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Chapter

Neuropsychological Alterations in Children Affected by Obstructive Sleep Apnea Syndrome

Marco Carotenuto, Rosa Marotta, Francesco Precenzano, Maria Ruberto, Lucia Parisi, Beatrice Gallai, Annabella Di Folco, Margherita Salerno, Agata Maltese, Francesca Felicia Operto and Michele Roccella

Abstract

Sleep-related breathing disorders are a group of clinical conditions ranging from habitual snoring to obstructive sleep apnea syndrome (OSAS) during the lifespan. In children, other risk factors are represented by adenotonsillar hypertrophy, rhinitis, nasal structure alteration, cleft palate, velopharyngeal flap surgery, pharyngeal masses, craniofacial malformations, genetic syndrome (i.e. Down syndrome, Crouzon syndrome, and Apert syndrome), genetic hypoplasia mandibular (i.e. Pierre Robin syndrome, Treacher Collins syndrome, Shy-Drager syndrome, and Cornelia De Lange syndrome), craniofacial traumas, chronic or seasonal rhinitis, asthma, neuromuscular syndromes, brainstem pathologies (i.e. Arnold-Chiari malformation and Joubert syndrome), achondroplasia, and mucopolysaccharidosis. OSAS may affect the executive functioning such as motivational ability, planning, behavior modulation, ability to complete an action program, identification of functional strategies to achieve the goal, problem solving, flexibility, monitoring and self-assessment of behavior in relation to results, change of task, or behavior in the light of emerging information, which may be all impaired by nocturnal intermittent hypoxia also during the developmental age. The clinical presentation of OSAS can mimic other neurobehavioral symptoms, such as ADHD syndrome, learning problems, or can exacerbate the Fragile X syndrome, and generalized non-convulsive epilepsy symptoms.

Keywords: sleep-related breathing disorders, pediatric OSAS, executive dysfunction

1. Introduction

Sleep-related breathing disorders are a group of clinical conditions ranging from habitual snoring to obstructive sleep apnea syndrome (OSAS), frequent in all ages of life. OSAS is a clinical condition still underdiagnosed both in adults and particularly in children, with high cost of care for general population [1, 2]. OSAS can be considered the most severe nocturnal respiratory disorder characterized by repeated episodes of obstructive and/or hypopnea during sleep caused by complete or partial

obstruction of the upper airways. The nocturnal episodes of total or incomplete breathing interruption are identified and recorded in the apnea/hypopnea index per hour (AHI), and the nocturnal oxygen desaturation is expressed as oxygen desaturation index per hour (ODI). In children, in contrast to the adult, definition of OSAS, which requires an AHI ≥ 5 episodes per hour of sleep lasting more than 10 seconds, with persistent thoracoabdominal movements [1], does not require so.

In 1976, OSAS syndrome was identified and described in pediatric age by Guilleminault et al. [3], and from that time on, studies on this pediatric pathology have multiplied, considering its important impact on all aspects of life often linked to the intermittent nocturnal hypoxia not ever associated with the nocturnal respiratory events (hypopneas and apneas).

2. Epidemiology

In the developmental age, prevalence in preschool and school age for primary snoring ranges from 3.2 to 12.1%, while for OSAS, it varies from 1.1 to 2.9%. The peak incidence is observed between 3 and 6 years and coincides with the age of maximum development of lymphatic tissue. In all the studies found in the literature, it can in fact be noted that the incidence of OSAS is greater in children with adenotonsillar hypertrophy [4].

The prevalence of OSAS in Italy shows a prevalence in children of 4.9% for primary snoring and of 1.8% for OSAS [5].

On the other hand, African American children were reported four to six times more likely to have OSAS than children of Caucasian origin [6], while the predisposition to OSAS in African Americans has been attributed to different upper airway anatomy and pharyngeal neuromotor control in addition to other genetic and environmental factors [6].

In clinical practice, there are many screening tests for the identification of sleep-related breathing disorders in pediatric age.

Furthermore, in children, sleep is less fragmented than adults because the behavioral awakenings seem to be less frequent in children than in adults with a lower incidence of daytime excessive somnolence.

3. Risk factors

OSAS is a complex and multifactorial syndrome, and it is believed that some specific genes may play a crucial role in its pathogenesis, particularly involved in the expression of the CLOCK gene [7], IL-10 polymorphisms [8], and insulin variable number of tandem repeat (INS VNTR) sequence regulation [9].

In general, there are some conditions that may predispose to OSAS, such as alterations of craniofacial structures, obesity with fat deposition on side walls of the pharynx, endocrine changes, alcohol intake, and cigarette smoking [10] both in adults and in children.

In pediatric population, the main risk factor is adenotonsillar hypertrophy [11, 12], but others are rhinitis [13], nasal structure alteration [14, 15], cleft palate, velopharyngeal flap surgery, pharyngeal masses, craniofacial malformations [16], genetic syndrome (i.e. Down syndrome, Crouzon syndrome, and Apert syndrome), genetic hypoplasia mandibular (Pierre Robin syndrome, Treacher Collins syndrome, Shy-Drager syndrome, and Cornelia De Lange syndrome) [17, 18], craniofacial traumas [19, 20], chronic or seasonal rhinitis [13],

asthma [21, 22], neuromuscular syndromes [23], brainstem pathologies (Arnold-Chiari malformation and Joubert syndrome) [24], achondroplasia [25], and mucopolysaccharidosis [26].

On the other hand, worldwide pediatric obesity tends to be prevalent in children with respiratory disorders during sleep; however, it does not represent the main risk factor unlike the adult and is even a complication of OSAS especially after the adenotonsillectomy [27, 28].

4. Pathophysiology

In OSAS, due to a reduction in the size of the upper airways and a reduction in the activity of the pharynx dilator muscles, there are an increase in critical pressure (transmural pressure value at which the area of the pharyngeal section is equal to zero) and an enormous reduction in the pharyngeal lumen [29].

The obstructive events will therefore lead to the appearance of hypoxemia and hypercapnia, which will first cause an increase in respiratory effort, and then a wake-up, of a few seconds, which will serve to restore the patency of the upper airways; all these will repeat cyclically during sleep, causing an alteration of the structure.

In the adult, there is a reduction in nonrapid eye movement (NREM) sleep and rapid eye movement (REM) sleep, and consequently, the major symptom is daytime sleepiness; in children, on the other hand, intermittent hypoxia has a role in the appearance of neocognitive deficits, which are the most common signs and symptoms in the case of OSAS in the developmental age [29].

Behavioral awakenings in the child with OSAS are less frequent than in adults, and this on the one hand allows the child to retain the benefits of sleep, and on the other hand, it can cause long periods of hypoventilation. Moreover, in children, the desaturation of O_2 can also be achieved during short apnea due to the reduced functional lung capacity and the most frequent respiratory rate in pediatric age [29].

In OSAS, there is also a state of chronic systemic inflammation, mainly linked to intermittent hypoxia, which promotes the activation of some factors responsible for inflammation such as C-reactive protein (PCR) and IL-6 and is therefore responsible for a state of oxidative stress [30].

Oxidative stress and increased production of oxygen-free radicals represent the pathophysiological substrate of the onset of cardiovascular, cerebrovascular, and metabolic complications [31, 32].

5. Clinical signs

Clinical signs of OSAS appear to be different in pediatric age with respect to adulthood, and therefore, the diagnostic and therapeutic management overlapping may be considered a severe clinical mistake.

In adults with OSAS, the most common presentation is excessive daytime sleepiness (EDS) that results from sleep fragmentation and from the frequent nocturnal intermittent hypoxic episodes [33], while in nonobese children, EDS is a rare complain. Conversely, children with OSAS tend to be not drowsy but rather hyperkinetic during the day, and often, these children are misdiagnosed with attention-deficit/hyperactivity disorder (ADHD) and treated with methylphenidate.

This common diagnostic mistake is derived from the lack of evaluation of sleep habits in children presenting with suspected hyperactivity behavior

that may highlight the presence of ADHD-like symptoms and not of ADHD syndrome [34, 35].

In pediatric age, the symptoms and major signs of suspected nocturnal respiratory problems are mainly oral breathing [36], nocturnal hyperkinesia, snoring or breathing pauses [37], nocturnal positional abnormalities [38], behavioral problems [39, 40], poor academic performance [41], failure to thrive and growth delay, recurrent airway infections [37], recent enuresis onset [42, 43], and night sweating and drooling [44].

6. Polysomnography (PSG)

Pediatric respiratory disorders during sleep find their diagnostic gold standard in the overnight polysomnography. This term commonly means the simultaneous and continuous recording during the night of functional parameters suitable for defining the cardiorespiratory events in relation to the various phases of sleep. Normally, during the test, two or more electroencephalogram (EEG) channels, two or more electromyographic channels, chest and abdomen movements, oronasal flow, oxygen saturation in the blood, and CO_2 measurement are recorded. The polysomnographic result must always be contextualized with the symptoms and signs and referred to the general clinical picture since there is not always a correspondence between the severity of the polysomnographic instrumental data (in terms of number of events and levels of O_2 desaturation) and the gravity of symptoms [45].

The severity identification of SRBD is identified by apnea/hypopnea index (AHI) and oxygen desaturation index (ODI). In pediatric age, AHI cut-off has been established between 1.2 and 1.3 nocturnal events per hour, while for ODI are conflicting and nonconclusive results.

7. Diagnosis and classification

For the diagnosis of OSAS, the anamnesis, the physical examination, and the polysomnographic examination that allows an early diagnosis and therefore an early therapy to prevent the development of complications are fundamental.

During the visit, a careful history assessment must be made, considering if there is the presence of familiarity for OSAS and if there are symptoms such as snoring, attention deficit, predominantly oral breathing, nocturnal hyperkinesia, behavioral problems and academic performance, recurrent airway infections, recently onset enuresis, night sweats, and nocturnal sialorrhea [43].

On physical examination, the signs and findings most closely linked to a high risk of respiratory disorders in sleep are adenotonsillar hypertrophy, rhinitis, macroglossia, and obesity [43].

Analyzing the oronasal flow is used to assess ventilation and to identify and differentiate central apnea from obstructive apnea, whereas hypopneas are more difficult to identify as they are not greater than 50% of respiratory flow. Analyzing thoracoabdominal movements and respiratory effort, on one hand, and quantitative and qualitative information on breathing, on the other hand, can be obtained.

The respiratory parameters are useful for the diagnosis of OSAS, and the American Academy of Sleep Medicine distinguishes respiratory events in central, obstructive, and hypopneic episodes [46].

Central apnea is caused by the damage to the nerve centers that regulate ventilation and is characterized by a complete cessation of ventilation with no thoracoabdominal movements. In the child, it can be an occasional event that becomes

pathological if there are more than three episodes per hour of sleep with a desaturation of >3% [46].

The obstructive apnea is instead caused by a complete or partial obstruction of the upper airways associated with inspiratory effort evidenced by the variation of thoracoabdominal movements in an attempt to overcome the obstruction. In children, even only one obstructive event per hour of sleep has a pathological character (AHI ≥ 1/h) [46].

Obstructive hypopnea consists of a reduction in oronasal flow >50%, with a desaturation of >3% for at least two respiratory cycles, and accompanied by thoracoabdominal movements [46].

Children may present four grades of OSAS severity classified by the Italian Society of Sleep Medicine [46] as follows:

minimum OSAS: AHI between one and three episodes per hour and/or the presence of continuous snoring for at least 50% of sleep associated with O_2 desaturations above 4% and average SaO_2 > 97%;
mild OSAS: 3 < AHI < 5 and average SaO_2 > 97%;
moderate OSAS: 5 < AHI < 10 and average SaO_2 > 95%; and
severe OSAS: AHI > 10 or with average SaO_2 < 95%.

Adenotonsillectomy is the main treatment in children, but if this failed or in the case of obese patients, continuous positive airway pressure (CPAP) or other positive pressure devices need to be considered [43].

8. The link between the severity of respiratory disturbance in sleep and neurocognitive disorders

According to many reports [47–49], neurocognitive alterations seem to be the direct effect of nocturnal intermittent hypoxia, sleep fragmentation, hormonal imbalance, systemic subclinical inflammation [50, 51], and endothelial dysfunction [52].

Nocturnal intermittent hypoxia causes a chronic state of neuroinflammation due to the production of proinflammatory cytokines such as interleukin (IL)-10, IL-6, IL-1, and TNF-α [53], although also serum C-reactive protein (CRP), pentraxin-3 (PTX-3), procalcitonin (ProCT), IL-33, and its soluble receptor ST2 (sST2) may be identified as putative biomarkers for OSAS severity almost in adults [54]. Interestingly, in children affected by OSAS and cognitive alteration, there is an increase in PCR and proinflammatory cytokines that are reduced following the adenotonsillectomy [51, 52].

Oxidative stress also directly and indirectly causes endothelial and vascular alterations that provoke an alteration in cerebral perfusion and play an important role in the onset of neurocognitive alteration in OSAS children [53].

Although IGF1, the insulin-like growth factor, is mainly produced by the liver under the stimulation of growth hormone (GH), its mechanism of action is mediated by its specific receptor, IGF1R, which is present on many cell types in many tissues, where it promotes cell proliferation and differentiation, especially at cartilage and muscle levels, so it is essential for growth processes in children. IGF1 can also be produced from other tissues as well as from the liver, including the brain, where it is synthesized without control by circulating GH. IGF1 promotes neuron survival and differentiation. It is involved in brain plasticity processes and regulates synapse formation, neurotransmitter release, and neuronal excitability. In children with OSAS, it was seen that high systemic levels of IGF1 appear to have a neuroprotective role because they reduce the risk of cognitive impairment [55, 56].

In children, sleep is essential for the processes of learning and memorization, and therefore, any alteration, such as its fragmentation, can cause impairment in the executive and behavioral functioning and in the emotional recovery [57].

Furthermore, in many children with OSAS and neurocognitive deficits, there was a high presence of ε4APOE allele, known to be present above all in people suffering from Alzheimer's disease [58]. Through magnetic resonance spectroscopy studies, it has been shown that in children with OSAS, there is a decreased hippocampal volume and focal reductions of gray matter in the frontal and parietal lobes [59, 60].

Moreover, in children with OSAS, in addition to the presence of neurocognitive disorders, a growth retardation is frequently found, in which at least three causes contribute to provoke it, namely, a feeding difficulty secondary to adenotonsillar hypertrophy, an increase in metabolic activity for respiratory effort during sleep, and an alteration of hormonal regulation with reduction of the nocturnal secretion of growth hormone and insulin-like growth factor [48].

Frequently endocrine alterations are associated with OSAS, as sleep fragmentation can have an impact on hormones that regulate glucose tolerance. In fact, diabetic children suffer more frequent and longer-lasting episodes of sleep apnea than healthy controls [61, 62].

However, in the developmental age, neurocognitive impairment due to OSAS seems to be more relevant than endocrinological and cardiovascular effects since it might not be reversible.

9. Executive functions: a complex construct

The executive functions (EFs) are defined as those cognitive skills necessary to plan, implement, and successfully complete a behavior aimed at a purpose. They do not represent a single entity but a complex of distinct, independent, and "subtly" interacting "subprocesses" necessary to perform a task and to achieve an end in an articulated and flexible way. Lezak et al. [63] attribute to them the concept of "umbrella term," as the umbrella is a compound of distinct elements that together support a "structure," in the same way that the executive functions constitute a unique and "meta-construct" all-inclusive to think, intuit, concentrate, adapt in order to achieve goals, and develop problem-solving strategies. EFs may be identified as a "module" of the mind that regulates the processes of planning, control, and coordination of the cognitive system, which, in turn, governs the activation and modulation of cognitive processes and schemes. EFs are transversal functions, differently from the so-called vertical functions (i.e. motor skills, language, reading, writing, calculation), and therefore, they can only be partially isolated and studied in their singularity. In this perspective, EFs are invisible as they are inextricably linked to the task and domain in which the activity is carried out and, therefore, cannot be analyzed independently of the performance. "They are higher-level, non-domain-specific cognitive functions, which enable us to formulate objectives/plans and to remember them over time; to choose and initiate actions that allow to achieve the objectives, to monitor the behavior and adjust it in order to reach those objectives" [64, 65].

On the other hand, the "label" of "skills that come into play in situations and tasks in which the use of routine behaviors and skills is no longer sufficient for their success" by addressing the set of mental processes aimed at development of adaptive cognitive-behavioral patterns in response to new and demanding environmental conditions [63].

EFs are essential and basic for the following:

- learning new actions;
- making the action plan and decision-making processes;
- selecting the correct answer and inhibiting the wrong one;
- correcting the errors;
- requiring the variable combinations of actions for new behaviors;
- conducting the complex activities;
- constant monitoring of behavior and evaluating the result; and
- having the ability to regulate and overcome the strong habitual responses.

Over the past 40 years, cognitive psychology and neuropsychology have paid particular attention to these skills, and despite the progress made in their study and description in the event of injury or developmental deficit, their multicomponent nature continues to make them difficult to analyze as well as a fully shared definition. The literature has provided different definitions and interpretations, and to date, there is still no unanimous agreement on the construct; different subdomains of executive functions are identified, which are the basis of other higher-order functions such as reasoning, problem solving, planning, understanding the behavior, and thinking of others.

Specifically, the main EFs are as follows:

- working memory: it is the ability to keep the plan and the work area mentally active and to have a mental set of reference on which to operate even in the presence of distracting tasks or situations;
- inhibition: it is the ability to self-control, to resist temptations, and to act impulsively; the ability to focus attention on relevant data by ignoring distractors and inhibiting inadequate motor and emotional responses;
- selective and sustained attention;
- flexibility: understood both in cognitive terms (shifting from one set to another based on information from the context) and in terms of creativity and sudden adaptation; and
- fluency: thinking ability capable of generating new and different solutions to a problem.

Their use is indispensable in all types of problem solving, not only the most complex and abstract ones such as solving mathematical problems, but also those related to the acquisition of social skills and the understanding of others' thoughts (metacognition) since the sensitivity to other people's goals, emotions, or desires requires an uncoupling from one's internal mental states. We turn to multiple domains that extend from the simple to the most complex and are in any case

interrelated. It is precisely the transversal nature and the structural complexity that characterizes them, associated with their slow development process, to explain why multiple neuropsychiatric disorders of the developmental age (pervasive developmental disorders, behavioral disorders, speech disorders, learning disorders, and disorders of the nonverbal area) present, with varying degrees of symptomatic severity, a common deficit for executive functioning. There are also motivated situations in which a deficiency of theirs manifests itself with clinical signs and symptoms that are often nuanced, nonspecific, and not immediately diagnostic (instability of behavior and emotionality, distractibility, difficulty in moving from one activity to another, and atypia communication). To this lively theoretical debate on what and what the EFs are, a new theoretical contribution has recently been added linked to the different types of cognitive and behavioral deficits that have emerged from injuries to the different areas of the prefrontal cortex, which has allowed a further classification in hot and cold executive functions [63].

The "hot" executive processes involve the emotional-emotional sphere and are associated with the activity of the ventromedial prefrontal cortex (VMPFC); the "cold" executive ones concern cognitive and nonemotional processing and are associated with the activity of the dorsolateral prefrontal cortex and can be measured by neuropsychological tests used in clinical practice (DLPFC) [66].

The "hot" executive functions recall phenomena such as empathy, the theory of the mind, emotional, and affective regulation, which coordinate the cognitive with the emotional sphere in order to adequately address the primary impulses with socially acceptable strategies. The "cold" executive functions intervene in cognitive, abstract, and decontextualized tasks (problem solving, abstraction, planning, working memory, and elaboration of strategies). Despite this distinction, they are closely related and combined in different situations of daily life.

In summary, the EFs are a particular set of cognitive operations activated in pursuit of objectives, responsible for planning, the ability to set goals, to classify, to know how to execute an order, to control and monitor one's behavior, to know how to order a series of activities in order to achieve a goal, and to manage, more generally, all mental activities [63].

These functions are modified in some pathological conditions such as posterior cranial fossa neoplasms [67], localized posttraumatic lesions to the frontal lobe [68], neurodegenerative syndromes (i.e. Parkinson's disease and Alzheimer's disease) [69, 70], cerebrovascular malformations (i.e. Moya-Moya syndrome) [71], ADHD [72], and OSAS [73].

The close relationship between cognitive functions has long been known and sleep, with particular reference to disorders respirators for which it has been widely demonstrated in the developmental age the association with learning disorders and more generally with alterations of the cognitive performance [74] that appears in such subjects dominated by slowness in concept development [75, 76] which however do not seem to be related to degree of severity of the respiratory disorder [77].

Several studies have focused on the role of the frontal lobes as possible relay zones between the OSAS and the cognitive alterations [78, 79]; however, studies conducted on executive functions of subjects with OSAS have pay attention exclusively to adulthood [79], leaving aside the impact of this disease in the developmental age.

In this context, the close interconnection between OSAS and alteration specifications charged to executive functions. Furthermore, as reported in other studies, the modified card sorting test (MCST) is related especially to changes in blood flow for the frontal and hippocampal regions [80]. These data reflect the conclusions of recent neuroimaging studies on subjects suffering from OSAS, which would present a level reduction of the gray substance of the fronto parietal regions and

hippocampus [81, 82], confirming the presence of an interconnection between sleep mode and performance also in subjects of the developmental age.

The neurocognitive OSAS effects have been known for over a century. In 1892, Sir William Osler described, in the child, an association between night snoring, upper respiratory tract obstruction, and intellectual retardation [83].

In 1889, William Hill confirmed what Osler had previously described and showed that the removal of adenoids and tonsils caused not only the disappearance of nighttime respiratory symptoms but also the recovery of intellectual function [84].

In general, children affected by OSAS may present many specific problems in different day-life functioning areas including reductions in working memory, speed movement, cognitive flexibility, and planning. As main effect of this alteration, learning ability and scholastic efficiency may be altered precociously [85].

The exact etiopathogenetic link between nocturnal respiratory disorders and daytime behavioral symptoms is not still known. Certainly, the fragmentation of sleep due to frequent microarousal, hypoventilation, and the imbalances in blood gases that these children experience during sleep plays an important role in the genesis of these disorders.

Brain studies in rodent models have shown that hypoxia and anoxia produce cellular damage [86] within the CA1 region of the hippocampus and adjacent cortex.

This laid the groundwork for further studies, which confirmed the reduction of gray matter in subjects with OSAS in the right upper temporal sulcus and in the left cerebellum area, areas dedicated to attention processes, working memory, and motor coordination. In fact, many studies [87, 88] have revealed reductions in gray matter in the inferior temporal gyrus, including the parahippocampal gyrus, extended toward the anterior temporal pole. The precise function of the average time frame is unclear. Recent attempts to link structural deficits resulting from OSAS with functional consequences have concluded that structural deficits are associated with memory impairment and difficulty in motor coordination, although these data are not conclusive [89].

On the other hand, the complete brain magnetic resonance imaging (MRI) scanning in OSAS subjects showed loss of gray matter in a single large region of the cerebellum, more dominant on the left. Patients with right focal lesions often show verbal deficits, while those with lesions on the left seem to suffer more from spatial deficits. The left region, in fact, is the one most involved in the development of the movement. Moreover, Yaouhi et al. [90] reported significant loss of gray matter in bilateral inferior parietal gyrus, right temporal cortex, occipital cortex, right thalamus, left putamen, left caudate nucleus and left pallidum, right hippocampal gyrus, right cerebellar hemisphere, and cerebellar vermis in OSAS subjects.

10. Conclusions

Motivational ability, planning, behavior modulation, ability to complete an action program, identification of functional strategies to achieve the goal, problem solving, flexibility, monitoring and self-assessment of behavior in relation to results, change of task, or behavior in the light of emerging information may be all impaired by nocturnal intermittent hypoxia also during the developmental age. The final effects of this impairment may be identified in such clinical condition mimicking other neurobehavioral symptoms, such as ADHD [34], while learning problems may be sustained by OSAS [91, 92], or in Fragile X syndrome [93], in epilepsy [94], and in EEG abnormalities [95], suggesting that the sleep screening may be considered as mandatory in neurodevelopmental disorders.

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