

ENDOCRINE ABNORMALITIES IN CHILDREN WITH OBSTRUCTIVE SLEEP APNEA

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Abstract

Introduction. Obstructive sleep apnea (OSA) is more common in children with obesity. Episodic nocturnal hypoxemia, hypercapnia and sleep fragmentation result in reduced release of GH (growth hormone) during sleep and onset of the short stature. In children with Down syndrome predisposition to SAO is dependent on oropharyngeal anatomical peculiarities and obesity is an aggravating factor. The association of hypothyroidism emphasizes the cognitive deficit due to trisomy 21 and obstructive sleep apnea. Compromising somatic growth is a powerful long-term consequence in children with OSA.

Material and method. We present the case of a 9 year and 11 months old boy with Down syndrome known with sleep apnea in which the periodic clinical and laboratory assessment identified the presence of thyroid hypofunction.

Results. The patient is obese (BMI = 22.5 kg / m² at the 95th percentile for gender and age), with mild subclinical hypothyroidism (TSH = 5.71 uIU/mL, FT3 = 6.82 pmol/L, FT4 = 14.27 pmol/L) and residual SAO after tonsils and adenoids ablation. Sleep polygraphy revealed mixed apnea, predominantly obstructive, with apnea-hypopnea index = 18.3/hour, average SaO₂ = 95%, desaturation index = 20.5/hour. Substitution with potassium iodide was initiated. It was recommended hypocaloric diet, lateral decubitus posture during sleep and reevaluation in order to initiate CPAP.

Conclusions. Annual assessment of thyroid function in patients with Down's disease is mandatory. Hypothyroidism, obesity and obstructive sleep apnea require interdisciplinary and individualized management in these patients.

Key words: obstructive sleep apnea, children, endocrine abnormalities

Introduction

Obstructive sleep apnea (OSA) is the most common type of apnea and it is due to structural abnormalities (changes in facial bones, jaw and tongue); enlarged tonsils and adenoids; decreased pharynx muscle tone; obesity, genetic syndromes, etc.^{1,2,3,4,5} OSA consists of repeated interruptions of breathing during sleep lasting more than 10 seconds and hypopnea episodes.^{4,6} Air circulation in the

upper airways is disrupted, affecting the body's oxygenation.¹ Transient changes in blood gases (hypoxia, hypercarbia) and sleep fragmentation occur.¹ These events lead to cardiovascular abnormalities (tachycardia, hypertension), digestive problems (regarding gastro-oesophageal reflux), endocrine issues (reduced secretion of growth hormone, etc.), restless sleep and frequent awakenings, etc.^{1,4,7,8,9} With time, complications occur: neuropsychiatric disorders (attention deficit, hyperactivity, irritability, aggression, memory disorders, school failure); growth deficiency; metabolic (increased insulin resistance); abnormal bone (infundibular sternum); cardio-pulmonary (pulmonary hypertension, cor pulmonale); frequent respiratory infections (recurrent otitis media).^{1,2,10} They alter the quality of life leading to debilitating diseases (arrhythmias, congestive heart and respiratory failure) and even premature death.

The diagnosis of sleep apnea is achieved by night polygraphy.^{2,5,6,9} This easy investigation which can be used in patients of any age is the gold standard in the management of sleep apnea. Early diagnosis and proper treatment of OSA prevent severe complications.¹

Some endocrine and metabolic conditions can be associated with OSA.^{1,3,4,5,11} There are more common in children with obesity. Episodic nocturnal hypoxemia, hypercapnia and sleep fragmentation result in reduced release of GH (growth hormone) during sleep and onset of the short stature.² Compromising somatic growth is a powerful long-term consequence in children with OSA. In children with Down syndrome predisposition to OSA is dependent of oropharyngeal anatomical characteristics and obesity is an aggravating factor. The association of hypothyroidism emphasizes the cognitive deficit due to trisomy 21 and obstructive sleep apnea.^{6,11} Increasing severity of OSA is associated with greater insulin resistance (IR) and suggests that OSA is independently associated with glucose intolerance and worsened glycemic control.^{1,4}

Purpose

To assess endocrine abnormalities in obstructive sleep apnea in children.

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Materials and Methods

We present the case of a 9 year and 11 months old boy with Down syndrome known with sleep apnea in which the periodic clinical and laboratory assessment identified the presence of thyroid hypofunction. He was evaluated by: anamnesis (history of snoring, witnessed apneas), clinical exam, laboratory assessment (haemathology, biochemistry, hormonal, etc.); thyroid ultrasounds, sleep polygraphy; consults (ENT, neurology, cardiology, endocrinology).

Results

Anamnesis revealed intense night snoring during early childhood; mouth breathing, macroglossia and tonsillar hypertrophy grade III. At age 6 adeno-tonsillectomy was performed. Sleep polygraphy made in 2012 after surgery revealed mild sleep apnea with apnea hypopnea index (AHI)=3/hour, mean SaO₂= 94% and desaturation index =18/hour (Figure 1). The patient was overweight (BMI=17.9

kg/m², at the 89th percentile for sex and age). In 2015 he was twice evaluated, in May, respectively in August. Actually, the patient is obese (in May: BMI = 20.8 kg/m², at 91th percentile for age and sex; in August: BMI = 22. 5 kg/m² at the 95th percentile for gender and age) (Figure 2). Intermittent snoring, vitamin D deficiency and hypocalcemia (Table 1), mild subclinical hypothyroidism (Table 2) and residual OSA after tonsils and adenoids ablation are present. Sleep polygraphy revealed mixed apnea, predominantly obstructive, with apnea-hypopnea index=18.3/hour, average SaO₂ = 95%, desaturation index=20.5/hour. Cardiological evaluation (physical exam, cardiac ultrasonography, electrocardiogram) revealed normal relations. Substitution with potassium iodide was initiated. It was recommended treatment with oral calcium and vitamin D, hypocaloric diet, lateral decubitus posture during sleep and reevaluation in order to initiate CPAP.

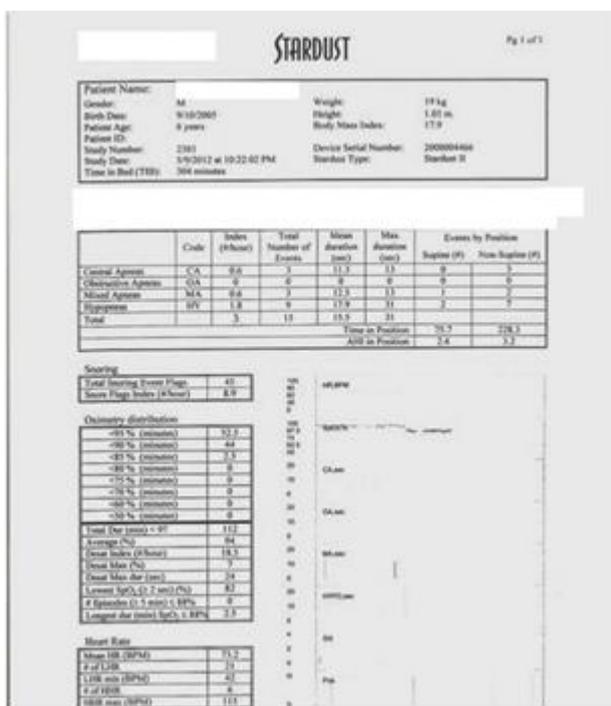


Figure 1. Sleep study (2012).

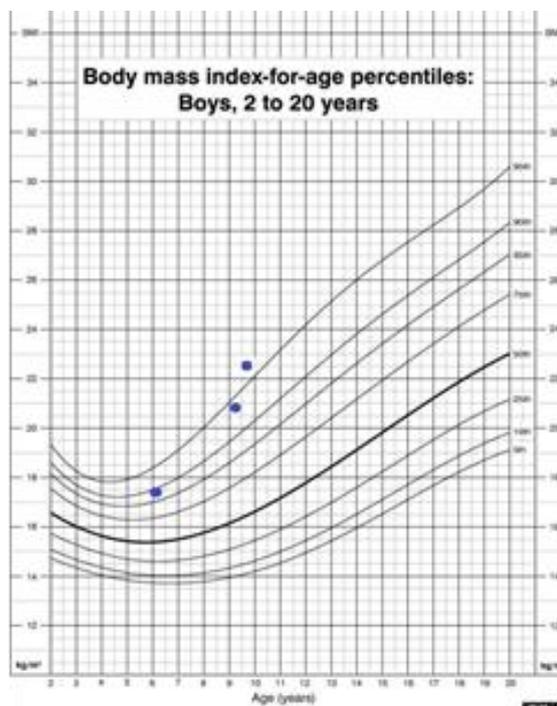


Figure 2. BMI evolution of the case presented.

Table 1. Biochemical evaluation.

Parameter	Result		Normal range
	May 2015	August 2015	
Total calcium (mmol/L)	2.24	2.28	2.3-2.75
Free calcium (mmol/L)	1.02	1.04	1.05-1.3
Magnesium (mmol/L)	0.99	-	0.7-1.05
Serum phosphate (mmol/L)	1.66	1.64	1.1-2
Alkaline phosphatase (U/L)	179	192	< 300
Total fat (g/L)	6.21	6.85	5-8
Glycemia (mg/dL)	87	90	60-99

Tabel 2. Hormone evaluation.

Parameter	Result		Normal range
	May 2015	August 2015	
FT3 (pmol/L)	6.82	6.24	4.1-7.9
FT4 (pmol/L)	14.27	16.66	11.6-21.5
TSH (uiU/mL)	5.71	4.37	0.66-4.14
25- hydroxy vitamin D (µg/L)	12.81	31.82	20-70
Parathormon	40.2	-	15-65

Predominance of male gender is one of the main risk factors for OSA.^{1,3} The etiology of OSA is multifactorial.³ It is associated with hypertrophic adenoids, hypertrophic rhinitis, low soft palate, deviations of oral structures, obesity and even hypothyroidism.^{1,4} Comorbidities of OSA could be hypertension, insulin resistance, etc. Obesity is an important determinant of sleep apnea (SA) even in children.¹ 1-3% of non obese children aged less than 8 years present OSA, while obese children show OSA 4-5 times more frequently. The association of obesity with adenotonsillar hypertrophy worsens the obstructive sleep apnea. In these patients, the first-line therapy is adenotonsillectomy.² The OSA complications are more common in the obese. Hygienic-dietary regime is addressed to weight reduction. Down syndrome is often associated with obesity and obstructive sleep apnea (OSA).^{7,8,12} In these children, obesity is an aggravating factor of OSA and BMI (Body Mass Index) and AHI (Apnea Hypopnea Index) correlates. In children with trisomy 21 obstructive sleep apnea (OSA) is frequent because of anatomical features. 60% of preschoolers with Down syndrome have sleep apnea, its incidence increasing with age.² Adenotonsillar hypertrophy contributes to worsening airway obstruction in these patients.² Neurocognitive impairment and OSA emphasizes nutritional status dependent pre-existing pathology. Identifying obstructive sleep apnea in children with trisomy 21 enables accurate and personalized interdisciplinary management of these cases.^{2,10}

Hypothyroidism is characterized by a low level of thyroid hormones which may cause abnormal soft tissue thickening (myxedema) in the upper airway, a reduction in breathing control and weakness of the muscles that determine upper airway patency.^{1,3,4,5,6} Hypothyroidism might cause OSA due mucoprotein deposition in the upper airway, decreased neural output to the upper airway musculature, obesity, and abnormalities in ventilator control. In patients with OSA, hypothyroidism is very uncommon.⁵ Hypothyroidism can be associated with severe cases of OSA.^{1,4} For OSA patients, the prevalence of clinical hypothyroidism is not higher than the in general population. It is essential to consider the risk factors for hypothyroidism when evaluating patients for sleep apnea as well as considering OSA risk factors when evaluating hypothyroid cases.⁴ Routine blood testing for TSH and FT4 should be recommended for OSA patients with severe obesity, persistent sleepiness despite adequate CPAP therapy and with overt hypothyroid symptoms and signs. Conservative management of OSA contains weight reduction, sleeping positions adjustment, etc.^{1,2,4}

However, when irreversible skeletal defects and/or obesity are present, OSA may persist despite treatment of endocrine disorders and may thus require complementary therapy. This is also frequently the case in patients with obesity, even after substantial weight reduction. Given the potential neurocognitive consequences and increased cardiovascular risk associated with OSA, CPAP therapy is recommended if OSA persists despite effective treatment of its potential causes.^{1,2,4}

Because some features of hypothyroidism are similar to symptoms of OSA, it is mandatory to consider the possible coexistence of the two conditions. Decreased cognitive function and obesity are common findings in both disorders.¹

Hypothyroidism is a well-known disorder in which OSA is relatively common. Hypothyroidism may contribute to sleep apnea through macroglossia or disruption of the muscles that control the upper airway.³ If hypothyroidism is causing sleep apnea, it is improved with thyroid hormone substitution. Although treatment with thyroid replacement therapy will normalize hormones levels and reduce symptoms, OSA often persists and requires continued therapy.¹

Undiagnosed or improperly treated OSA leads to significant morbidity, sometimes with irreversible consequences despite appropriate but late treatment. The consequences of OSA are correlated with episodic nocturnal hypoxemia, hypercapnia and sleep fragmentation.^{2,4} Snoring in OSA changes the sleep architecture, reducing the release of GH during sleep.²

Hypothyroidism is particularly common in children with Down syndrome.¹¹ Although the association between Down's syndrome (DS) and thyroid dysfunction is well recognized, the cause of this condition is not known. Patients with trisomy 21 have an increased prevalence of both congenital hypothyroidism (28 times higher than in the general population) and acquired thyroid dysfunction.¹¹

Beyond the newborn period, the incidence of elevated TSH values in Down syndrome increases. Mild plasma thyrotropin (TSH) elevation with normal thyroxine (T4) levels is the most commonly seen pattern of thyroid dysfunction in DS.¹¹ These biochemical deviations decreased with age – 70% of individuals with subclinical hypothyroidism in the first test had become normal in the second one, like in the case presented.

This is a treatable cause of mental retardation, thus early detection and treatment are essential in order to maximize cognitive abilities in this already impaired population. Current health supervision guidelines for

children with DS suggest reviewing results of the newborn thyroid function screen, then repeating thyroid function tests at the age of 6 months and 12 months, and then annually.¹¹ Because of the high prevalence of thyroid dysgenesis in Down syndrome, patients with thyroid dysfunction, lifelong treatment with L-thyroxine should be started without delay.¹¹

OSA may have consequences on hormonal axes.¹ Variable degrees of hypogonadism are associated with OSA.¹ This impairment of pituitary-gonadal axis is linked to the degree of hypoxia and disordered breathing, independently of increasing age or obesity. In male patients, hypogonadism improves with CPAP. In females higher AHI (apnea-hypopnea index) is associated with lower serum estradiol and progesterone, suggesting that OSA may be associated with impaired ovarian function. OSA is also associated with hypoxia-induced sympathetic activation, which may contribute to hypertension via the stimulation of renin-angiotensin-aldosterone system.¹

OSA is associated with a reduction in total sleep time and with sleep fragmentation, which can affect glucose tolerance as shown by several epidemiological studies.^{1,2} Hypothyroidism and OSA show some clinical overlap.¹ An increased prevalence of OSA (between 25 and 35%) has been reported in patients with hypothyroidism. Central

apnea may also be encountered in this setting. The main pathophysiological determinant of OSA in hypothyroidism seems to be pharynx narrowing due to soft tissue infiltration by mucopolysaccharides and protein.⁶ These findings support the recommendation that thyroid hormones and TSH be measured in all patients with suspected or confirmed OSA, even if the prevalence of hypothyroidism is low.^{4,3,11}

Conclusions

The positive correlation between AHI and TSH supports the fact that thyroid function test screening is necessary in children with OSA. The measurement of TSH levels in suspected OSA cases may help both differential diagnosis between OSA and hypothyroidism, as well as diagnosis of subclinical hypothyroidism. Upper airway obstruction is related to obesity and male gender and not to hypothyroidism per se. Although testing of thyroid function is not recommended as part of the routine workup of patients with OSA, in Down syndrome is important to establish whether hypothyroidism is present. Annual assessment of thyroid function in patients with Down's disease is mandatory. Hypothyroidism, obesity and obstructive sleep apnea require interdisciplinary and individualized management in these patients.

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