

Review of respiratory sleep disorders in children with genetic and metabolic diseases

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ABSTRACT

Sleep is an important physiological process for the optimal functioning of the human body. Respiratory sleep disorders in children can be found in any age group with a prevalence of 2-5%. Genetic and metabolic syndromes in children associate a higher prevalence of sleep pathology. Polysomnography represents the gold standard investigation for evaluation and monitoring of breathing disorders associated with sleep. Early detection of sleep pathology in children and periodic monitoring plays an important role in improving quality of life of these patients.

Keywords: sleep, sleep-related breathing disorders, SASO, genetic and metabolic diseases

GENERAL DATA

Sleep is a neurophysiological process that involves partial and reversible suspension of consciousness, playing an essential role in the functioning of the body. During life, the duration, quality and architecture of sleep undergo changes adapted to the stage of body development, most of which take place in the first 5 years of life and play an essential role in the development of the human brain. A sleep with optimal duration and quality will play an important role in somatic development, memory and learning processes, in cognitive and behavioral development [1].

Studies have shown that the human body has an important variability in optimal duration of sleep depending on age. Thus, newborns spend 80% of their time sleeping, preschoolers and small children need 10-12 hours of sleep [2] while teenagers sleep approximately 8-10 hours. Another equally important aspect related to sleep is represented by its quality, referring to hemostatic and circadian processes that participate in regulating the sleep-wake rhythm. Similar to other processes in the body, sleep has an internal organization of a rhythmic type called sleep architecture, which involves the repeti-

tion of REM and NonREM sleep cycles with a certain periodicity.

Changing the qualitative or quantitative aspects related to sleep determines a negative impact on the growth and development of children, especially when they associate an underlying pathology that could interfere with the normal development of sleep. Many of the medical problems related to sleep in the child with or without an underlying pathology are often underdiagnosed as a result of the limited knowledge related to sleep medicine [2].

The pathology associated with sleep in children includes non-respiratory sleep disorders (hypersomnia, insomnia and parasomnias) and respiratory sleep disorders. These include, in the vast majority of cases, the spectrum of obstructive breathing disorders associated with sleep but also other entities such as central sleep apnea, congenital central hypoventilation syndrome, apnea of prematurity, life-threatening respiratory events and respiratory events self-limiting.

Classification and definition of sleep-related disorders in children is shown in table 1.

The spectrum of respiratory sleep disorders in children includes distinct entities, although they

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TABLE 1. Classification of sleep-related disorders in children

Spectrum of Obstructive Respiratory Disorders associated with sleep in children	Non-respiratory disorders associated with sleep in children
1. Primary snoring: habitual snoring (>3 nights/week) in absence of apneas, hypopneas, frequent microawakenings and changes in blood gas measurements	1. Hypersomnia: spectrum of disorders (which includes Narcolepsy) characterized by excessive daytime sleepiness
2. Syndrome of increased resistance in the upper respiratory tract: snoring accompanied by respiratory effort, frequent micro-awakenings but without obstructive events or changes in blood gas measurements	2. Insomnia: sleep disorder characterized by difficulty of initiating or maintaining sleep
3. Obstructive hypoventilation: snoring and increased partial pressure of CO ₂ at the end of expiration but without the occurrence of obstructive events	3. Parasomnias: non-respiratory disorders involving abnormal behavior during sleep (somnambulism, sleep paralysis and nightmares)
4. Obstructive Sleep Apnea Syndrome (OSA): partial or complete obstruction of the upper respiratory tract that causes recurrent respiratory events (hypopnea, obstructive or mixed apnea) associated with changes in ventilation, normal blood oxygenation and sleep pattern	

(after "Obstructive sleep-disordered breathing in 2 to 18 years-old children: diagnosis and management. EUR Respir J. 2016", modified)

most often describe a linear evolution that has primary snoring as its starting point. This snoring type has the risk of becoming permanent and thus facilitates the appearance of structural changes in the tissues of the upper respiratory tract that will determine, in the first phase, installation of increased resistance and later the appearance of Obstructive Sleep Apnea Syndrome (OSAS). Studies have shown that 2-3% of children who presented habitual snoring later developed OSA, which indicates the important role in the early recognition and evaluation of this frequently encountered symptom in the pediatric population[4,5].

The present article aims to review the epidemiological and clinical characteristics of the entities that brings together sleep-related breathing disorders in children diagnosed with genetic syndromes and metabolic diseases.

METHOD AND RESULTS

Epidemiology of sleep-related breathing disorders

The first cases of OSAS described in pediatric population were reported and published in 1976 by Guilleminault Christian, who refers to a category of children who presented adenotonsillar hypertrophy. The author identified a characteristic phenotype of these children who presented periods of apnea during sleep [6]. Currently, OSAS represents an important health problem for children. This pathology registers a growing evolution with the increase in the incidence of obesity in the pediatric population and with a negative impact on life quality of children and their families. The guidelines developed in 2012 by the American Pediatric Association

(AAP) reported a prevalence of OSA in the pediatric population of 1.2-5.7% [7] while the European Respiratory Society (ERS) mentioned, in 2016, that OSAS prevalence varies in the range 0.1-13%. Most of the studies conducted reported an average value of 1%-4% [8].

The biggest variations in the prevalence of OSAS were obtained with the description of the prevalence of habitual snoring. Thus, values obtained varied between 3% and 35% with reporting an average value of 7.45% [8,9,10].

Factors that determine the appearance of respiratory disorders associated with sleep in children

1. Genetic and metabolic factors

Children diagnosed with genetic syndromes or metabolic diseases have an increased risk of developing sleep-related breathing disorders (SRBD) as a result of the underlying pathology that causes changes in the central nervous system, neuromuscular tone and craniofacial anatomical structures [11]. In 2017, the ERS reported that the most common cause of SRBD in children under 2 years of age is represented by comorbidities such as craniofacial anomalies, neuromuscular diseases or genetic diseases[12]. The risk of SRBD occurrence increases in children diagnosed with complex pathologies not only as a result of the natural evolution of underlying disease but also as a consequence of the respiratory complications that may appear (recurrent respiratory infections, prolonged hospitalizations, alteration of the respiratory mucociliary clearance with the need for aspiration of secretions and assisted cough). All these complications have a negative impact on life quality of children. During the

life of a patient, association of factors with negative impact can cause the appearance of new forms of respiratory disorders other than those known to be associated with the underlying pathology.

Prader-Willi syndrome (SPW) is a congenital condition based on the lack of gene expression at the level of chromosome 15 (deletion 15q11-q13). In 60% of cases, they show maternal uniparental disomy at the level of the same chromosome [13].

The prevalence of SPW is 1 case in every 10,000-20,000 newborns, with an estimated number of approximately 400,000 cases. There is an equal distribution between sexes [14,15]. Clinical evaluation of these patients highlights the presence of muscle hypotonia that begins early during life, weight curve with unsatisfactory evolution, hypogonadism, and the fact that infants suck with difficulty. Other clinically features are represented by hypostatus and presence of short hands and legs as a result of growth hormone deficiency but also of other hormones, hyperphagia and obesity with early onset as well as cognitive and compartmental disorders. SPW represents the most common genetic cause of morbid obesity in humans [14].

Association of risk factors characterized by moderate craniofacial anomalies (micrognathia, small nasopharynx or oropharynx) with muscle hypotonia, obesity secondary to hypothalamic dysfunction and hyperphagia, determines the premise of upper airway narrowing during sleep and the appearance of sleep-related breathing disorders. Studies carried out until now describe OSAS as the most frequent SRBD that occurs in pediatric patients diagnosed with SPW with a prevalence that varies between 35-92% [16,20] Other studies have shown that a fairly large number of children with this syndrome associates, in variable proportions, central apnea, alveolar hypoventilation, excessive daytime sleepiness and alteration of sleep architecture. Association of central apnea episodes seems to be the consequence of neural immaturity at the level of the brain stem, hypothalamic dysfunction and abnormal chemosensitivity for CO₂ and O₂ during sleep [21].

Most children diagnosed with SPW develop early clinical signs of growth hormone deficiency that cause hypostatus, increased distribution of adipose tissue and decreased muscle strength. Recent studies have demonstrated the important role of early administration (before age of 2 years) of growth hormone replacement therapy [22]. Despite the numerous studies that have demonstrated the beneficial role of hormonal therapy, careful monitoring of pediatric patients is recommended because substitution therapy can increase risk for developing obstructive events through adenotonsillar tissue hyperplasia [23].

Genetic syndromes characterized by craniofacial anomalies associate an increased risk for developing obstructive forms of respiratory disorders associated with sleep. The most frequently encountered are represented by Apert syndrome and Crouzon syndrome, which affect the middle segment of the face, as well as Pierre Robin syndrome, which is characterized by significant changes at the mandibular level.

The characteristic phenotype for Pierre Robin Syndrome (SPR) is represented by the combination of micrognathia with glossoptosis and airway obstruction through narrowing of the hypopharynx or oropharynx [23-28]. Research studies have identified a prevalence of OSAS in children with SPR that varies between 46-100% regardless of the association or not of characteristic symptoms for SRBD.

Neuromuscular diseases such as Duchenne Muscular Dystrophy (DMD) and Spinal Muscular Atrophy (SMA) are characterized by progressive muscle weakness that facilitates respiratory failure. The progressive damage of respiratory muscles leads over time to the appearance of alveolar hypoventilation and changes in blood oxygenation, physio pathological elements that will begin initially in REM sleep, later also in NREM sleep as the disease progresses. Other factors with a negative impact on evolution of these conditions are represented by important skeletal deformities (kyphoscoliosis, rib cage deformities) to which obesity secondary to corticotherapy is associated, as well as loss of ambulation [29].

Duchenne muscular dystrophy (DMD) is a genetic disease, usually transmitted x-linked recessively, which occurs as a result of the mutation of the Dystrophin gene. It affects about 1 case in every 3600-6000 male newborns. DMD begins shortly after the acquisition of walking and causes progressive damage to the striated muscles both at the skeletal level and at the level of the muscles involved in breathing and the myocardium function. Progressively, the child has difficulty in walking, later loss of ambulation and respiratory signs and symptoms appear (ineffective cough, reduced respiratory mucociliary clearance, recurrent respiratory infections, chronic respiratory failure, etc.) and also, respiratory sleep disorders. Decline of respiratory function starts in the early stages of the disease even in patients who initially received corticotherapy and progress through adolescence with the onset of restrictive changes secondary to skeletal deformities (scoliosis, kyphosis, etc.) [30].

The respiratory disorders associated with sleep in pediatric patients diagnosed with DMD, are mostly represented by OSAS and affects children from the early stages of the disease, becoming progressively more pronounced with the progression of the disease [31].

Spinal muscular atrophy (SMA) is a genetic neuromuscular condition characterized by the mutation of the motoneuron 1 gene. It is clinically characterized by progressive muscle weakness and bilateral proximal muscle atrophy. The progression of the disease determines damage to the intercostal muscles that participate in the breathing process, but also the installation of OSAS during REM sleep [32,33].

The difficulty of identifying nocturnal symptoms by the family and the early onset of SRBD in patients diagnosed with neuromuscular diseases requires periodic evaluation and monitoring this category of patients with polysomnography [34] and transcutaneous capnography.

Mucopolysaccharidoses (MPS) include a group of lysosomal storage diseases caused by errors in glycosamine catabolism that determine the accumulation of mucopolysaccharides in body tissues [35]. Polysomnography and nocturnal oximetry studies have shown an increased prevalence of OSAS (68-95%) associated with MPS. Association of the particular facial phenotype (short neck, widened base of the nose, mandibular anomalies) with cervical spinal anomalies but also with the deposits of glycosaminoglycans at various levels – oral cavity, tongue, nose, pharynx posterior wall and the lymphoid tissue at this level, will determine narrowing of the upper airways and increased resistance [36-45] especially during REM sleep. Adenotonsillar hypertrophy is found in almost all patients diagnosed with MPS and is a consequence of the glycosaminoglycans deposits found at the lymphoid tissue level [45].

2. Obesity

Numerous studies have shown that obesity is one of the most important risk factors for the occurrence of SRBD in both adults and children. The nar-

rowing of upper airways caliber is secondary to depositing the fat tissue at the anterior cervical level and by infiltrating airways with adipocytes [46]. The peak incidence for pediatric obesity is recorded in adolescence. There is an increased risk for OSAS in obese children compared to those with normal weight [46]. Research studies have shown that the value of the Body Mass Index increases directly proportionally with the risk of OSAS [47,48].

3. Adenotonsillar hypertrophy

The most common risk factor for developing the obstructive form of SRBD in children is represented by adenotonsillar hypertrophy. Physiological growth of the lymphoid tissue can be accentuated by the appearance and maintenance of a chronic inflammation in the upper respiratory tract, as happens in allergic rhinitis, bronchial asthma and exposure to passive smoking [49]. Children diagnosed with allergic rhinitis have a three times higher risk of developing sleep related disorders and the cone inflammation due to allergy may represent an independent risk factor for adenotonsillar hypertrophy [50].

CONCLUSIONS

Respiratory sleep disorders in children are frequently found in patients diagnosed with genetic and metabolic syndromes compared to the general population. The negative impact on their quality of life requires the development of guidelines and programs for monitoring the underlying pathology. Polysomnography remains the gold standard investigation for the diagnosis and monitoring of disorders breathing associated with sleep in children.

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