THE ROLE OF CORTISOL IN NEUROCOGNITIVE PERFORMANCE IN OBSTRUCTIVE SLEEP APNEA PATIENTS

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Abstract

Obstructive sleep apnea consists in recurrent episodes of partial obstruction of the upper airways which can determine cessation of breathing during sleep causing intermittent hypoxia. The obstructive sleep disorders are encountered predominantly in obese patients with or without metabolic syndrome, that can affect the quality of life and life expectancy by increasing the cardiovascular risk of coronary artery disease, conductance disturbances, malignant arrhythmias, promoting atherogenic processes, determining sudden death and impairing several domains of cognitive function.

Key words: obstructive sleep apnea, neurocognitive function, cortisol levels and rhythm.

INTRODUCTION

Obstructive sleep apnea consist in recurrent episodes of partial obstruction of the upper airways which can determine cessation of breathing during sleep causing intermittent hypoxia. The obstructive sleep disorders are a group of disorders encountered predominantly in obese patients with or without metabolic syndrome, that can affect the quality of life and life expectancy by increasing the cardiovascular risk of coronary artery disease, conductance disturbances, malignant arrhythmias, promoting atherogenic processes, determining sudden death and impairing several domains of cognitive function (1).

Obstructive sleep apnea and intermittent hypoxia are related directly with negative effects on neurocognitive function and neurobehavioral impairments. The main cognitive functions that are impaired: memory, attention span, psychomotor performance, vigilance and executive functions. Cortisol elicits effects on the development and maintaining neurocognitive function, control of memory and attention span (2). Given these well-

known facts it has been hypothesized that cortisol levels can be a potential pathway for neurocognitive dysfunction in obstructive sleep apnea patients (3).

Neurocognition and cortisol rhythm interference in sleep disorders

The neurocognitive dysfunction in obstructive sleep apnea and the underlying mechanisms are not clearly understood for some reasons. The comorbidities associated with obstructive sleep apnea such as hypertension and vascular atherogenic lesions – increased carotid intima-media thickness– can determine neural injuries per se, so it is essential to make a correct assessment of the neurocognitive status in this category of patients (1).

There are a variety of tests that evaluate the neurocognitive and executive functions, but they present limitations for the comparisons of neurologic and cognitive deficits observed in patients with obstructive sleep apnea. Hypoxia resulting from sleep fragmentation is the main physiopathological substrate responsible for the neurocognitive dysfunction (4).

The main pathway disrupted by hypoxia is the hypothalamic-pituitary-adrenal axis, with direct impact upon cortisol, a hormone with a rhythmic diurnal secretion and activity. Nocturnal variations of blood cortisol levels are related with sleep duration and REM activity (5).

The amygdala and the hippocampal region present an important quantity of corticosteroid receptors. Taking into account the relation between cortisol levels and cognitive function, we may consider that this hormone could have a substantial role in the neurocognitive patients suffering from obstructive sleep apnea syndrome (5).

Several studies have demonstrated that correction of hypoxia during the continuous positive airway pressure is associated with the normalization of cortisol levels in patients suffering from sleep apnea

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(6). Summarizing these theoretical aspects it has been launched the hypothesis that alteration of cortisol rhythms is biologically linked with neurocognitive dysfunction related to obstructive sleep apnea syndrome.

A recent study examined the evolution of cortisol levels in 55 patients diagnosed with obstructive sleep apnea having a mean apnea index of 30. (2) The age range of the patients was between 29 and 65 years old. The exclusion criteria were represented by patients suffering from major medical illnesses, psychiatric diagnosis with psychotropic medication and drug or alcohol abuse. Blood was collected using a venous catheter every 2 hours starting at 6.00 AM on a 48 hours interval to assess cortisol levels. Plasma cortisol levels were determined using ELISA. The second day sleep physiology was evaluated by polysomnography. All patients have compiled the following day a battery of tests consisting in 7 cognitive domains represented by Wechsler Adult Intelligence Scale-Revised, Digit Symbol, Digit Span, Letter-Number Sequencing Test, Symbol Search Test; Brief Visuospatial Memory Test-Revised (BVRT); Hopkins Verbal Learning Test-Revised (HVLT); Trail Making Test parts A and B, Digit Vigilance Test; Stroop Color-Word Test and Word Fluency Test (7).

All patients included in the study completed the Center for Epidemiologic Studies of Depression Scale and a score above 16 indicated a diagnosis of depression. This study demonstrated an association between neurocognitive dysfunction, obstructive sleep apnea syndrome and nocturnal cortisol levels. The severity of sleep apnea and hypoxia episodes was correlated with the neurocognitive impairment and night-time cortisol levels were a significant predictor to this association. The main cognitive functions that are related the most with the night-time cortisol high levels are represented by learning process, long time memory and working memory (7).

This study demonstrated that night-time cortisol circadian variations were a significant predictor of neurocognitive impairment above the apnea-hypopnea indices, sustaining the hypothesis that neurocognitive dysfunction could be secondary to the alterations of the hypothalamic-pituitary-adrenal axis activity (8).

The psycho-neuro endocrine literature provides data about high levels of cortisol in hippocampal region related to decline in neurocognitive function (8).

Furthermore, there are data that a prolonged exposure to high-levels of glucocorticoids can affect working time and learning memory. Structural changes

in hippocampal region are also related to cortisol night-time high levels. Night-time levels of cortisol are more related to memory and learning dysfunction due to hippocampal alteration than the daytime levels (9).

There is a complex relationship between sleep obstructive disorders in general and sleep obstructive apnea in particular and hormones rhythms. A series of studies revealed an alteration in the cortisol and testosterone secretion in obstructive sleep apnea patients. Cortisol and testosterone levels were measured in three salivary samples collected after sleep in the morning, noon and evening periods. A psychometric scale evaluation was used to assess memory function, attention span and sexual function disturbances (10).

Ghiciuc *et al.* compared obese with sleep apnea disorder and non-apneic obese patients and found significant change in cortisol and testosterone diurnal secretion rhythm between the two categories of patients – with an increased secretion rate during daytime and a morning decreased secretion of testosterone in the sleep apnea - obese patients (10).

This pattern of studies has begun in neuropsychiatric centers of research. Pediatric population is susceptible of being more affected in this time frame of life by attention span disorders, short and long memory impairment, alteration of concentration levels due to the scholastic and intellectual requirements.

Chan-Soon Park *et al.* designed a prospective study that enrolled 80 pediatric patients with obstructive sleep apnea disorder and measured the salivary cortisol levels, while comparing them to the severity of the apnea. The results shown that severity of sleep apnea correlates with an increased level of salivary cortisol (11).

Children that after 2 complete polysomnographic studies had an apnea-hypopnea index >5 had the highest level of salivary cortisol, meaning the greatest activation of the hypothalamic-pituitary-adrenal axis while the subgroup having an apnea-hypopnea index <1 the salivary cortisol levels were accordingly low (11).

The neurocognitive evaluation, testing the level of attention span, long and short term memory, and mental concentration were all in favor of the subgroup with low salivary cortisol and low activation of the hypothalamic-pituitary-adrenal axis (11).

Furthermore, Jong-Hyun Jeong *et al.* treated the suitable pediatric population by adenotonsillectomy, measured the salivary cortisol levels and tested the neurocognitive parameters depicted previously before and after the intervention. Adenotonsillectomy was

associated with statistic significant improvements in apnea-hypopnea indexes, with the normalization of salivary cortisol and improvements in the neurocognitive test results at six months from the surgical moment (12).

Given these data we can conclude that sleep deprivation and sleep obstructive apnea syndrome can generate a disruption in the cortisol circadian rhythm that is consequent to the hypothalamic-pituitary-adrenal axis activation that can result in the alteration of neurocognitive functions. The internal biomolecular mechanisms, the complex pathophysiology and all its clinical implications remain to be clarified in the future.

Conflict of interest

The author declares that he has no conflict of interest concerning this article.

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