excluded. Families who participated received a $50 gift card for parents and a small toy for children as a token of appreciation.

2.2 | Measurements

Parents completed three questionnaires (the Pediatric Sleep questionnaire, the Conners' Early Childhood scale, and the KINDL questionnaire) during the clinical appointment that generally took between 20 and 30 min. Demographic information such as gender, age, ethnicity, height and weight were obtained from the Pediatric Sleep Questionnaire. Body mass index (BMI = weight in kg/height in m^2) and BMI percentiles, adjusted for age and gender, were calculated. The study population was classified into three weight groups according to the BMI percentile threshold recommended by Centers for Disease Control for pediatric populations: underweight (BMI <5th percentile), normal weight (BMI ≥5th percentile and <85th percentile) and overweight/obese (≥85th percentile).

2.2.1 | Obstructive sleep symptoms

The Pediatric Sleep Questionnaire is a well-validated tool in pediatric populations that includes a sleep-related breathing disturbance (SRBD) scale[20] to screen for SDB in children aged 2–18 years. The 22-item SRBD scale contains questions regarding obstructive sleep symptoms such as habitual snoring, apnea or nocturnal breathing. Responses options were “yes,” “no,” or “don't know.” “Don't know” or “not available” responses were considered missing. A threshold score ≥0.33, which is a positive response to at least 33% of answered questions, showed a sensitivity of 78% and a specificity of 72%[20] and was the cut-off point to identify children at high risk for SDB.[21]

2.2.2 | Behavioural data

The Conners' Early Childhood (EC) questionnaire[22] is a comprehensive parent report tool and well-validated instrument designed to assess a wide range of behavioural, emotional and social concerns and major developmental milestones in toddlers and preschool-aged children from 2 to 6 years old. The behavioral assessment includes seven indicators of potential problematic areas such as inattention/hyperactivity, defiant/aggressive behaviors, social functioning/atypical behaviors, anxiety, mood and affect and physical symptoms. The new versions of the

Conners EC also include three Global Index (GI) Scores: restless-impulsive, emotional lability and total GI. There are 190 questions and response options vary from 0 to 3 or from 0 to 2. Raw scores are converted to standard T-scores adjusted by age and gender with a range of 0 to 100, mean of 50, and *SD* of 10. The cut-off point of the scale is as follows: T-score between 60 and 64 (mean + 1–1.5 *SD*) for high average score, T-score ≥65 (mean + ≥1.5 *SD*) for elevated T-score and T-score ≥70 for very elevated score associated with a greater number and/or frequency of reported concerns than typically reported in general pediatric populations. The Conners EC has shown strong psychometric properties in all the overall scales and factors.[22–25] The internal reliability obtained for the parents' form was 0.89 (Cronbach's alfa coefficient) and the content validity for all the contents (modified kappa or Pearson correlations) was higher than 0.76.

2.2.3 | Quality of life data

Generic health-related QoL was investigated using the KINDL questionnaire, specifically validated for preschool and young school aged children under than 8 years of age. The KINDL consists of a 24 Likert-scaled items associated with six dimensions: physical well-being, emotional well-being, self-esteem, family, friends and everyday functioning (school or nursery school/kindergarten). Response options range from 1 to 5 (never, seldom, sometimes, often, and always) and reverse scoring is applied to some items. Transformed summary score for subscales has a range from 0 to 100. High scores for the items and subscales of the KINDL questionnaire correspond to a higher health-related QoL. Split half reliability of 0.80 is good and discriminant validity meets psychometric standards.[26]

2.2.4 | Obstructive sleep apnea

Finally, a nocturnal polysomnogram (PSG) was performed in a subgroup of patients with clinical suspicion of OSA. Sleep studies were scored by an experienced pediatric sleep technologist using the alternative rule recommended by the American Academy of Sleep Medicine.[17,18] The apnea-hypopnea index (AHI), the main variable assessed, was calculated as the average of apneas (obstructive, mixed and central) and hypopneas per hour of sleep. Pediatric sleep apnea was considered in those cases with an AHI ≥1. The study population was categorized into three severity groups of OSA: mild OSA (AHI 1–4.9), moderate OSA (AHI 5.0–9.9), and severe OSA (AHI ≥10).

2.3 | Statistical analysis

Statistical analysis was conducted using SPSS 15.0 (IBM). To ensure accuracy, data were double-entered. The characteristics of the sample population were summarized by means and *SD* for normally distributed continuous variables, medians and interquartile ranges for non-normally distributed continuous variables, and counts and/or percentages for categorical variables with 95% confidence intervals. The χ^2 test was used to evaluate differences in the frequency of positive screening for SDB and OSA according to dichotomized demographic and craniofacial characteristics of the study population. The non-parametric test, *U* the Mann–Whitney, was used to compare differences in mean T-scores for behavioral problems and scores for assessed dimensions of QoL between children with positive and negative screening for SDB and between children with AHI ≥1 and <5 compared to children with AHI ≥5. Analysis of variance (ANOVA) was used to compare differences in mean T-scores for behavioral problems and scores for assessed dimensions of QoL between children with no-OSA, mild OSA and moderate/severe OSA. All *p* values reported are two-tailed with statistical significance set at <.05.

3 | RESULTS

A total of 96 children were recruited. Of those, one child was excluded in the final analysis due to the presence of another congenital craniofacial anomaly. Thus, the final sample size included was 95. The mean participant age was 5.1 ± 1.5 years, 49.5% were male, 64.2% were Caucasian and 73.7% had cleft lip and palate as the cleft diagnosis. Those and other demographic and anatomical features of the study population are shown in Table 1.

TABLE 1 Summary of the main characteristics of the study population

	All the population *N* = 95 (%)
Age (mean ± *SD*)	5.1 ± 1.5
Male	47 (49.5%)
Ethnicity	
Caucasian	61 (64.2%)
Asian	26 (27.4%)
African-American	4 (4.2%)
Other ethnicities	4 (4.2%)
Craniofacial anomaly	
Isolate cleft palate	16 (16.8%)
Cleft lip and palate	70 (73.7%)
Pierre Robin sequence with cleft palate	9 (9.5%)
Uni/bilateral	
Unilateral cleft	38 (54.3%)
Bilateral cleft	32 (45.7%)
Weight group	
Underweight	8 (8.4%)
Normal weight	76 (80.0%)
Overweight/obese	11 (11.6%)

TABLE 2 Frequency of SDB, presence and severity of OSA in a sample of children with nonsyndromic with cleft palate anomalies according to the demographic and anatomical characteristics

	Negative screening for SDB *N* = 81	Positive screening for SDB *N* = 14	No-OSA (AHI <1) *N* = 4	Mild OSA (AHI ≥1 and <5) *N* = 16	Moderate/severe OSA (AHI ≥5) *N* = 6
Age (mean ± *SD*)	5.1 ± 1.5	4.9 ± 1.5	4.5 ± 1.1	5.2 ± 1.4	5.2 ± 1.7
Male	38 (80.9%)	9 (19.1%)	0 (0.0%)	8 (66.7%)*	4 (33.3%)
Ethnicity					
Caucasian	50 (82.0%)	11 (18.0%)	3 (16.7%)	11 (61.1%)	4 (22.2%)
Asian	23 (88.5%)	3 (11.5%)	1 (16.7%)	4 (66.6%)	1 (16.7%)
African-American	4 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
Other ethinicities	4 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)
Craniofacial anomaly					
Isolated CP	11 (68.6%)	5 (31.2%)*	0 (0.0%)	2 (33.3%)	4 (66.7%)*
CLP	62 (88.6%)	8 (11.4%)*	2 (15.4%)	10 (76.9%)	1 (7.7%)*
RS with CP	8 (88.9%)	1 (11.1%)	2 (28.6%)	4 (57.1%)	1 (14.3%)
Uni/bilateral					
Unilateral cleft	34 (89.5%)	4 (10.5%)	1 (10.0%)	7 (70.0%)	2 (20.0%)
Bilateral cleft	28 (87.5%)	4 (12.5%)	1 (25.0%)	3 (75.0%)	0 (0.0%)
Weight group					
Underweight	6 (75.0%)	2 (25.0%)	1 (25.0%)	2 (50.0%)	1 (25.0%)
Normal weight	66 (86.7%)	10 (13.2%)	3 (16.7%)	12 (66.6%)	3 (16.7%)
Overweight/obese	9 (81.8%)	2 (18.2%)	0 (0.0%)	2 (50.0%)	2 (50.0%)

Abreviations: CLP, cleft lip and palate; CP, cleft palate; OSA, obstructive sleep apnea; RS, Robin sequence, SDB, sleep-disordered breathing.
*$p < .05$.

3.1 | Positive screening of SDB

Overall, 14.7% of children screened positive for SDB. The frequency of positive SDB was calculated according with each specific characteristic of the study population. Children with isolated cleft palate were more likely to screen positive for SDB compared to children with cleft lip and palate (31.3% vs. 11.4%, $p = .046$). Nevertheless, no significant differences were found in the frequency of SDB among children with other anatomical and demographic characteristics (diagnosis, unilateral/bilateral, gender, racial background or weigh groups according to the BMI percentile) (see Table 2).

3.2 | Obstructive sleep apnea

Of the 95 children who were enrolled in the study, 26 (27.4%) underwent a full-night diagnostic PSG for clinical reasons. The decision to undergo PSG was made by the clinical team; responses to the questionnaires were not available to the treating clinicians. The PSG results were reviewed and sleep apnea (AHI ≥1) was identified in 22 (84.6%) of 26 children. Of those, 72.7% had mild OSA and 27.3% had moderate/severe OSA. The mean AHI was 1.9 ± 9.0 (maximum AHI = 83.4). First, we assessed the frequency of OSA according to demographic and anatomical characteristics of the study population. Significant differences in the frequency of OSA were only found between genders (100% of boys vs. 71.4% of girls, $p = .044$). Second, we investigated differences in the frequency of moderate/severe OSA according to demographic and anatomical characteristics of the study population. In this case, we found that children with isolated cleft palate were more likely to have AHI ≥5 compared to children with cleft lip and palate (66.7% vs. 9.1%, $p = .013$) (Table 2).

3.3 | Behavior assessment in children with positive screening for SDB

Children who screened positive for SDB showed elevated T-scores (≥65) for anxiety and physical symptoms when compared to those who screened negative (Table 3). Moreover, those who screened positive for SDB had significant higher T-score not only for anxiety and physical symptoms, but also for inattention/hyperactivity, internalizing behavior problems (social functioning/atypical behavior and social functioning) and mood/affect (Table 3). High T-score for GI restless-impulsive and total GI were also observed (see Table 3).

TABLE 3 Differences in mean T-score for behavioral problems among children with positive and negative screening for SDB, and children without OSA, mild and moderate/severe OSA

	Study population 2–6 years *N* = 85	Negative SDB *N* = 72	Positive SDB *N* = 13	*p* value	No-OSA (AHI <1) *N* = 4	Mild OSA (AHI ≥1 and <5) *N* = 15	Moderate/severe OSA (AHI ≥5) *N* = 6	*p** value
Inattention/ hyperactivity	55.4 ± 12.6	53.9 ± 11.4	64.2 ± 15.7	**.02**	66.0 ± 20.8	56.1 ± 14.6	64.2 ± 7.7	.11
Defiant aggressive behavior	53.8 ± 10.6	52.8 ± 9.6	59.3 ± 14.4	.14	62.0 ± 6.1	52.3 ± 11.3	65.2 ± 12.1	**.04**
Defiant temper	53.3 ± 9.9	52.3 ± 9.2	58.5 ± 12.6	.10	65.0 ± 8.2	51.6 ± 10.2	62.8 ± 9.2	**.03**
Aggression	52.0 ± 12.8	51.2 ± 12.1	56.4 ± 15.8	.21	49.7 ± 9.0	52.3 ± 14.6	58.3 ± 18.8	.23
Social functioning/ atypical behaviors	53.2 ± 8.6	51.9 ± 7.3	60.6 ± 11.7	**.004**	57.3 ± 9.9	55.3 ± 11.7	56.7 ± 7.9	.47
Social functioning	52.5 ± 8.9	51.2 ± 8.0	59.5 ± 10.9	**.01**	58.0 ± 10.2	52.9 ± 10.2	56.2 ± 10.8	.52
Atypical behaviors	53.6 ± 9.9	52.6 ± 9.0	59.2 ± 12.9	.06	52.8 ± 6.9	56.9 ± 12.8	55.8 ± 8.0	.91
Anxiety	53.9 ± 11.8	51.8 ± 9.8	65.4 ± 15.3	**.04**	74.3 ± 13.7	56.0 ± 11.9	57.0 ± 7.4	.68
Mood and affect	51.8 ± 8.9	50.7 ± 8.2	57.5 ± 10.5	**.03**	58.0 ± 9.3	52.3 ± 10.5	59.2 ± 8.4	.09
Physical symptoms	52.6 ± 11.8	50.2 ± 9.1	66.1 ± 15.9	**.001**	66.3 ± 15.2	54.6 ± 12.3	59.0 ± 8.8	.52
GI restless impulsive	53.8 ± 12.2	52.3 ± 10.8	61.9 ± 16.0	**.047**	67.8 ± 19.2	53.8 ± 14.8	62.2 ± 7.9	.06
GI emotional lability	52.9 ± 9.7	52.0 ± 8.6	57.9 ± 13.4	.19	54.3 ± 15.8	51.1 ± 8.4	59.4 ± 17.0	.44
Total GI	53.6 ± 11.1	52.2 ± 9.7	61.7 ± 14.7	**.04**	65.3 ± 15.0	53.1 ± 13.0	61.7 ± 10.1	**.045**

Note: *p** value indicates differences in mean T-scores between children with mild and moderate/severe OSA. When we compared the T-score between the three groups (no-OSA, mild OSA and moderate/severe OSA) differences were also significant for defiant temper ($p = .02$). Significant p values ($p < .05$) are in bold.

Abbreviations: GI, Global Index; OSA, obstructive sleep apnea.

Finally, since the 22-item SRBD scale contains six question items related to behaviour, a sensitivity analysis was conducted using only the 16 items of the SRBD scale. High T-scores were found for aggressive behaviour, defiant temper, anxiety, physical symptoms, GI emotional lability and total GI, but not for inattention/hyperactivity. However, in this second sensitivity analysis differences persisted significant only for physical symptoms ($p = .005$) and were close to be significant for GI emotional lability (0 = 0.07).

3.4 | Behavior assessment in children with OSA

Differences in mean T-score for behavioral problems among children with (AHI ≥1) and without OSA (AHI <1) were statistically significant only for anxiety ($p = .02$). Nevertheless, children with moderate/severe OSA compared to children with mild OSA showed elevated T-scores (≥65) that were statistically significant for two of the assessed externalizing behavior problems, defiant temper and aggressive behavior, but not for the other externalizing and internalizing behavior problems that were investigated (see Table 3). When we compared the three OSA groups (No-OSA, mild OSA and moderate/severe OSA) using ANOVA, differences were also significant for defiant temper ($p = .02$) and aggressive behavior ($p = .05$). Finally, we did not observe elevated T-scores (≥65) for any of the three GI composites among children with moderate/severe OSA compare to children with mild OSA, but we found high T-scores for GI Restless-Impulsive and total GI. Differences were statistically significant only for total GI (Table 3).

3.5 | Quality of life in children with positive screening for SDB

Children who screened positive for SDB had lower scores for emotional and family well-being compared to children who screened negative for SDB (see Table 4).

3.6 | Quality of life in children with OSA

No significant differences were found for the different assessed dimensions of QoL among children with (AHI ≥1) and without (AHI <1) OSA. However, differences between children with moderate/severe OSA compared with children with mild OSA were statistically

TABLE 4 Quality of life scores in children with and without SDB, and in children without OSA and with mild and moderate/severe OSA

	Study population 3–7 years *N* = 89	Negative SDB *N* = 77	Positive SDB *N* = 12	*p* value	No-OSA (AHI <1) *N* = 4	Mild OSA (AHI ≥1 and <5) *N* = 15	Moderate/Severe OSA (AHI ≥5) *N* = 6	*p** value
Physical well-being	84.5 ± 12.3	85.1 ± 11.2	80.2 ± 17.8	.41	81.3 ± 8.8	90.0 ± 12.2	81.2 ± 10.4	.09
Emotional well-being	88.8 ± 9.9	90.0 ± 8.7	80.7 ± 13.4	**.01**	81.3 ± 7.2	88.7 ± 8.6	83.3 ± 14.1	.52
Self-esteem	73.5 ± 14.0	73.6 ± 12.9	72.9 ± 20.6	.99	71.9 ± 6.3	77.9 ± 15.1	60.4 ± 16.6	.08
Family	75.6 ± 12.9	76.9 ± 11.9	66.7 ± 15.8	**.04**	71.9 ± 8.1	77.1 ± 9.6	59.4 ± 15.2	**.006**
Friends	79.1 ± 11.0	79.5 ± 10.2	76.6 ± 15.6	.45	71.9 ± 8.1	80.8 ± 14.6	71.9 ± 6.6	.055
Everyday functioning (school)	82.2 ± 13.1	84.1 ± 11.4	75.6 ± 19.4	.14	81.3 ± 6.3	85.9 ± 16.0	73.7 ± 13.5	.16

Note: p^* value indicates differences in quality of life scores between children with mild and moderate/severe OSA. Significant p values ($p < .05$) are in bold.
Abbreviation: OSA, obstructive sleep apnea; SDB, sleep-disordered breathing.

significant for family well-being (Table 4). Differences in QoL scores between the three OSA groups (no-OSA, mild and moderate/severe OSA) using ANOVA were also significant for family well-being ($p = .009$).

4 | DISCUSSION

This study has demonstrated that a sizable proportion of children with repaired cleft palate screen positive for SDB. Positive screening for SDB in children with cleft, using the 22-item SRBD scale, is associated with high frequencies of externalizing and internalizing behavioral problems, poorer emotional and family well-being. In a subset of children who underwent PSG, higher AHI is associated with externalizing problems and lower family well-being. These results are important given that from our experience pediatric cleft populations are infrequently referred to sleep clinics, except in specific situacions,[27] despite the established high risk for a constellation of breathing disorders, due to adenotonsillar hypertrophy related to a reduced upper airway dimensions and additional pathophysiological factors such palatal muscles dysfunction. These findings, therefore, suggest that children with cleft palate may benefit from SDB screening and OSA diagnosis even in those cases with clinical suspicions in the absence of formal screening. In typically developing children, recurrent and persistent SRBDs have been associated with neuropsychological impairments. Even short-term hypoxia exposure from high altitude has been shown to induce significant executive and memory deficits in healthy children. Learning difficulties and behavioral problems are commonly observed in children with CL/P.[16,28–30] Richman in a review about academic performance and neurocognitive functioning from infancy to young adulthood suggested that intellectual functioning in cleft populations was within the normal range and point out the importance of considering environmental and biological factors as well.[28] According to parents and teachers one-third of children with CL/P report learning difficulties by the end of the primary school.[14] Internalizing behavioral problems, such as social inhibition, may contribute to learning difficulties in children with CL/P due to decrease expectations by teachers and peers. However, knowledge about externalizing behavioral problems, such hyperactivity or impulsivity, that could affect academic achievements is still reduced in this pediatric population.[31] While the reasons for the learning difficulties in children with cleft conditions are likely multifactorial and related to impairments in hearing, speech, cognition, behavior and other factors, the presence of SDB may contribute as well. Nevertheless, little is known about the association between the different comorbidities related to CL/P and how impact on neurodevelopment.

In the last two decades, interest in the assessment of health-related QoL in children with CL/P has increased. Studies have investigated the impact of CL/P on the QoL of patients and caregivers.[17–19,32] Findings have included evidence of no significant differences in self-reported health-related QoL,[17] and mixed findings of lower parental QoL.[18,32] Up to now little is known about the

impact of SDB on QoL in this population. One study of infants with clefts concluded that SDB in early infancy was associated with lower QoL at 3 years of age.[16] Similarly, in the current study we have shown that children younger than 8 years old with cleft anomalies and SDB have lower emotional and family well-being QoL compared to children with cleft in the absence of SDB. Severity of OSA was associated only with lower scores for family well-being.

The major strength of the study is that it provides information about the associations of obstructive sleep symptoms and OSA, with specific areas of behavior and QoL in young children with CL/P. Screening of SDB was based on a well-validated questionnaire and in a subgroup of children there were objective data about diagnosis and severity of OSA. Study limitations include the small sample size of children with specific types of cleft that reduce the power to detect group differences, the vast majority of children were Caucasian and English speakers. Another limitation was the lack of a non-cleft control group. Children with Pierre Robin sequence were included as they have a non-syndromic cleft palate anomaly, although mandibular hypoplasia may impact the findings in this group. In addition, the study is cross-sectional and cannot support strong causal interpretations. Not all children underwent polysomnography so objective data are only available in a subgroup who sought clinical referral. The AHI was calculated as the average of obstructive, mixed and central apneas and hypopneas per hour of sleep and although the number of central apneas was low it is plausible that it could impact the severity of OSA. Last, while the SDB screening tool is validated in the general pediatric population it has not been validated in children with cleft.

In conclusion, the presence of SDB symptoms and moderate/severe sleep apnea appears to have an impact on neurobehavioral outcomes and QoL of children younger than 8 years of age and their caregivers. Further studies are needed to examine whether early treatment of breathing disorders might have an impact on behavior and QoL in pediatric cleft populations.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

Data are not available, because belong to the University of Michigan.

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4.2. ARTICLE 2

Association between Habitual Snoring, Middle Ear Disease, and Speech Problems in Young Children with Non-syndromic Cleft Palate Anomalies

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- **Citation**: International Journal of Oral and Maxilofacial Surgery. 2022 Mar;51(3):332-337.
- **Objectives:**
  Aim 3 To investigate the frequency of habitual snoring, the cardinal symptom of Sleep-Disordered Breathing, and other upper airway symptoms such as otitis media and speech difficulties in children with orofacial clefts.
  Aim 4 To assess the association between otitis media, speech problems, and habitual snoring in the same pediatric population.
- **Impact factor**: 2.58
- **Quartile**: Q1
- **Field:** Otorhinolaryngology, Oral Surgery, Medicine

Resum

Associació entre el ronc, otitis mitja i problemas del llenguatge en nens amb anomalies palatines congènites no-sindròmiques

Introducció: La freqüència tant dels trastorns respiratoris del son, com de la patología d'oïda mitja i dels trastorns del llenguatge és elevada en població pediátrica amb fissura palatina. Estudis en població pediátrica general han trobat una associació entre la presencia de símptomes obstructius respiratoris durant el son, otitis mitja i problemas del llenguatge. No obstant, aquesta associació, que podria ser de gran interés en el diagnòstic dels trastorns respiratoris del son, moltes vegades infradiagnòsticats en nens amb padadar fes i altes malformacions craneofacials, no ha estat mai estudiada en aquesta población pediàtrica.

Mètodes: Aquest estudi transversal va incloure nens de 2,0 a 7,9 anys amb diferents tipus de fissures palatines congènites no-sindròmiques. Els pares van completar el qüestionari de son pediàtric i un qüestionari sobre patología de l'oïda mitja. També es van realizar audiogrames i avaluació del llenguatge.

Resultats: Noranta-cinc nens van ser inclosos. Un 15,2% de les famílies van reportar la presència de ronc de forma habitual (>3-4 vegades/semana), 97,6% patología de oïda mitja i un 17,1% problemes del llenguatge. Els nens amb fissura palatina aïllada en comparació amb aquells amb llavi leporí i fissura palatina va presentar amb més freqüència ronc de forma habitual (37,5% vs 10,3%, p=0,007) i episodios d'otitis mitja durant el primer any de vida (92,3% vs 58,2%, p=0,021). Per altre banda, els nens amb llavi leporí i paladar fes van presentar amb més freqüència otits mitja serosa en comparació amb nens amb seqüència de Pierre Robin (86,4% vs 57,1%, p=0,049). El ràtio de risc de presentar ronc de forma habitual en la población d'estudi va ser 7,4 vegades superior en aquells nens amb almenys un episodi d'otitis mitja durant l'últim any (95% interval de confiança 1,55–35,15, p=0,012). Per últim, els nens amb problemes del llengutage reportats pels pares van mostrar una tendència a presentar ronc de forma habitual (30,8% vs 11,5%, p=0,076).

Conclusions: Els factors anatòmics tenen un paper important en la freqüència dels símptomes relacionats amb la via aèrea superior en nens amb fissura palatina. Episodis recents d'otitis mitja es van associar a un augment en la freqüència del ronc habitual.

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Research Paper
Cleft Lip and Palate

Association between habitual snoring, middle ear disease, and speech problems in young children with non-syndromic cleft palate anomalies

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M. Moraleda-Cibrián, S. P. Edwards, S. J. Kasten, S. A. Warschausky, S. R. Buchman, L. M. O'Brien: Association between habitual snoring, middle ear disease, and speech problems in young children with non-syndromic cleft palate anomalies. Int. J. Oral Maxillofac. Surg. 2019; xxx: xxx–xxx.

Abstract. The purpose of this study was to investigate the association between habitual snoring (HS), middle ear disease (MED), and speech problems in children with cleft palate. This cross-sectional study included children aged 2.0–7.9 years with non-syndromic cleft palate anomalies. Parents completed the Pediatric Sleep Questionnaire and a questionnaire about MED. Audiograms and speech assessment were also conducted. Ninety-five children were enrolled; 15.2% of families reported HS, 97.6% MED, and 17.1% speech problems. HS (37.5% vs 10.3%, $P = 0.007$) and early episodes of MED (92.3% vs 58.2%, $P = 0.021$) were more likely to be reported for children with isolated cleft palate when compared to those with cleft lip and palate. Children with cleft lip and palate had a higher frequency of MED with effusion compared to those with Robin sequence (86.4% vs 57.1%, $P = 0.049$). The odds ratio for HS in children with ≥ 1 episode of MED in the last year was 7.37 (95% confidence interval 1.55–35.15, $P = 0.012$). There was a trend for children with speech problems reported by parents to have HS (30.8% vs 11.5%, $P = 0.076$). Anatomical factors play a role in the frequency of upper airway symptoms in children with cleft palate. A recent history of at least one episode of MED was associated with an increased frequency of HS.

Key words: children; cleft palate; otitis media; Pierre Robin sequence; snoring; speech delay.

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Every year, one in 700 newborns in the United States is born with cleft palate. Studies suggest that approximately 70% of cleft palates are non-syndromic[1,2]. This midface congenital anomaly includes a heterogeneous group of orofacial clefts. The development of both facial and airway structures is critical for mastication, swallowing, and other upper airway functions such as breathing, hearing, and speech[3–6].

Habitual snoring (HS), the cardinal symptom of sleep disordered-breathing (SDB), is frequently reported in children with cleft palate[7–12]. It is estimated that the prevalence of SDB symptoms is almost three-fold higher in children with syndromic and non-syndromic cleft palate than in children without craniofacial anomalies[9–11]. However, this complex medical problem, associated with significant morbidity when untreated[13–18], is frequently overlooked in children with craniofacial anomalies, likely due to other medical problems. Of note, children with repaired cleft palate are at high risk for middle ear disease (MED) and speech problems, two medical conditions routinely assessed in this pediatric population[3,5,19–22]. The common risk factors, peak incidence, and close pathophysiology between MED and HS has prompted some authors to suggest that these two conditions may be related in general pediatric populations[23–25]. Long-term sequelae of MED, such as hearing impairment, may play a critical role in speech difficulties[22]. In addition, children with a repaired cleft palate and reduced cross-sectional upper airway are at an increased risk for SDB symptoms and also for speech problems[26,27].

Therefore, the purpose of this study was to investigate the frequency and characteristics of HS, MED, and speech problems in young children with non-syndromic cleft palate anomalies and to assess the association between HS in children with cleft palate with and without MED and speech delay.

Patients and methods

All children included in this study were followed at the Craniofacial Anomalies Program at C.S. Mott Children's Hospital, University of Michigan. In order to have a homogeneous sample, only families of children with specific non-syndromic cleft palate anomalies were invited to participate in this cross-sectional study. Inclusion criteria were as follows: (1) age 2.0–7.9 years, (2) confirmed diagnosis of a non-syndromic cleft palate anomaly that included isolated cleft palate, cleft lip and palate, or Pierre Robin sequence with cleft palate, (3) lack of other major medical problems, and (4) primary caregiver able to read and write English. A total of 270 records were reviewed for eligibility, and written informed consent was obtained from 99% (95/96) of the parents/guardians invited to participate.

Parents completed the Pediatric Sleep Questionnaire and a questionnaire about MED during the clinical appointment. Audiogram and speech assessments were also conducted by specialized healthcare professionals. Demographic and anatomical characteristics of the study population were extracted from the medical records and included sex, age (calculated from date of birth), ethnic background, and confirmed orofacial cleft based on genetic results and/or clinical report. Height and weight were collected from the medical records. Body mass index (BMI, kg/m^2) and BMI percentiles, adjusted for age and sex, were calculated (https://www.bcm.edu/cnrc-apps/bodycomp/bmiz2.html#CDC). This study was approved by the Institutional Review Board at the University of Michigan.

Habitual snoring

The Pediatric Sleep Questionnaire (PSQ) was used to investigate SDB symptoms in the study population[28]. The PSQ consists of 70 questions; of these, 22 items constitute the sleep-related breathing disturbance scale (SRBD). The PSQ is a validated tool widely used in research to screen sleep disturbance in children ≥2 years of age[9,12,27]. Habitual snoring, the key SDB symptom and main variable for this specific research, was considered in those cases with a positive answer to question A2 of the SRBD (''Snores more than half of the time?'').

Middle ear disease

A brief questionnaire designed by the study team was used to investigate the main characteristics of MED. This included 17 questions about the characteristics of the episodes, such as the number of ear infections in the last year, duration and severity, presence of fluid, onset of MED, pharmacological treatment, tympanostomy tube insertion, and suspicions for hearing loss or speech problems. Questions about allergies and exposure to tobacco smoke at home were also included. A positive history of MED was considered in those cases with at least one positive response to characteristics of MED. Early MED included children whose first episode of MED occurred during the first 12 months of life. Recurrent acute otitis media was considered in those children who reported ≥3 acute episodes of otitis media in the past 12 months, and chronic otitis media with effusion in those cases with MED accompanied by effusion that lasted at least 3 months. Finally, the study population was classified into three hearing impairment categories according to audiogram results performed during the clinical appointment: normal hearing, mild hearing loss, and moderate-to-severe hearing loss.

Speech assessment

A speech-language pathologist (MB) applied the Pittsburgh Weighted Speech Scale[29], a standardized method for auditory-perceptual velopharyngeal insufficiency assessment based on five speech components: nasality, nasal emission, nasal grimace,phonatory characteristics, and articulation. The weighted score for each component and the sum of all scores were calculated by one of the study authors (MM). The study population was divided into four groups according to the velopharyngeal insufficiency status: 0 = competent velopharyngeal mechanism, 1–2 = borderline competent, 3–6 = borderline incompetent, ≥7 = incompetent velopharyngeal mechanism. Moreover, a question about suspicions for speech problems was also included in the MED questionnaire (''Do you think your child's ear infections affect his/her speech or language?'').

Statistical analysis

Data were double-entered in all cases to ensure accuracy. The three main outcome variables were HS, MED, and speech problems. Analysis of variance (ANOVA) was used to compare means and standard deviations (SD) for continuous variables (age and BMI) and the χ^2 test (or Fisher's exact test) was used to compare categorical variables. An unadjusted bivariate analysis was first performed using the χ^2 test to investigate differences in the frequency of HS, MED, and speech problems among the three groups of children with different non-syndromic orofacial clefts, and to assess differences in the frequency of HS between children with specific characteristics of MED, with and without speech problems, and further to investigate the frequency of HS, MED, or speech problems between children with and without allergies and with and without exposure to smoke at home. The Bonfer-

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roni post-hoc test was used for multiple group comparisons. All tests were two-tailed. In the case that the χ^2 test result was statistically significant, logistic regression was performed to evaluate the risk for HS. Odds ratios (OR) and corresponding 95% confidence intervals (CI) were calculated from the logistic regression models. Analyses were conducted using SPSS 15.0 (IBM Corp., Armonk, NY, USA). Differences were considered statistically significant if the *P*-value was <0.05.

Results

A total of 270 medical records of children attending the Craniofacial Anomalies Program at C.S. Mott Children's Hospital were reviewed. The records of 95 children with a non-syndromic cleft palate who met the inclusion criteria were included in the final analysis. The children in the study population ranged in age from 2.5 to 7.8 years; the mean age was 5.1 years (SD 1.5 years). All children had a BMI within normal limits. These and other characteristics of the sample are reported in Table 1.

Habitual snoring and other sleep disordered-breathing symptoms in children with cleft palate

Habitual snoring was reported by 15.2% of families with children with non-syndromic cleft palate, heavy or loud breathing by 27.8%, breathing through the mouth by 31.8%, and dry mouth on waking up in the morning by 18.8%. No significant difference in the frequency of HS was found between boys and girls (57.1% vs 42.9%, $P = 0.503$). Children with isolated cleft palate were more likely to report HS than children with cleft lip and palate and children with Robin sequence (37.5% vs 10.3% vs 12.5%, $P = 0.024$) (Fig. 1). Differences in frequency of HS remained statistically significant between children with isolated cleft palate and children with cleft lip and palate (37.5% vs 10.3%, $P = 0.007$). However, there were no statistically significant differences in the frequency of HS between children with isolated cleft palate and children with Robin sequence (37.5% vs 12.5%, $P = 0.204$).

Characteristics and consequences of middle ear disease

The vast majority of children with cleft palate (97.6%) had a positive history of MED, and of those, 63.2% had their first episode of MED during the first year of life. Children with isolated cleft palate were more likely to have early symptoms of MED when compared to children with cleft lip and palate (92.3% vs 58.2%, $P = 0.021$), as well as those with Robin sequence (92.3% vs 50.0%, $P = 0.027$) (Fig. 1). The overall frequency of recurrent acute otitis media was 15.8% (isolated cleft palate 18.8%, cleft lip and palate 14.3%, and Robin sequence 22.2%; $P = 0.78$). The frequency of otitis media with effusion was high (83.3%) overall, particularly in children with cleft lip and palate compared to those with Robin sequence (cleft lip and palate 86.4% vs Robin sequence 57.1%, $P = 0.049$). Chronic otitis media with effusion was not reported by any family. The vast majority of children in the study population (95.8%) had undergone tympanostomy tube insertion. Audiograms were performed in 93 of the 95 children and 1.1% had severe hearing impairment. There was a trend for children with otitis media with effusion to be more likely to have hearing loss (mild, moderate, or severe) when compared to children without (43.8% vs 15.4%, $P = 0.056$).

Speech problems

Overall, speech problems were reported by 17.1% of families and an incompetent/borderline incompetent velopharyngeal mechanism was present in 41.5% of children according to the Pittsburgh Weighted Speech Scale results. No statistically significant differences in the frequency of incompetent velopharyngeal mechanism were found between genders (58.8% male vs 41.2% female, $P = 0.330$), ethnic backgrounds ($P = 0.392$), and cleft palate anomalies ($P = 0.438$) (see Table 1).

Habitual snoring, middle ear disease, and speech: association, environmental and anatomical risk factors

Children with a cleft palate anomaly who reported at least one episode of MED in the last 12 months were more likely to have HS when compared to those children who did not (25.5% vs 4.4%, $P = 0.005$; OR 7.37, 95% CI 1.55–35.15, $P = 0.012$). After adjusting for age, gender, ethnic background, and subtype of cleft anomaly, the odds of HS in children with at least one episode of MED in the last 12 months persisted (OR 10.06, 95% CI 1.56–64.89, $P = 0.015$). Moreover, there was a trend for children with longer episodes of MED (between 2 and 4 weeks) to be more likely to report HS compared to those who reported shorter episodes of MED (<2 weeks) (35.7% vs 14.8%, $P =$

Table 1. Summary of demographic data and the main characteristics of the study population.

	Total population ($N = 95$)	Habitual snoring ($n = 14$)	Middle ear disease ($n = 80$)	Velopharyngeal insufficiency ($n = 34$)
Age (years), mean ± SD	5.1 ± 1.5	4.5 ± 1.5	5.2 ± 1.5	5.4 ± 1.4
BMI (kg/m^2), mean ± SD	15.4 ± 1.6	15.3 ± 1.8	15.4 ± 1.6	15.0 ± 1.3
Sex				
Male	47 (49.5%)	8 (57.1%)	42 (52.5%)	20 (58.8%)
Female	48 (50.5%)	6 (42.9%)	38 (47.5%)	14 (41.2%)
Race background				
White	61 (64.2%)	11 (78.6%)	57 (71.3%)	25 (73.5%)
Asian	26 (27.4%)	2 (14.3%)	17 (21.3%)	8 (23.5%)
Black and African-American	4 (4.2%)	0 (0%)	2 (2.5%)	1 (2.9%)
Others	4 (4.2%)	1 (7.1%)	4 (5%)	0 (0%)
Orofacial diagnosis				
Isolated cleft palate	16 (16.8%)	6 (42.9%)	13 (16.3%)	5 (14.7%)
Cleft lip and palate	70 (73.7%)	7 (50.0%)	59 (73.8%)	24 (70.6%)
Robin sequence with cleft palate	9 (9.5%)	1 (7.1%)	8 (10%)	5 (14.7%)
Allergies	36 (37.9%)	2 (14.3%)	28 (35%)	16 (47.1%)
Smokers at home	20 (21.1%)	4 (28.6%)	18 (22.5%)	8 (23.5%)

BMI, body mass index; SD, standard deviation.

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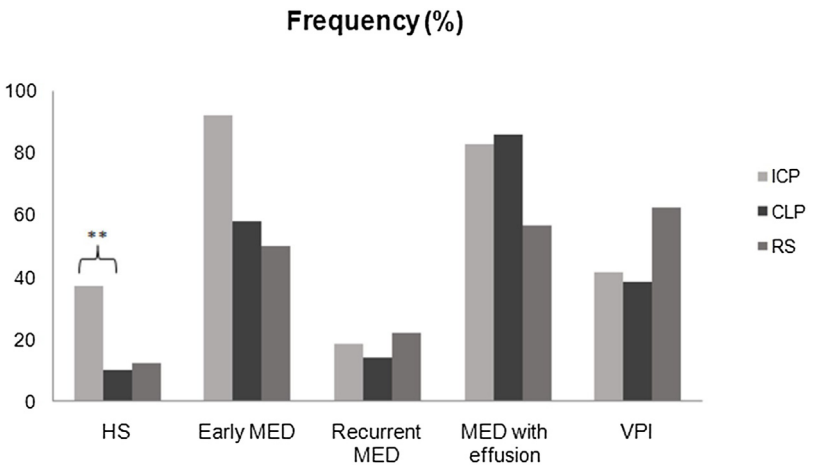

Fig. 1. Frequency of habitual snoring, middle ear disease, and velopharyngeal insufficiency in relation to the specific cleft palate diagnosis. HS, habitual snoring, MED, middle ear disease; VPI, velopharyngeal insufficiency. Cleft diagnosis: ICP, isolated cleft palate; CLP, cleft lip and palate; RS, Pierre Robin sequence with cleft palate.*$P < 0.05$, **$P < 0.01$ (after Bonferroni test adjustment).

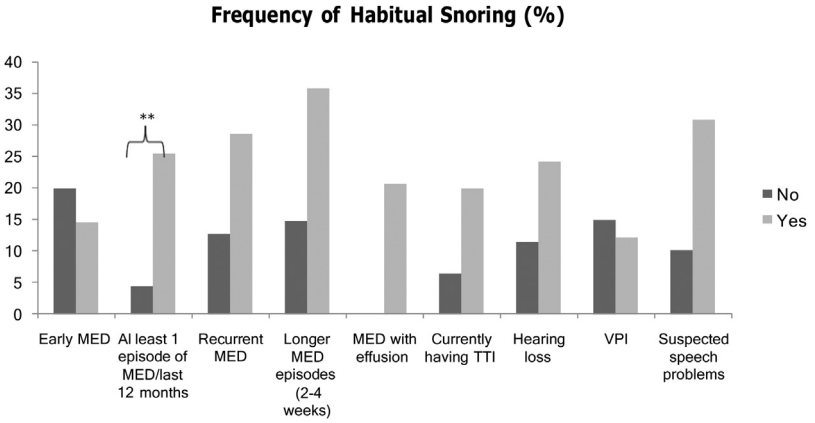

Fig. 2. Frequency of habitual snoring in the study population in association with characteristics and consequences of middle ear disease and speech problems.
MED, middle ear disease; TTI, tympanostomy tube insertion; VPI, velopharyngeal insufficiency. Note: Hearing loss results are based on audiogram report. *$P < 0.05$, **$P < 0.01$ (after Bonferroni test adjustment).

0.076). Similarly, the frequency of HS was higher among children with effusion compared to those without (20.6% vs 0%, $P = 0.084$) and among children who had a tympanostomy tube inserted compared to children who did not (20.0% vs 6.5%, $P = 0.090$). However, after adjusting by Bonferroni post-hoc test, only the correlation between HS in children with at least one episode of MED in the last 12 months persisted. Fig. 2 summarizes the frequency of HS according to the characteristics of MED.

No differences in the frequency of HS were found among children with an incompetent/borderline incompetent velopharyngeal mechanism and children with a competent/borderline competent velopharyngeal mechanism (incompetent 12.1% vs competent 14.9%, $P = 0.723$). There was a trend for children with speech problems reported by parents to be more likely to have HS when compared to those whose parents did not report speech problems (30.8% vs 11.5%, $P = 0.076$).

Of the 95 children, 36 (37.9%) reported a history of allergies and 20 (21.1%) were exposed to tobacco smoke at home. No significant difference was found between children with and without a history of allergies and the frequency of HS (allergies 5.9% vs no allergies 20.7%, $P = 0.056$) or the main characteristics of MED (early disease, recent episodes, recurrent disease, duration, presence of fluid, or tympanostomy tube insertion). Allergies were not associated with a higher frequency of hearing loss (allergies 17.6% vs no allergies 40.7%, $P = 0.022$). No statistically significant difference in the frequency of HS was found between children who lived with smokers at home and those who did not (smokers at home 21.1% vs no smokers 13.7%, $P = 0.427$). Similarly, the frequency of hearing impairment between children with and without exposure to smoking at home did not differ significantly (26.3% vs 33.8%, $P = 0.534$).

Discussion

This cross-sectional study showed that recent episodes of otitis media in children aged 2–7 years with a repaired cleft palate were associated with an increased frequency of HS, a key characteristic of

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SDB. Moreover, there was a trend for children with speech difficulties reported by their parents to have more frequently HS. The study findings also suggest that in children with a cleft palate, intrinsic factors such as the type of cleft anomaly play a role in the frequency of HS and specific MED symptoms.

The presence of craniofacial anomalies in a newborn has compromised the morphology of upper airway symptoms from birth predisposing to early obstructive sleep symptoms. In a previous study performed at the University of Michigan, the frequency of SDB in symptomatic children with craniofacial malformations referred to the sleep clinic was greater than 70%[30]. The issue is important, because SDB is frequently overlooked in children with cleft palate, likely due to the complexity of this medical condition, lack of general knowledge, and even difficulties in access to a sleep clinic. Interestingly, approximately 80% of children with cleft palate and other craniofacial anomalies snore. Moreover, snoring and other nocturnal breathing symptoms reported by the parents, such as mouth breathing and dry mouth, were associated with a high frequency and greater severity of SDB[30]. Therefore, an important step in the diagnosis and prevention of the significant morbidity associated with SDB in children with cleft palate is to recognize the key characteristic of this common medical condition and identify potential risk factors.

It is well known that otitis media is one of the most common infection processes in children with cleft palate. The present study provides evidence that most young children with cleft palate had their first episode of otitis media during the first year of life, a critical developmental period for hearing and speech. In children with cleft palate, the abnormal insertion of the muscles responsible for the opening of the Eustachian tube is considered one of the causes of MED. Nevertheless, other anatomical and environmental factors such as reduced dimensions of the airway or environmental exposures might also play a role. Interestingly, risk factors involved in the pathophysiology of MED in the general pediatric population are also linked to HS, and have prompted some authors to hypothesize that these two medical conditions may be related in children without craniofacial malformations[23,24]. Gozal et al. showed that HS was associated with increased odds of MED and also the need for tympanostomy tube placement[23]. Similarly, Tauman et al. found that children who had undergone tympanostomy tube insertion had increased odds of snoring and adenotonsillectomy (OR 3.4, 95% CI 1.6–7.2)[24]. A previous study conducted in children with cleft palate found that the sphenopalatine angle was smaller in those children with hearing loss compared to children who had normal hearing[6]. Moreover, in the present study, an association was found between the orofacial diagnosis (isolated cleft palate, cleft lip and palate, and Robin sequence) and HS or specific characteristics of MED. Environmental factors, reported by parents, such as allergies or exposure to smoke at home, were not associated with a higher frequency of HS or a higher frequency of severe hearing loss. It appears that intrinsic factors related to the dimensions/characteristics of the upper airway play a significant role in the pathophysiology of MED and HS compared with environmental factors in children with cleft palate.

Speech is an upper airway function that shares anatomical and embryonic development with breathing. Otitis media and speech difficulties are symptoms frequently reported and routinely assessed in children with cleft palate. Nevertheless, HS is often underestimated in this pediatric population. We have previously shown that specific characteristics of resonance during speech assessment are associated with an increased risk for SDB in children with craniofacial malformations[27]. Moreover, the results of the current study also suggest that even speech problems reported by parents could be associated with an increased frequency of HS in children with cleft palate.

Several strengths of this study should be noted. This study was specifically designed to assess the association between three common medical conditions related to the upper airway – HS, MED, and speech – in a pediatric population with cleft palate. The homogeneous sample, focused on young children with a specific craniofacial anomaly, provides clear data about these common comorbidities during a developmental period. The increased frequency of HS in children with cleft and specific characteristics of MED should be considered an important finding to take into account to screen for SDB. Polysomnography is considered the gold standard for SDB diagnosis. Nevertheless, in pediatric populations with multiple medical concerns, sleep diagnoses may be overlooked. Screening for SDB symptoms in this population – via simple office-based assessments – may provide more timely referral, diagnosis, and management. Despite these strengths, there are several limitations. Questionnaires, rather than direct assessment, were the tools use to evaluate some of the main variables such as HS and MED characteristics in the study population. Another limitation is the small sample sizes of children with the specific types of cleft, which reduced the power to detect group differences.

In summary, children with a non-syndromic cleft palate anomaly who reported a recent history of at least one episode of MED were more frequently reported to have HS, a key characteristic of SDB. Moreover, a trend for children with cleft and speech problems reported by their parents to be more likely to have HS was observed. The study findings support the need for screening and evaluation of SDB in children with MED and speech problems as a standard of care during this critical developmental period in this pediatric population.

Funding

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Competing interests

The authors have no conflicts of interest to declare.

Ethical approval

This study was approved by the Institutional Review Board at the University of Michigan (ID HUM00054515).

Patient consent

Written informed consent was obtained from parents or guardians in all cases.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version,

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4.3. ARTICLE 3

Sleep-Related Movement Disorders and Growing Pains: Differences in Daytime and Bedtime Behavior in 2-6 year old Children with Cleft Palate

- **Authors**: **Moraleda-Cibrián M**, Sean E, Kasten S, Warschausky S, Buchman S, O'Brien LM.
- **Citation**: Sleep Medicine. 2021 Sep;85:303-308.
- **Objectives**:
  Aim 5 To investigate the frequency of other sleep disorders such as sleep-related movement disorders (periodic limb movements and restless legs syndrome) and growing pains symptoms in young children with orofacial cleft.
  Aim 6 To determine whether periodic limb movements, restless legs syndrome and/or growing pains play a role in daytime (internalizing and externalizing symptoms) and bedtime behavior in this patient population.
- **Impact Factor**: 2.96
- **Quartile**: Q1.
- **Field**: Medicine

Resum

Trastorns del moviment relacionats amb el son i dolors creixement: diferències en comportament diürn i nocturn en nens de 2 a 6 anys amb fissura palatina

Introducció: Els problemes del comportament són comuns en nens amb trastorns del son. No obstant fins ara, tot i l'elevada freqüència dels trastorns del comportament en nens amb paladar fes, cap estudi ha investigat l'associació entre els trastorns del moviment relacionats amb el son (síndrome de cames neguitoses i moviments periòdics de cames) i els problemes conductuals en aquesta població pediàtrica. Per tant, l'objectiu d'aquest estudi era avaluar la freqüència i l'impacte dels trastorns del moviment relacionats amb el son i els dolors de creixement en el comportament diürn i nocturn en nens de curta edat amb fissura palatina.

Mètodes: Estudi transversal sobre el son i el comportament en nens de 2,0-6,9 anys amb fissura palatina. Els pares van completar el Qüestionari de Son Pediàtric, que inclou preguntes sobre moviments periòdics de cames, síndrome de cames neguitoses, dolors de creixement, somnolència diürna, latència i duración del son, i el Qüestionari de la infantesa primerenca de Conner amb preguntes sobre les dificultats de comportament.

Resultats: Entre els 71 nens amb fissura palatina (52,1% de sexe masculí) el 14,1 % va resultar positius en el cribratge per moviments periòdics de cames, el 8,5% van reportar símptomes de cames neguitoses i 9,9% dolors de creixement. Els nens amb cribratge positiu per moviments periòdics de cames i cames neguitoses van presentar amb més freqüència somnolència diürna (moviments periòdics de cames: 40,0% vs. 4,9%, p= 0,001; cames neguitoses 33,3% vs. 7,7%, p=0,04) i augment de la latència de son (moviments periòdics de cames 80% vs. 32,8%, p=0,005; cames neguitoses 100% vs. 33,8%, p=0,002) en comparació amb aquells que no van presentar aquests símptomes. Aquestes diferències no van ser significatives en nens amb i sense dolors de creixement. A més, els nens amb moviments periòdics de cames i cames neguitoses van presentar més afectació de l'estat d'ànim (58,2 ± 7,6 vs. 50,7 ± 8,4, p=0,01) i símptomes somàtics (66,2 ± 15,2 vs. 49,9 ± 9,5, p=0,0001). Per altra banda, la somnolència diürna es va associar amb un increment en la freqüència de problemes conductuals d'externalització, psiquiàtrics i somàtics. Mentre que els nens amb latència allargada van reportar amb més freqüència símptomes emocionals i somàtics, i aquells amb un temps de son reduït més dificultats conductuals d'internalització.

Conclusions: Els pares de nens de curta edat amb fissura palatina van reportar amb freqüència moviments periòdics de cames, cames neguitoses i dolors de creixement. Diferències en el comportament diürn i nocturn, prèvies al son, van ser objectivades en funció de la presència dels diferents tipus de trastorns dels moviments estudiats. La somnolència diürna i altres variables de son podrien intervindre en els problemes de comportament en nens amb paladar fes i trastorns del moviments relacionats amb el son.

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Original Article

Sleep-related movement disorders and growing pains: differences in daytime and bedtime behavior in 2–6 year old children with cleft palate

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ABSTRACT

Background: Behavioural difficulties are common in children with sleep disorders. However, up to now no study has investigated the association between sleep-related movement disorders (SRMD) and behavior in children with craniofacial cleft. The aim of this study was to assess the frequency and impact of SRMD and growing pains in daytime/bedtime behavior in young children with cleft palate.

Methods: Cross-sectional survey study of sleep and behavior in 2.0–6.9 year old children with cleft palate. Parents completed the Pediatric Sleep Questionnaire, which queries reports of periodic limb movements (PLMS), restless leg syndrome (RLS), growing pains, daytime sleepiness, sleep latency/duration, and the Conners' Early Childhood Questionnaire which asks about behavioral difficulties.

Results: Among 71 children with cleft palate (52.1% boys) 14.1 % screened positive for PLMS, 8.5% reported RLS and 9.9% growing pains. Children who screened positive for PLMS and RLS were more likely to report sleepiness (PLMS 40% vs. 4.9%, $p = 0.001$; RLS 33.3% vs. 7.7%, $p = 0.04$) and long sleep latency (PLMS 80% vs. 32.8%, $p = 0.005$; RLS 100% vs. 33.8%, $p = 0.002$) compared to those who did not endorse the respective sleep problems. Children who reported PLMS had a higher T-score for emotional (58.2 ± 7.6 vs. 50.7 ± 8.4, $p = 0.01$) and somatic symptoms (66.2 ± 15.2 vs. 49.9 ± 9.5, $p = 0.0001$). Sleepiness was associated to an increased frequency of externalizing, psychiatric and somatic problems. While children with long sleep latency reported more emotional and somatic symptoms, and those with reduced sleep duration more internalizing difficulties.

Conclusions: Parents of young children with cleft palate reported frequently PLMS, RLS and growing pains. Daytime/bedtime behavior varies depending on the presence of SRMD. Sleepiness and sleep variables might play a role on behavioural problems in children with cleft and SRMD symptoms.

1. Introduction

Sleep-related movement disorders (SRMD) encompass a wide range of stereotypical and non-purposeful movements that occur during wake-sleep or sleep–wake transition or during sleep. It is estimated that, in general pediatric populations, the frequency of restless legs syndrome (RLS) is about 2% and varies from 5% to 26% for periodic limb movements (PLMS) [1–5]. Several large population studies have shown an association between RLS and PLMS; despite the pathophysiology of RLS and PLMS being unclear.

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Emerging evidence of common risk factors for RLS and PLMS such as dopaminergic system dysfunction, low iron stores and genetic susceptibility have been proposed [2,6]. In addition, several authors have suggested that RLS and growing pains are frequently overlapping, and largely familial [7,8].

The role of sleep in cognitive and behavioural development has been widely recognized in school age children and adolescents [9–11]. Nevertheless, this association is still unclear in younger pediatric populations. The prevalence of attention-deficit/hyperactivity disorder (ADHD) is about 5–7% in general pediatric populations, but increase up to 30–35% in children with RLS or PLMS symptoms [12–14]. Behavioural problems are common in children with craniofacial clefts. Richman et al. found that up to 50–60% of children with cleft lip and palate and isolated cleft palate have internalizing behavior that increased in girls over nine years of age [15]. However, less is known about risk for externalizing behavior such inattention/hyperactivity, impulsivity disorder or aggressiveness, behavioral traits of likely neuropsychiatric disorders in children with craniofacial clefts [16,17]. Causes of behavioral problems in children with cleft could be multifactorial (genetics/developmental, environmental, sleep disorders and other medical problems). However, an increased risk for behavioral difficulties due to untreated obstructive sleep apnea or insufficient sleep duration in pediatric populations with and without craniofacial anomalies it has been recognized [11,18–20]. To date, no study has assessed whether SRMD or growing pains may play a role on daytime functioning in the pediatric cleft population who may be a particularly susceptible cohort to SRMD and growing pains related functional difficulties, given their high frequency of cognitive and behavior difficulties. Therefore, the purpose of this study was to investigate the frequency of PLMS, RLS and growing pains symptoms in young children with non-syndromic cleft palate, and to determine whether PLMS, RLS and/or growing pains play a role in daytime (internalizing and externalizing symptoms) and bedtime behavior in this patient population.

2. Material and methods

2.1. Study population

The study was approved by the Institutional Review Board at the University of Michigan. This cross-sectional study was part of a larger investigation specifically designed to assess frequency of different sleep disorders in young children with cleft palate, the most common craniofacial malformation, and to assess daytime and bedtime behavior. Families of consecutive children with cleft palate seen in the Craniofacial Anomalies Program whose primary caregiver was able to read and write English were selected and approached by a study team member (MM). Children were included if they were between 2.0 and 6.9 years old with a confirmed diagnosis of cleft palate and no other major medical problems such as suspected developmental delay, syndromic cleft palate, neurological or behavioural disorders. Written informed consent was obtained from parents.

2.2. Measurements

Parents of enrolled children completed the Pediatric Sleep Questionnaire (PSQ) [21], and the Conners' Early Childhood Questionnaire [22] during the clinical appointment (see below). Data extracted from medical records included gender, age, racial background, weight, height and confirmed diagnosis of cleft palate. Body Mass Index (BMI = weight in Kg/height in m^2) and BMI percentiles, adjusted for age and sex, were calculated.

2.2.1. Sleep-related movement disorders and growing pains

The PSQ is a well-validated tool widely used in research to screen sleep disorders in children aged 2–18 years. The PSQ contains 70 questions and includes several validated component scales. The PLMS scale of the PSQ was used to screen for PLMS in children with cleft palate (Appendix 1) [23]. This scale includes six items: four items about nighttime awakenings and daytime symptoms (A16, A44, B1, B7), one item about restless legs syndrome symptoms (RLS) (A13) and one item about growing pains (A13b). The questions about RLS and growing pains have double weight assigned in the PLMS scale and were also evaluated separately. Responses options were 'yes', 'no', or 'don't know'. 'Don't know' or 'not available' responses were considered missing. The PLMS score varies from 0.0 to 1.0. Children with a threshold score ≥0.33 were considered to have high risk for PLMS. In general pediatric populations, a score ≥0.33 has a sensitivity of 0.79, and a specificity of 0.56 for 5 or more PLMS per hour of sleep [23].

2.2.2. Sleepiness and bedtime behavioral assessment

In order to assess the frequency of daytime sleepiness the four-item sleepiness subscale of the PSQ was used: 1) unrefreshed in morning; 2) problem with sleepiness; 3) sleepy per teacher; and 4) hard to wake up [21]. High risk for sleepiness was considered present in those children with a threshold score ≥0.33. Sleep latency was collected from the PSQ. Long sleep latency was considered when the average to fall sleep was ≥30 min. Total sleep time (TST) weekdays was also reported on the PSQ. Suboptimal sleep duration was considered when TST was more than 1 h less than the minimum recommended time by the National Sleep Foundation per age.

2.2.3. Daytime behavioral assessment

The Conners' Early Childhood questionnaire is a comprehensive parent report tool designed to assess a wide range of behavioural, emotional, social concerns, and major developmental milestones (adaptive skills, communication, motor skills, play and pre-academic/cognitive) in toddlers and preschool-aged children from 2 to 6 years old [22]. The Conners' Early Childhood is well validated instrument which contains 190 questions. The behavioural assessment of the Conners' Early Childhood includes seven indicators of potential problematical areas such as inattention/hyperactivity, defiant/aggressive behaviours, social functioning/atypical behaviours, anxiety, mood and affect and physical symptoms. Response options vary from 0 to 3 or from 0 to 2. Raw scores were converted to standard T-scores adjusted by age and gender with a range of 0–100, mean of 50, and standard deviation (SD) of 10. 'High average score' was defined as a T-score between 60 and 64 (mean ± 1–1.5 SD) and is associated with a slightly higher number and/or frequency of reported concern. For the current study, a high average T-score or above was considered clinically significant.

2.3. Statistical analysis

The main variables of the study were frequency of PLMS, RLS and growing pains symptoms, daytime sleepiness, sleep latency, sleep duration and T-scores for daytime behavioural problems. The study population was divided into three age groups (toddlers <3 years, pre-schooler 3.0–5.9 years and school aged children 6.0 years and older) and into three weigh groups according to the BMI percentile threshold recommended by Centers for Disease Control.

Data were summarized by means and SD for continuous variables, and percentages for categorical variables with 95% of confident intervals. The χ^2 test was used to examine differences between categorical variables such demographic data (gender, BMI groups, racial background) and the presence of the main variables of the study (PLMS, RLS, growing pains, daytime sleepiness, long sleep latency and suboptimal TTS according to age). Moreover, comparisons of continuous variables such as mean sleep latency and T-scores for behavioral problems were conducted using the student t-test. All test results were two-tailed and differences were considered statistically significant if the p-value was <0.05. Analyses were conducted using SPSS 15.0 (IBM, Armonk, NY).

3. Results

A total of 80 children with non-syndromic cleft palate aged 2.0–6.9 years were enrolled. Of these, nine children were excluded due to the presence of other craniofacial or congenital anomalies, syndromes, autism and developmental delay. Therefore, the final sample size was n = 71. The mean participant age was 4.8 ± 1.3 years, 52.1% were boys and 62.0% were Caucasian. Among the 71 children, 56 (78.9%) were of normal weight according to the BMI percentile. Summary of the main characteristics of the study population are shown in Table 1.

3.1. Periodic limb movements, restless legs syndrome and growing pains symptoms

The PLMS score was ≥0.33 in ten children (14.1%), six (8.5%) reported RLS symptoms, and seven (9.9%) growing pains. None of the children were diagnosed or on treatment for these conditions. Caucasian children were more likely to report PLMS symptoms compared to children of other races (20.5% vs 3.7%, p = 0.049). Moreover, the mean age in children with growing pains was higher compared with children without (Table 2). But, no other statistically significant differences were found in the frequency of SRMD and growing pains according to the other demographic characteristics in the study population (Table 2). Two thirds (66.7%) of children who reported RLS symptoms screened positive for PLMS, while only 40% of children who screened positive for PLMS reported RLS symptoms (p = 0.0001). Moreover, most children with growing pains symptoms screened positive for PLMS (85.7% vs. 6.3%, p = 0.0001), while only few of them reported RLS symptoms (14.3% vs. 7.8, p = 0.56). The frequency of positive screening for sleep disordered breathing (SDB) was higher in those children who screened positive for PLMS compared to those who did not (40.0 vs. 13.1%, p = 0.035). Nevertheless, this association was not found in children who reported RLS symptoms (33.3 vs. 15.4%, p = 0.26), nor for those who reported growing pains (14.3 vs. 17.2%, p = 0.85).

Table 1
Demographic and other characteristics of the study population.

	N (%) (n = 71)
Age (mean ± SD (years))	4.8 ± 1.3
BMI percentile (mean ± SD)	44.9 ± 31.6
Boys	37 (52.1)
Race	
Caucasian	44 (62.0)
Asian	21 (29.6)
African-American	3 (4.2)
Other	3 (4.2)
PLMs score (mean ± SD)	0.1 ± 0.2
Positive screening for PLMS	10 (14.1)
RLS symptoms	6 (8.5)
Growing pains symptoms	7 (9.9)
Sleepiness score (mean ± SD)	0.1 ± 0.2
Sleep Latency (mean ± SD (minutes))	24.7 ± 17.2

SD standard deviation, PLMS periodic limb movements, RLS restless legs syndrome.

3.2. Sleepiness, sleep latency and sleep duration

Overall, seven children (9.9%) screened positive for daytime sleepiness. Children who screened positive for PLMS and those who reported RLS symptoms were more likely to have daytime sleepiness compared with children who screened negative for PLMS and RLS. There was a trend for children with growing pains to have daytime sleepiness. See Table 2.

Sleep latency ≥30 min was reported by 28 children (39.4%) in this study population of young children with cleft palate. Among the total population, no statistically significant association was found in the mean sleep latency between age groups. Nevertheless, children with RLS symptoms and positive screening for PLMS reported more that 20–30 min on average to fall sleep compared to those who did not reported PLMS or RLS symptoms. Differences on mean sleep latency were not statistically significant for children with and without growing pains (Table 2). The mean of sleep duration in the study population on weekdays was 10.2 ± 0.9 h. Suboptimal TST was higher in the younger age group (toddlers 100%, pre-schoolers 11,5% vs. school aged children 0%, p = 0.0001). No association was found between suboptimal TTS and positive screening for sleepiness (10.0% vs. 9.8%, p = 0.99). However, long sleep latency was reported by 100% of children who screened positive for daytime sleepiness and only 32.8% of those children who screened negative for sleepiness (p = 0.001).

3.3. Association between sleep-related movement disorders/ growing pains, and daytime/bedtime problems

The T-score for inattention/hyperactivity was high (≥60) in twenty-two children (31.0%). Forty per cent of children who screened positive for PLMS, 50% with RLS symptoms, and 28.6% with growing pains had a high T-score for inattention/hyperactivity, but differences in T-score for inattention/hyperactivity were not statistically significant between children with and without PLMS, RLS or growing pains. Nevertheless, children who screened positive for PLMS had a high T-score that was statistically significant for mood/affect problems and for physical symptoms compared with children who screened negative for PLMS (T-score mood/affect 58.2 ± 7.6 vs. 50.7 ± 8.4, p = 0.01, T-score physical symptoms 66.2 ± 15.2 vs. 49.9 ± 9.5, p = 0.0001). Moreover, there was a trend for children who screened positive for PLMS compared to those who did not to have a high mean T-score for defiant aggressive temper, defiant temper and atypical behavior. See Table 3. In the same way, children who reported growing pains trended to have a high T-score for defiant aggressive temper, defiant temper, social functioning and mood/affect problems compare with children who did not report growing pains (Table 3). But differences in mean T-scores for any of the seven indicators of potential problematical areas were not statistically significant among children with and without RLS symptoms.

Finally, we examined the association of the frequency of high T-score (≥60) of the seven assessed indicators of potential problematical behaviours with positive screening for daytime sleepiness, long sleep latency and suboptimal TST. Children with positive screening for sleepiness had a significantly elevated T-score for a variety of daytime problems (externalizing behaviour, emotional/psychiatric and somatic symptoms), while children with long sleep latency reported statistically significant elevated T-scores for emotional and somatic symptoms and children with suboptimal TTS per age for internalizing problems (Table 4).

Table 2
Differences in demographic characteristics and sleep variables or symptoms (mean sleep latencies, frequency of long sleep latency and frequency of sleepiness) among children with positive or negative screening for PLMS, RLS, and growing pains.

	Positive PLMS (n = 10) N (%)	Negative PLMS (n = 61) N (%)	p value	Positive RLS (n = 6) N (%)	Negative RLS (n = 65) N (%)	p value	Positive Growing pains (n = 7) N (%)	Negative Growing pains (n = 64) N (%)	p value
Age (mean ± SD years)	5.0 ± 1.2	4.7 ± 1.3	0.45	4.5 ± 1.2	4.8 ± 1.3	0.58	5.6 ± 1.1	4.7 ± 1.3	**0.07**
BMI percentile (mean ± SD)	54.6 ± 33.1	43.4 ± 31.3	0.34	51.8 ± 37.3	44.3 ± 31.3	0.65	47.9 ± 32.5	44.6 ± 31.7	0.80
Boys	7 (70.0)	30 (49.2)	0.22	4 (66.7)	33 (50.8)	0.46	5 (71.4)	32 (50.0)	0.28
Caucasian	9 (90.0)	35 (57.4)	**0.049**	4 (66.7)	40 (61.5)	0.80	6 (85.7)	38 (59.3)	0.17
Mean Sleep Latency (min)	44.0 ± 23.0	21.5 ± 13.9	**0.01**	52.5 ± 22.7	22.1 ± 14.3	**0.02**	33.9 ± 19.5	23.7 ± 16.8	0.22
Long Sleep Latency (>30 min)	8 (80.0)	20 (32.8)	**0.005**	6 (100.0)	22 (33.8)	**0.002**	4 (57.1)	24 (37.5)	0.31
Sleepiness	4 (40.0)	3 (4.9)	**0.001**	2 (33.3)	5 (7.7)	**0.04**	2 (28.6)	5 (7.8)	0.08

PLMS periodic limb movements, RLS restless legs syndrome, SD standard deviation, p-value <0.05, in bold, was considered statistically significant.

Table 3
Differences in mean T-score for behavioral problems among children with positive or negative screening for PLMS, RLS, and growing pains.

	Positive PLMS (n = 10)	Negative PLMS (n = 61)	p value	Positive RLS (n = 6)	Negative RLS (n = 65)	p value	Positive Growing pains (n = 7)	Negative Growing pains (n = 64)	p value
Inattention/Hyperactivity	61.2 ± 12.9	53.7 ± 11.6	0.11	57.3 ± 19.4	54.5 ± 11.3	0.74	59.4 ± 8.5	54.3 ± 12.3	0.18
Defiant Aggressive Behavior	59.1 ± 9.7	52.8 ± 31.3	0.08	56.3 ± 16.0	53.4 ± 10.0	0.68	58.1 ± 5.5	53.2 ± 10.8	0.07
Defiant Temper	58.5 ± 9.4	52.4 ± 9.5	0.08	53.8 ± 15.1	53.2 ± 9.2	0.93	57.0 ± 4.7	52.9 ± 10.0	0.08
Aggression	54.0 ± 12.6	51.4 ± 13.0	0.55	57.0 ± 15.5	51.2 ± 12.6	0.41	52.9 ± 9.4	51.6 ± 13.2	0.76
Social Functioning/Atypical Behaviors	54.6 ± 10.7	52.3 ± 7.5	0.53	58.5 ± 10.1	52.1 ± 7.6	0.18	51.0 ± 9.5	52.8 ± 7.8	0.64
Social Functioning	50.5 ± 10.3	52.3 ± 8.2	0.61	57.2 ± 8.5	51.6 ± 8.4	0.18	46.3 ± 7.5	52.7 ± 8.4	0.07
Atypical Behaviors	60.8 ± 13.5	51.8 ± 8.0	0.07	58.2 ± 13.9	52.6 ± 8.9	0.38	59.6 ± 13.5	52.3 ± 8.7	0.20
Anxiety	61.0 ± 15.0	52.6 ± 10.7	0.12	56.2 ± 8.4	53.6 ± 11.9	0.51	54.4 ± 13.5	53.7 ± 11.6	0.90
Mood and Affect	58.2 ± 7.6	50.7 ± 8.4	**0.01**	54.8 ± 10.2	51.5 ± 8.5	0.47	57.0 ± 7.4	51.2 ± 8.6	0.09
Physical Symptoms	66.6 ± 15.2	49.9 ± 9.5	**0.0001**	60.5 ± 13.1	51.1 ± 11.0	0.14	56.7 ± 11.5	51.4 ± 11.3	0.28

PLMS periodic limb movements, RLS restless legs syndrome, p-value <0.05, in bold, was considered statistically significant.

Table 4
Differences in the frequency of behavioral problems according to the presence of daytime sleepiness, long sleep latency and reduced sleep duration.

	Positive Sleepiness (n = 7)	Negative Sleepiness (n = 64)	p value	Long Sleep Latency (n = 28)	Normal Sleep Latency (n = 43)	p value	Sub-optimal TST (n = 10)	Normal TST (n = 61)	p value
Inattention/Hyperactivity	42.9	29.7	0.47	28.6	32.6	0.72	30.0	31.1	0.94
Defiant Aggressive Behavior	71.4	20.3	**0.03**	35.7	18.6	0.10	50.0	21.3	0.053
Defiant Temper	71.4	17.2	**0.01**	25.0	20.9	0.69	40.0	19.7	0.15
Aggression	57.4	10.6	**0.09**	21.4	18.6	0.77	20.0	19.9	0.98
Social Functioning/Atypical Behaviors	42.9	18.8	0.14	28.6	16.3	0.21	60.0	14.8	**0.001**
Social Functioning	42.9	21.9	0.22	35.7	16.3	0.06	50.0	19.7	**0.04**
Atypical Behaviors	28.6	21.9	0.69	21.4	23.3	0.86	30.0	21.1	0.54
Anxiety	71.4	21.9	**0.005**	39.3	18.6	0.054	40.0	24.6	0.31
Mood and Affect	57.1	9.4	**0.01**	25.0	7.0	**0.03**	20.0	13.1	0.56
Physical Symptoms	85.7	15.6	**0.0001**	42.9	9.3	**0.001**	20.0	23.0	0.84

TST total sleep time, p-value <0.05, in bold, was considered statistically significant.

4. Discussion

We have demonstrated that sleep-related movement disorders, daytime and bedtime dysfunctional problems such as sleepiness, inattention/hyperactive, and long sleep latency are commonly reported by parents of young children under seven years of age with a repaired cleft palate. It appears that daytime and bedtime behavior varies widely depending on SRMD and growing pains. While difficulties with sleep onset were reported in the three groups of children with SRMD and growing pains compared to those without symptoms, differences in mean sleep latency were only statistically significant in children with positive screening for PLMS and RLS with an increased sleep latency of about 30 and 20 min respectively compared to children without RLS or PLMS symptoms. The presence of PLMS and RLS play a role in bedtime problems and also daytime sleepiness, while growing pains did not play a role in bedtime or in daytime behavior. In addition, daytime sleepiness or isolated findings of PLMS of SRMD might partially contribute to inattention/hyperactivity in young children with cleft palate, the most common developmental behavioural disorder behavior.

Results of the present study differ from previous studies in older children. While the frequency of inattention/hyperactivity was high in children with SRMD compared to children without symptoms, no statistically significant differences in inattention/hyperactivity were found in the present study of children younger than seven years of age. Furthermore, it appears that only the presence of PLMS symptoms was associated with increased T-scores for specific daytime behaviors such as emotional and somatic problems, and could potentially increased externalizing and internalizing symptoms. In addition, the presence of growing pains symptoms was associated with a trend for increased T-scores for externalizing symptoms.

Screening for PLMS, RLS and growing pains could be challenging in children under school age as there is currently a lack of tools

specifically developed to assess these medical conditions in pediatric populations. Efforts to make a clinical diagnosis of RLS based on informant descriptions in young children are problematic and polysomnography is not always available to diagnose PLMS in pediatric populations.

Sleep difficulties are common in school age children and adolescents, which affect up to 40% of children in general pediatric populations. Causes of sleep disruption in children are multifactorial such as environmental or cultural factors, genetics, sleep-disordered breathing (SDB) and other sleep disorders or medical conditions [11,24]. A robust association has been reported in the literature between sleep disruption and daytime behavioral problems [11,14,19,24–26]. Recent studies have also suggested that sleepiness might contribute to externalizing behavior [11,24]. Spruyt and Gozal (2011) in a review suggested that contrary to adults, daytime sleepiness in children may display not only as 'inactive' behavior, but also as an 'overactive' behavior such as hyperactivity or aggressive behavior [24]. Therefore, daytime sleepiness should be considered as a potential factor involved in daytime behavior in pediatric populations. In the current study, children who reported SRMD especially those who screened positive for PLMS were more likely to have daytime sleepiness compared to those without. Of note, children who screened positive for daytime sleepiness had significantly more externalizing behaviour, as well as emotional and somatic symptoms. In contrast, suboptimal TST was associated with significantly more internalizing difficulties, and children with long sleep latency more emotional and somatic problems.

The main strength of our study is that we investigated for the first time both the frequency of different SRMDs and growing pains in children with congenital clefts as well as the impact on daytime function (sleepiness, internalizing and externalizing behaviors), bedtime difficulties (sleep latency) and sleep duration in the same pediatric population. Secondly, the target study population younger than seven years is important since early identification of sleep problems may provide a window of opportunity to intervene and potentially minimize development of inattention/hyperactivity and other behavioral problems prior to increasingly challenging academics pursuits. Third, children with non-syndromic cleft palate, after excluding children with neurological or behavioural disorders, should now be considered a high-risk study population due to the increased risk for later behavioral problems. Finally, children without PLMS, RLS or growing pains were the comparison group rather than typically developing children.

This study has a number of limitations. First, the assessment of SRMD symptoms was based on the parental report from the PSQ rather than polysomnography to identifiy PLMS. The PSQ is a validated tool for screening SRMD in pediatric populations but has not been specifically validated in children with clefts. Nevertheless, a previous study in a large pediatric population without craniofacial anomalies has shown that a score $\geq$0.33 had a sensitivity of 0.79, and a specificity of 0.56 for $\geq$5 PLMs per hour of sleep [23]. Moreover, use of this screening tool has clinical applicability since polysomnography is labor intensive, expensive, and not easily employed in pediatric populations with other medical conditions. Another limitation is that RLS screening was based on a single question rather than the pediatric RLS criteria proposed Picchietti et al. [27] and insufficient to formally diagnose RLS and distinguish it from several mimics.

The present study suggests that daytime symptoms and bedtime difficulties differ widely in young children with cleft palate and symptoms of PLMS, RLS or growing pains. In addition, while causes of behavioral, emotional or somatic problems are multifactorial, it appears that daytime sleepiness secondary to sleep disruption or suboptimal TST may play a role in early daytime symptoms in this pediatric population. Therefore, screening of sleep problems such as SRMD should be considered in children with cleft palate and behavioral problems. Further studies aiming to assess behavior on pediatric populations with these medical conditions are needed.

Credit author statement

Marta Moraleda-Cibrián: conceptualization, methodology, formal analysis, investigation, resources, data curation, writing the original draft and the editing version of the manuscript, visualization, project administration. Sean Edwards, Steven Kasten, Seth Warschausky and Steven Buchman: review and editing the manuscript. Louise M. O'Brien: conceptualization, methodology, formal analysis, data curation, review and editing the original draft and the final version of the manuscript, supervision.

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Conflict of interest

The authors do not have any conflicts of interest to declare.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2021.07.026.

Appendix 1

PLMS scale includes six items (A13 and A13b have double weight assigned in the PLMS score)

A13 Does your child describe restlessness of the legs when in bed?

A13b Does your child have 'growing pains' that are worst in bed?

A16 At night, does your child usually get out of bed (for any reason)?

A44 Does your child wake up more than twice a night on average?

B1 Does your child wake up feeling unrefreshed in the morning?

B7 Does your child wake up with headaches in the morning?

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5. DISCUSSION

Results of the present study have demonstrated that a sizable proportion of preschoolers and young school age children with non-syndromic cleft palate anomalies, non-selected for sleep or behavioral problems, screen positive for SDB or report habitual snoring, the key symptom of SDB. The incidence of positive screening for SDB compared to other studies in pediatric cleft populations was similar to the study of Silvestre (15%),[57] and a little bit lower compared to other two studies probably due to the younger age of the current study population.[43,54] Nocturnal PSG, performed in a subgroup of patients with clinical suspicion of OSA objectively identified the presence of OSA in more than 80% of children; notably more than 25% were diagnosed with moderate-severe OSA. These findings are consistent with the results of MacLean and a previous study of Moraleda-Cibrián et al in children with syndromic and non-syndromic craniofacial malformations.[58,59] Interestingly, according to the outcomes of the present study, and in concordance with previous literature, the increased frequency of SDB and OSA in the study population of non-syndromic cleft represent approximately 1.5-fold, and more than 20-fold higher respectively compared to other investigations in general pediatric populations.[32] Our findings further show: (1) a higher frequency of positive screening for SDB in children with isolated cleft palate, (2) a higher frequency of OSA in males, and (3) a higher AHI in children with isolated cleft palate. Therefore, evaluation of OSA should be highly recommended in this pediatric population due to the established high risk and severity for a constellation of breathing disorders especially in those cases with clinical suspicions even in the absence of formal screening.

The presence of craniofacial anomalies in a newborn has compromised the morphology of upper airway symptoms from birth, predisposing to obstructive symptoms.[171] The upper airway is part of the respiratory system between the nostrils or lips and the trachea. This structure represents a common anatomical pathway for different human functions and it is involved not only in breathing, but also in olfaction, coordination of swallowing and ventilation, protection from aspiration of food, defense of infection, and

speech.[171,172] Otitis media and speech difficulties are symptoms frequently reported and routinely assessed in children with cleft palate.[69,87,90,173–177] In the present study the vast majority of families reported that children with non-syndromic cleft had the first episode of otitis media through the first year, a critical developmental period for hearing and speech.[171,172] The abnormal insertion of the muscles responsible of the opening of Eustachian tube is considered the main cause of MED in this pediatric population. Nevertheless, apart from the reduced dimensions of the airway, upper airway infections, environmental exposures, and other risk factors also play a role in obstructive sleep symptoms. Interestingly, although literature is limited, several years ago it was hypothesized that if habitual snoring and MED share pathophysiological and anatomical mechanisms these two medical conditions may be linked in children without craniofacial malformations.[42,84] This cross-sectional study confirms, for the first time, this association in children with clefts and shows that recent episodes of otitis media in children aged 2-7 years with a repaired cleft palate are associated with an increased frequency of habitual snoring. Moreover, it appears that intrinsic factors related to the dimensions/characteristics of the upper airway play a significant role in the pathophysiology of otitis media and habitual snoring compared with environmental factors in children with cleft palate. Similarly, we have previously shown that specific characteristics of resonance during speech assessment were associated with an increased risk for SDB in children with craniofacial malformations,[91] suggesting that findings of speech assessment may provide additional information about SDB risk. Results of the current study also suggest that parentally-reported speech problems could be associated with an increased frequency of habitual snoring in children with cleft palate. Therefore, these findings support the need for screening and evaluation SDB in children with MED and speech problems as a standard of care during this critical developmental period.

In typically developing children, persistent sleep-related breathing disturbances have been associated with behavioral and cognitive impairments.[61,117,119,178] Even short-term hypoxic exposure from high altitude has been shown to induce significant executive and memory deficits in healthy children.[179] Learning difficulties and behavioral problems are common in children with CL/P.[52,180–184] Factors involved in school under-achievement in this pediatric population are likely multifactorial from hearing and speech difficulties to cognition and behavioral impairment, and SDB or other medical problems. Behavioral problems, that sometimes start early in life, can lead to reduced academic achievement and sever developmental impairment throughout childhood. Internalizing behavioral problems, such social isolation, are frequently reported in cleft populations and may contribute to learning difficulties due to decreased expectations by peers and teachers even when intellectual functioning is within the normal range.[135,180,185] A recent New Zealand study of 378 children with orofacial clefts aged 5-12 years found that while over 90% of children with CL/P had normal prosocial skills, they may not be easily accepted by their peers which may result in behavioral problems.[185] Externalizing behavior problems have been associated among general pediatric populations with snoring and other symptoms of SDB.[61,178] Externalizing behavioral traits such inattention/hyperactivity, aggression or impulsivity that can emerge early in the course of development, persist across developmental stages, occur in a multitude of developmental disorders and directly impact on learning skills and academic achievements. However, externalizing behavioral problems have been less investigated in this pediatric population.[183,186] Nopoulos in a study published in 2010 found substantially elevated hyperactivity/impulsivity/inattention scores in boys with isolated CL/P compared to a healthy comparison group, directly related to the volume of the ventromedial prefrontal cortex, an area of the brain with an important role in these behaviors.[186]

Nevertheless, while the high risk for SDB and behaviour problems have been recognized in children with cleft, little is known about the association between snoring or sleep-related breathing disorders and neurobehavioral impairment in this pediatric population. MacLean et al in a observational follow-up study of infants with history of CL/P concluded that neurocognition was within normal range at least at 3 years of age despite high AHI in infancy.[52] Interestingly, findings of the present study demonstrate in preschool and young school age children with non-syndromic cleft palate that positive screening for SDB was associated with significant higher T-scores for inattention/hyperactivity and internalizing behaviour problems, and moderate/severe OSA with externalizing problems (defiant temper and aggressive behaviour). These findings are consistent with data from previous studies about the impact of SDB in pediatric populations without craniofacial malformations.[61,178] O'Brien et al found that the risk for SDB based on PSQ data was twice as high among children with conduct problems compared to those without.[61] Moreover, some studies have suggested the potential reversibility of behavioral impairment after treatment of disparate childhood sleep disorders.[165,187,188] Thus, studies to assess risk factors for learning and behavioral difficulties in young children with cleft such SDB are needed to investigate its contribution and potential reversibility of these common developmental comorbidities in children with cleft palate.

The impact of SDB on health-related QoL in children with cleft was also investigated in the current study. Six dimensions of QoL (physical well-being, emotional well-being, self-esteem, family, friends and everyday functioning (school or nursery school/kindergarten)) based on the KINDL questionnaire, a generic health-related QoL, were evaluated.[189] The assessment found lower scores for family well-being in children who screened positive for SDB and in children identified with moderate/severe OSA, while lower scores for emotional well-being were only reported in children who screened positive for SDB. Previous studies had investigated the impact of the presence of this craniofacial anomaly on QoL of patients and caregivers.[167–170,190–192] A self-reported study

about health-related QoL suggested that the impact of cleft was higher in adolescents.[169] Smith et al in a prospective study of infants up to 3 years of age demonstrated that QoL scores were within a normal range independently of AHI.[52] Regarding family well-being, QoL outcomes were lower for caregivers of young children with cleft.[170,190] Results of the present study add to this literature by demonstrating an association between different sleep-disordered breathing disrturbances and families' and/or emotional well-being, and severity of OSA and QoL of preschool and young school children with cleft.

Daytime dysfunction has been also associated with reduced or disrupted sleep in pediatric populations without craniofacial malformations.[61,116,117,126,193–195] Nowadays insufficient sleep is the most common sleep problem in children and adolescents with significant associated behavioral problems.[140,196–198] However, knowledge about the frequency and impact on daytime and bedtime behavior of SRMD and growing pains, sometimes misinterpreted as restless legs, in children with orofacial cleft is still limited despite their high risk for behavior problems.

Results of the present study found that between 8 and 14% of parents of young children with cleft palate reported PLMS, RLS and/or growing pains. Of note, screening for SRMD and growing pains could be challenging especially in children under school age. Efforts to make a clinical diagnosis of RLS based on informant descriptions in young children are problematic and PSG is not always available to diagnose PLMS in pediatric populations. Thus, validated pediatric tools such the PLMS scale designed by Chervin, a six-items scale included in the PSQ to screen PLMS, RLS and growing pains with a reasonable validity and reliability,[116] could help to identify SRMD in pediatric populations in order to refer them to sleep clinics and to confirm the diagnosis. However, available data about the frequency of pediatric SRMD based on the PLMS scale is lackling[116] Difficulties in falling sleep, restless sleep and inattetion/ hyperactivity are more frequently reported in general pediatric populations with RLS and PLMS than in controls.[194,199,200] Results of the current study showed that sleep onset difficulties were reported in all three

groups (PLMS, RLS and growing pains). However, differences in mean sleep latency and daytime sleepiness were only statistically significant in children with positive screening for PLMS and RLS compared to those with negative screening.

Regarding behavioral problems, our findings differ from previous studies in older children without craniofacial malformations.[116] Differences in T-scores for social functioning, inattention/hyperactivity or aggressive behavior, internalizing and externalizing difficulties respectively, among the three groups were not statistically significant. However, the presence of PLMS symptoms was associated with increased T-scores for specific daytime behaviors such emotional and somatic problems and may partially contribute to inattention/hyperactivity with higher mean T-scores (>60) in children who screened positive for PLMS compared to those who screened negative. Similarly, T-scores were higher for defiant aggressive and temper behavior and for social functioning and emotional problems in children with growing pains compared with those without, but not quite statistically significant. Thus, while bedtime disturbance and daytime sleepiness were statistically significant for children with cleft who screened positive for PLMS and RLS, externalizing behavioral problems were closer to be significant in children with PLMS symptoms and growing pains. These findings are important since they might contribute to differentiate SRMD and growing pains based on clinical features in pediatric populations. However, further studies are needed to confirm daytime and bedtime differences between these three movement disorders. The interrelation between sleep disruption and inattention/hyperactivity or other externalizing behavioral problems is likely bidirectional and multifactorial. Different explanations have been postulated. Several studies have suggested that unrecognized daytime sleepiness might contribute to aggressive and other externalizing behavior problems.[61,116,195] Contrary to adults, daytime sleepiness in children may manifest not only as ‘inactive’ behavior, but also as an ‘overactive’ behavior such as hyperactivity or aggressive behavior.[195] Results of the present study showed that daytime sleepiness was frequently reported in children who

screened positive for SRMD especially those with PLMS symptoms and plausibly due to a higher sleep disturbance compared with the other groups. Of note, children with daytime sleepiness had significantly more externalizing/internalizing behaviour difficulties compared to children without daytime sleepiness. Therefore, while daytime and bedtime behaviors vary widely depending on the presence of SRMD and growing pains, outcomes related to daytime sleepiness are consistent with previous studies in general pediatric populations.[61,116,195]

This research study has several strengths. First, this study provides information in young children with CL/P about the frequency of obstructive sleep symptoms and OSA, the association of different upper airway symptoms, the relationship of obstructive sleep symptoms with specific areas of behavior and QoL, and the frequency and behavioral impact of SRMD and growing pains. Second, screening of SDB was based on a well-validated questionnaire and in a subgroup of children there were objective data about diagnosis and severity of OSA based on polysomnographic results. Third, the high frequency and severity of OSA in children who underwent polysomnography suggest that children with cleft palate may benefit from OSA evaluation. Fourth, the increased frequency of habitual snoring and specific characteristics of MED should be considered an important finding to take into account to screen SDB in pediatric clefts populations that may provide more timely referral, diagnosis, and management of sleep diagnoses that are frequently overlooked. Differences in daytime functioning (such as sleepiness, internalizing and externalizing behaviors), bedtime difficulties (long sleep latency) and sleep duration (decreased) between children with SRMD and growing pains found in the present study may contribute to understand better overlaps and disconnects between PLMS, RLS and growing pains. However, further studies based on objective data are needed to confirm these clinical features. This study population - focused on children up to seven years of age with a specific craniofacial anomaly - provides important data about the frequency of specific sleep disorders, and associations with upper airway symptoms

and comorbidities that represents a window of opportunity to intervene and potentially minimize development of behavioral problems prior to increasingly challenging academic pursuits. Finally, comparison between children with cleft with and without sleep and/or upper airway symptoms rather than typically developing children should be considered also a strength of this research study.

Despite these strengths, there are several limitations. First, the small sample size of children with specific types of clefts, such as those with Pierre Robin sequence, which reduces the power to detect group differences. Another limitation was the lack of a non-cleft control group. However, the goal of this study was to determinate the frequency of SDB and its associations to other upper airway symptoms within the cleft population. Third, while the PSQ is a validated tool widely used for screening SDB (and less frequently SRMD) in general pediatric populations, it has not been specifically validated in children with clefts despite the high risk for SDB and behavioral problems. Moreover, objective data was available only in a subgroup of children who were referred for clinical PSG. Another limitation is that RLS screening was based on a single question rather than the pediatric RLS criteria proposed Picchietti et al and insufficient to formally diagnose RLS and distinguish it from several mimics.[103] Finally, the study is cross-sectional and cannot support causal interpretations.

6. CONCLUSION

1. In preschoolers and school age children with cleft palate Sleep-Disordered Breathing symptoms are common. However, evaluation of sleep apnea should be highly recommended, especially in those cases with clinical suspicions even in the absence of formal screening, due to the established high risk in this pediatric population.

2. The presence of Sleep-Disordered Breathing symptoms and moderate/severe sleep apnea were associated with high frequencies of externalizing and internalizing behavioral problems, and lower emotional and family well-being.

3. The study findings also suggest that in children with a cleft palate, intrinsic factors such as the type of cleft anomaly play a role in the frequency of habitual snoring and specific middle ear disease symptoms.

4. A recent history of at least one episode of middle ear disease was associated with an increased frequency of habitual snoring. Therefore, screening and evaluation of Sleep-Disordered Breathing should be considered in children with upper airway symptoms, particularly with middle ear disease, as a standard of care in a critical developmental period.

5. Sleep related-movement disorders and growing pains symptoms have been also frequently reported by parents of young children with non-syndromic cleft palate.

6. Interestingly, the present study suggests that daytime symptoms and bedtime difficulties differ widely in young children with cleft palate and symptoms of periodic limb movements, restless legs syndrome or growing pains. Finally, screening of sleep problems such as Sleep-related movement disorders should be also considered in children with cleft palate and behavioral problems.

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Barcelona, 5 d'Abril de 2022

A qui correspongui,

Jo, Marta Moraleda Cibrián amb DNI 44008579, declaro que el projecte de recerca de la tesis doctoral amb títol 'Sleep-Disordered Breathing in Children with Cleft Palate':

- Va ser aprovat pel comité ètic de la Universitat de Michigan
- És un treball original
- Ha complert els codis ètics i de bones pràctiques.

Atentament,

Barcelona, 5.4.2022

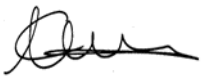
Barcelona, 11 d'Abril de 2022

A qui correspongui,

Louise O'Brien i Carme Monasterio Ponsa, com a directores de la tesis doctoral titulada 'Sleep-Disordered-Breathing in Children with Cleft Palate' declaren que:

- El projecte de recerca va ser aprovat pel comité ètic de la Universitat de Michigan
- És un treball original
- Ha complert els codis ètics i de bones pràctiques.

Atentament,



Louise M. O'Brien

Carme Monasterio Ponsa