Obstructive Sleep Apnea-Hypopnea Syndrome in Children: Beyond Adenotonsillar Hypertrophy

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Abstract The prevalence of obstructive sleep apnea-hypopnea syndrome in the general childhood population is 1%-2% and the most common cause is adenotonsillar hypertrophy. However, beyond adenotonsillar hypertrophy, there are other highly prevalent causes of this syndrome in children. The causes are often multifactorial and include muscular hypotonia, dentofacial abnormalities, soft tissue hypertrophy of the airway, and neurological disorders. Collaboration between different specialties involved in the care of these children is essential, given the wide variability of conditions and how frequently different factors are involved in their genesis, as well as the different treatments to be applied. We carried out a wide literature review of other causes of obstructive sleep apnea-hypopnea syndrome in children, beyond adenotonsillar hypertrophy. We organized the prevalence of this syndrome in each pathology and the reasons that cause it, as well as their interactions and management, in a consistent manner.

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Síndrome de la apnea-hipoapnea obstructiva del sueño en el niño: más allá de la hipertrofia adenoamigdalar

Resumen La prevalencia del síndrome de la apnea-hipoapnea obstructiva del sueño en la población infantil general es del 1-2% y su causa más frecuente es la hipertrofia adenoamigdalar. Las prevalencias en las otras causas de este síndrome, más allá de la hipertrofia adenoamigdalar, son elevadas. En muchas de estas enfermedades los motivos por los que se genera el síndrome de la apnea-hipoapnea obstructiva del sueño son multifactoriales (hipotonia...
Introduction

In over three quarters of cases, obstructive sleep apnea-hypopnea syndrome (OSAHS) in children has its main origin in an obstruction caused by adenotonsillar hypertrophy (ATH). However, we must not forget that the airway is not only affected by anatomical factors, but also by neurological, functional and infectious alterations that should also be taken into account.

In approximately 20% of cases of OSAHS in children, the main cause is not ATH. Many childhood diseases can cause OSAHS, so it is essential for otolaryngologists, pediatricians, and the different specialists in charge of these diseases to be aware of this fact. Knowing the physiopathology of OSAHS will help to improve its management which, in these cases, should always be multidisciplinary.

An extensive literature review of these other causes of OSAHS in children has been conducted, going beyond ATH. We have attempted to order these according to the criteria of the author and in line with the objective, reviewing the most relevant aspects in relation to the prevalence of OSAHS in each case, the reasons that cause OSAHS, its interactions and management (Table 1).

Nasal and Sinus Pathology

This group includes diseases affecting the nose, particularly in the form of atresia of the choanae (Charge syndrome) and paranasal sinuses (cystic fibrosis). Clinically, Charge syndrome is diagnosed through the combination of choanal atresia, coloboma, characteristic ears, with or without hypoacussis, involvement of the cranial nerves, and various anomalies of the temporal bone.

Cystic fibrosis affects multiple organs and systems, causing anomalous, and thick secretions from the exocrine glands. The main cause of morbidity and mortality is pulmonary involvement, which causes 95% of deaths.

Craniofacial Malformations

The Committee for Nomenclature and Classification of Craniofacial Anomalies deriving from the American Cleft

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Classification of the Diseases Causing OSAHS for Reasons Other Than Adenotonsillar Hypertrophy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nose and sinuses</td>
<td>Choanal atresia (Charge), cystic fibrosis</td>
</tr>
<tr>
<td>Craniofacial malformations</td>
<td>Cleft palate, dysostosis, and craniosynostosis</td>
</tr>
<tr>
<td>Adenotonsillar hypertrophies</td>
<td>Deposit diseases, drepanocytosis, obesity</td>
</tr>
<tr>
<td>Macroglossias</td>
<td>Down syndrome, Beckwith–Wiedemann syndrome</td>
</tr>
<tr>
<td>Laryngeal pathologies</td>
<td>Laryngomalacia, stenosis</td>
</tr>
<tr>
<td>Dwarfisms</td>
<td>Achondroplasia</td>
</tr>
<tr>
<td>Connective tissue pathologies</td>
<td>Marfan syndrome, Ehlers–Danlos syndrome</td>
</tr>
<tr>
<td>Muscular hypotonias</td>
<td>Neuro muscular diseases, Prader–Willi</td>
</tr>
<tr>
<td>Brainstem alterations</td>
<td>Arnold–Chiari, Möbius syndrome, Klippel–Feil syndrome</td>
</tr>
<tr>
<td>Other neurological pathologies</td>
<td>Epilepsy</td>
</tr>
</tbody>
</table>

Palate–Craniofacial Association proposed a simple classification, divided into 5 categories (Table 2).

This publication reviews facial fissures, dysostosis, which are characterized by a defect of normal ossification of fetal
cartilages. Dysostosis includes well-known syndromes such as Pierre-Robin sequence, Nager syndrome, Goldenhar or Treacher-Collins. Cases suffering craniosynostosis are characterized by an early closure of one or more cranial sutures, producing abnormal growth, and development of the skull. Cases of craniosynostosis are classified into simple and syndromic. The latter include the syndromes of Apert, Crouzon, Carpenter, Muenke, Pfeiffer and Saethre-Chotzen.

Adenontal Hypertrophies

Diseases causing an exaggerated hypertrophy of the adenontal tissue or those where the hypertrophy involves a disproportionate obstructive capacity were reviewed: drepanocytosis, thalassemia, mucopolysaccharidoses, and obesity.

Drepanocytosis appears through the substitution of a glutamic acid amino acid by valine in the polypeptide chain of hemoglobin. This leads to a lower oxygen pressure causing erythrocytes to become deformed and acquire a sickle shape. This altered shape hinders the circulation of blood cells which then obstruct blood vessels. These red blood cells also have a shorter life, thus causing anemia.

Mucopolysaccharidoses are group of hereditary metabolic diseases caused by the absence or malfunction of certain enzymes which are necessary to process glycosaminoglycan molecules. An excessive accumulation of mucopolysaccharides in the tissue means that affected patients have a dysmorphic phenotype, with a characteristic face and multisystemic involvement.

Thalassemia is a kind of hereditary anemia in which there is a decrease of the synthesis of one or more polypeptide chains of hemoglobin.

Macroglossia

The group of macroglossia includes some diseases in which this feature is one of the most descriptive and conditioning of OSAHS: Beckwith–Wiedeman syndrome and, particularly, Down syndrome. Down syndrome or trisomy 21 is characterized by the presence of a variable degree of mental retardation and particular physical features that confer a recognizable appearance.

Laryngeal Pathologies

Regarding the group of laryngeal pathologies, different diseases may lead to OSAHS in children. Laryngomalacia is a congenital alteration characterized by a decrease in the laryngeal tone, with supraglottic collapse and stridor upon inhalation.

Dwarfisms

Many of the different syndromes associated to a small size have been associated to OSAHS. However, achondroplasia is the one that has generated more publications. Achondroplasia is derived from a DNA modification that generates abnormalities in cartilage formation. Patients suffering achondroplasia present a very characteristic physical appearance due to the arrested development of cartilage in the epiphysis of the bones. Thus, they present a small height with shortening of the limbs and increase of the cranium, whereas the thorax maintains a normal size.

Connective Tissue Pathologies

This group includes the syndromes of Marfan, Ehlers–Danlos and Loeyes Dietz. In the case of Marfan syndrome there is a reduction in the amount and function of fibrillin protein. This causes an alteration of the elasticity of some tissues, as well as considerable growth, instability, and hypotonia. It is associated with cardiovascular lesions with aortic dilatation, which are the main cause of mortality among these patients.

Muscular Hypotonia

A group based on the term muscular hypotonia has been established, where this feature is common and a decisive factor in causing OSAHS. Neuromuscular diseases represent a set of hereditary or acquired diseases which present clinical symptoms mainly characterized by the presence of weakness, accompanied by muscular atrophy or pseudohypertrophy, myotonia, muscular contractures, myalgias, and occasionally, sensory disorders. They can be classified into 5 groups (Table 3).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Classification of Neuromuscular Diseases.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Muscular dystrophies: Duchenne or congenital</td>
</tr>
<tr>
<td>2.</td>
<td>Congenital I and metabolic myopathies</td>
</tr>
<tr>
<td>3.</td>
<td>Neuromuscular junction disorders: myasthenia</td>
</tr>
<tr>
<td>4.</td>
<td>Peripheral neuropathies: Charcot–Marie–Tooth</td>
</tr>
<tr>
<td>5.</td>
<td>Anterior horn cell disease: spinal muscle atrophies</td>
</tr>
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</table>

The groups with the greatest repercussion in the literature and in clinical practice in relation to OSAHS are muscular dystrophies and spinal muscle atrophies. Prader–Willi syndrome is characterized by muscular hypotonia, small size, incomplete sexual development, cognitive alterations, behavioral problems and chronic feeling of appetite which causes patients to eat in excess and become obese.

Brainstem Alterations

This group includes syndromes as diverse as Möbius, Klippel–Feil and Arnold–Chiari syndromes, the latter being particularly relevant with regard to its association with OSAHS.

Arnold–Chiari malformation is characterized by a variable degree of cerebellar herniation through the foramen magnum, which causes compression of the brainstem. It may be associated to myelomeningocele and myelodysplasia and accompany other craniofacial malformations, like dysostosis. There are 2 classic types: I and II, the latter associated to a more severe malformation.
Other Neurological Alterations

The last group is conceived as other neurological diseases, among which epilepsy is one of the most frequent.

Prevalence

The prevalence of OSAHS among the general population of children is of 1%–2% and, when we view the prevalence in other causes of OSAHS other than ATH, it can be observed that the prevalence is clearly elevated (Table 4).

In addition, many of the subjects suffering the syndromes and diseases reviewed may attend an otolaryngology clinic for different reasons prior to a diagnosis of OSAHS (choanal atresia, Goldenhar, cystic fibrosis, Down syndrome, achondroplasia and laryngomalacia, for example). In these cases, knowledge of the frequent association between OSAHS and other sleep disorders should lead the otolaryngologist to initiate the relevant diagnostic mechanisms to approach the situation as early as possible.

Physiopathology

In many of these diseases, the reasons that generate sleep disorders, particularly OSAHS, are multifactorial (muscular hypotonia, dentofacial alterations, hypertrophy of the soft tissues of the airway, neurological alterations). Collaboration between the different specialists involved is essential given the considerable variability of disease, frequent contribution of different factors to its genesis and multiple treatments that must be applied.

Table 5 shows a summary of the main physiopathological facts that condition this higher prevalence of OSAHS. In the majority of cases, we must also add the ATH inherent to this age range. The table only mentions this hypertrophy in those diseases in which the obstructive consequences are disproportionate in relation to those of the general population.

In the case of syndromic craniosynostosis, the majority of publications agree in highlighting midfacial hypoplasia as the most important cause of OSAHS. In dolichocephaly, the main reason for the higher prevalence of OSAHS seems to be an excessive growth of the adenotonsillar lymphoid tissue or its chronic infection, secondary to functional hypotonia. Several physiopathological mechanisms have been mentioned which would contribute to the prevalent association between obesity and OSAHS. These include an increase in the critical closure pressure of the airways, fatty infiltration of the structures of the upper airway, abnormalities in the ventilation response and an ATH with a greater obstructive effect than in children with normal weight.

In Down syndrome there are several reasons for this high prevalence of OSAHS, mainly relative macroglossia due to midfacial and mandibular hypoplasia, as well as frequent hypertrophy of the lingual tonsil. In fact, the tongue is smaller, but the space where it should be located is even smaller than in normal subjects. To this we must add other factors specific to the syndrome, such as muscular hypotonia, increased propensity toward laryngomalacia, gastroesophageal reflux, obesity, hypothyroidism and alterations in the regulation of the autonomous nervous system. All these conditions can favor the onset of OSAHS.

The association between OSAHS and laryngomalacia has generated a new pathological concept. Based on a publication by Amin, the concept of state-dependent laryngomalacia or late-onset laryngomalacia has taken root. These affect children older than 3 years in whom the obstructive symptoms are only manifested while eating, doing exercise or sleeping. It is likely that, among these last patients, ATH causes an increase in negative suction pressure by the diaphragm and this highlights the laryngomalacia.

In the case of achondroplasia, the reasons argued to explain the increased prevalence of OSAHS are compression of the breathing centers of the brainstem and obstruction of the upper airway. The latter cause is derived from the presence of an altered brainstem during growth, increased mandibular plane angle, excessive growth of the lower half of the face and mandibular hypoplasia, all of it added to a greater muscular hypotonia and a certain degree of laryngotracheomalacia.

A good control of breathing during sleep requires anatomical and functional integrity of the breathing circuits and the lower cranial nerves that control the upper airway, particularly IX and X. In the case of Arnold–Chiari syndrome, these structures will be affected by the herniation and compression of the brainstem typical of the malformation.

Several reasons for the superior prevalence of OSAHS among epileptic patients have been highlighted. In addition to classical factors such as obesity and alteration of the anatomy of the upper airway, the effects of nocturnal convulsions and the altered brain function that can be caused by changes in the neural control of breathing or in muscle tone have also been mentioned.

The use of antiepileptic drugs has also been implicated. Several studies have demonstrated that the prevalence of OSAHS among epileptic children is higher in the case of those with refractory epilepsy who, therefore, require multiple drugs. Several of these drugs, such as gabapentin,
carbamazepine and valproic acid can lead to weight increase, and benzodiazepines and barbiturates can affect the muscle tone of the upper airway.

**Interactions**

It is well-known that, when OSAHS is not treated correctly, it is capable of causing negative consequences in affected children (neurocognitive, growth or cardiovascular and metabolic) which will evidently condition their quality of life.

Many of the diseases reviewed involve negative interactions which increase the risk of these comorbidities and, in turn, OSAHS may increase the inherent complications of any concomitant diseases. For example, neurocognitive deterioration increases when OSAHS is associated to Charge, Treacher-Collins, craniosynostosis, obesity, Down syndrome, neuromuscular disease or Prader–Willi syndrome.

Cardiovascular alterations may also worsen when OSAHS appears in Down syndrome or in neuromuscular diseases. Pulmonary hypertension, right heart failure and cor pulmonale are more prevalent in Down syndrome associated to OSAHS. Most sleep alterations, particularly OSAHS in patients with neuromuscular disease, increase the level of respiratory and cardiovascular complications (greater risk of pulmonary hypertension and cor pulmonale) and have a greater tendency toward neurocognitive deterioration.

Obesity in children associated to OSAHS increases the possibility of suffering the negative neurocognitive, cardiovascular and metabolic consequences of this disease. In sleep apnea-hypopnea syndrome (apneahypopnea syndrome), children present 4 times more nocturnal oxygen desaturations and a risk of hypercapnia 7 times higher than children with OSAHS but without sleep apnea-hypopnea syndrome. The consequence of this observation is that these children suffer a greater risk of vascular occlusion an a higher prevalence of cerebrovascular accidents, which are the most significant causes of morbidity and mortality in children suffering sleep apneahypopnea syndrome.

In achondroplasia, one of the most significant interactions is that OSAHS can worsen the hypogrowth of these patients. It is well known that OSAHS inhibits the secretion of growth hormone in children. Therefore, the association could worsen the delay of growth in achondroplasia. A greater risk of aortic dilation can be observed in Marfan syndrome associated to OSAHS.

Lastly, if epilepsy favors the onset of OSAHS, this could in turn increase the possibility of suffering epileptic crises by causing greater fragmentation in sleep architecture. Sleep deprivation and hypoxia, characteristic of OSAHS, favor epileptic crises.

**Treatment**

Treatment of OSAHS in these special patients should be interdisciplinary, due to its difficulty and because various particularities are present, which physicians should be aware of.

Many of the diseases described are treated by adenotonsillectomy (AT) as the first therapeutic option. However, due to the diversity of factors causing OSAHS, the rate of persistence is much higher in cases of Down syndrome, sleep apnea-hypopnea syndrome, achondroplasia and syndromic craniosynostosis, than among the general population.
For example, AT in Down syndrome presents high rates of persistence which, in many series, are close to 50%, and in some cases even exceed 70%. Zandieh reported a rate of persistence of nearly 85% in a series of 13-year-olds suffering syndromic craniosynostosis and undergoing AT.

In this group of patients, AT will also entail higher rates of perioperative complications, for example, in Charge, Down syndrome and achondroplasia. In the case of Down syndrome, Goldstein pointed out that these complications were 5 times more frequent and that operated children took longer to return to a normal oral diet than children without Down syndrome.

Many of these diseases also require more intensive treatments, such as maxillofacial surgery, particularly in cases of facial malformations with mandibular hypoplasia and Pierre Robin sequence, in syndromic craniosynostosis, and, occasionally, in Down syndrome.

Continuous positive airway pressure (CPAP) or tracheotomy in some extreme cases, is also an alternative in several of these syndromes, such as Charge, Down syndrome, achondroplasia, Pierre-Robin, Treacher-Collins and other craniofacial malformations. In specific cases with mandibular hypoplasia in Pierre-Robin, Treacher-Collins and Down syndrome it has been reported that the natural growth of the child will allow CPAP to be removed without requiring any additional treatment.

CPAP can present various problems, such as greater difficulty to adapt masks due to the inherent facial alterations in Charge and other malformations and even a worsening of glossoptosis with an increase of airway obstruction.

Several of these diseases also have specific and highly effective treatments to resolve OSAsHs, including supraglottoplasty in laryngomalacia, non-invasive ventilation in neuromuscular diseases and surgical decompression of the brainstem in Arnold-Chiari malformation.

Treatment of the growth hormone is highly effective in Prader-Willi syndrome, with a notable growth response and an improvement of muscular strength. However, this therapy has also been associated with sudden death, particularly during the first months of treatment, perhaps due to an increase of OSAHS.

Several recent publications point to the onset of respiratory infections as the main cause of mortality related to hormone treatment. This situation has led to the recommendation of a polysomnography assessment prior to initiating hormone treatment, and to treating these children with adenotonsillar surgery or CPAP when OSAHS is diagnosed.

Lastly, in relation to epilepsy, successful treatment of OSAHS, either with CPAP or AT, improves the frequency and intensity of epileptic crises.

An extensive literature review of the causes of childhood OSAHS beyond ATH has been conducted. As far as we have been able to establish, this is the first and most thorough review of this subject in our country. Its relevance lies in the significant prevalence of OSAHS in all of them, as well as the need to understand its pathophysiology and interactions in relation to OSAHS. A better knowledge of these extremes by all the specialists involved should lead to their necessary collaboration in approaching the pathology, as well as an improvement of the results of treatment and the quality of life of these patients.

Conflict of Interest
The authors have no conflicts of interest to declare.

References


