Cholinergic Markers and Cytokines in OSA Patients

The role of inflammation and dysfunction of the cholinergic system in obstructive sleep apnea (OSA) has not exhaustively clarified. Thus, in this study, we explore the non-neuronal cholinergic system and the balance of T helper (Th) 17- and T regulatory (Treg)-related cytokines in OSA patients. The study includes 33 subjects with obstructive sleep apnea and 10 healthy controls (HC). The expression levels of cholinergic system component, RAR-related orphan receptor (RORc), transcription factor forkhead box protein 3 (Foxp3) and cytokines were evaluated. Th17- and Treg-related cytokines, choline levels and acetylcholinesterase (AChE), butyrylcholinesterase (BuChE) activity were quantified in OSA and control subjects. AChE and nicotinic receptor 7 subunit (7nAChR) gene expression and serum levels of choline, AChE and BuChE were lower in OSA patients than in the HC group. Compared with the HC group, OSA patients exhibited an increased expression, secretion and serum levels of pro-inflammatory cytokines, a reduced expression, secretion and serum levels of transforming growth factor (TGF) and reduced Foxp3 mRNA levels. The Th17/Treg-related cytokine ratio was higher in the OSA group. Our results confirm and reinforce the hypothesis that OSA may be considered a systemic inflammatory disease, and that an imbalance of non-neuronal cholinergic and pro/anti-inflammatory cytokines may contribute to development and progression of comorbidities in OSA subjects. The evaluation of Th17/Treg-related cytokine may provide an additional explanation for OSA pathogenesis and clinical features, opening new directions for the OSA management.

OSA is a major primary sleep disorder characterized by repetitive nocturnal complete (apnea) or partial (hypopnea), collaps of the upper airway during sleep accompanied by oxyhemoglobin desaturation and/or electroencephalography (EEG) and vegetative arousals. Nocturnal OSA symptoms include sleep fragmentation, diminished amounts of slow wave and rapid eye movement (REM) sleep, nocturia and insomnia. Daytime symptoms include headache, depressive symptoms, cognitive alterations, fatigue and, in particular excessive daytime sleepiness (EDS), with different patterns between men and women. EDS is not always present in OSA patients, and it does not invariably correlate with the severity of the disease, showing inter-individual differences with different responses to ventilatory treatments, albeit these aspects need to be better elucidated.

The hypothesis that systemic inflammation contributes to OSA risk and to OSA syndrome (OSAS)-associated morbidities is particularly interesting and has been under investigation as far back 1990, though in a small number of patients and with an under-representation of the female population. Clinical studies of OSA and inflammation have yielded conflicting results and suggested that there are patient-specific or OSA-specific factors that predict inflammation, but which have not yet been fully identified.

Dyugovskaya et al. showed that in patients with OSA, various subpopulations of T cells acquire an activated phenotype with the downstream consequence of increased cytotoxicity against endothelial cells. Furthermore, this activation process is associated with an increased intracellular content of the pro-inflammatory mediators Tumor necrosis factor (TNF) α and interleukin (IL)-8 and, a decrease of the anti-inflammatory cytokine IL-10, in accord with the observation that in OSA patients repetitive airway obstructions causing intermittent hypoxia induces activation of nuclear factor-κB (NF-κB) and upregulation of pro-inflammatory genes.

Over the years many studies have clarified and well documented the bidirectional relationship between the nervous system and the immune system and the expression of most cholinergic system components in
immune cells. IL-6 can go through the blood-brain barrier inducing neuroinflammation or neurodegeneration and also causing impairment of neurocognitive functions. The cross talk between the vagus nerve and the immune system was mainly ascribed to inhibiting the immune system [11]. Vagus nerve regulates the production of acetylcholine (ACh) in immune cells, that control inflammation through negative feedback by the binding to α7nAChR expressed by immune cells [11]. Sukys-Claudino et al. have speculated that a deficient cholinergic transmission plays a role in the pathogenesis of OSA in non-Alzheimer’s disease (AD) patients [12] and, a significant role of ACh in wakefulness and breathing was evidenced by Otuyama et al. in individuals with sleep-disordered breathing [13]. The study by Nardone et al. linked, in OSA patients, the impaired cognitive performance with a dysfunction of the cholinergic system [14]. Based on this, our aim is to investigate, in OSA patients, the non-neuronal cholinergic system and the Th17- and Treg-related cytokines and if nicotinic receptor α7 subunit is involved in Th17/Treg polarization and the synthesis of proinflammatory cytokines.

This preliminary study has some limitations. First of all, it may be biased, since the small differences in subject characteristics and the sample size, does not allow to significantly categorize male and female group and establish a clear relationship between sex and cholinergic and immune system in OSA patients. Since only 24% of patients have 15 AHI < 30, evaluation of cholinergic and immunological parameters did not give significantly differences respect to patients with AHI > 30.

Although underpowered, this study may provide interesting results for further investigation to better assess the mechanistic and functional relationship between sleep disordered breathing, inflammatory cytokines and non-neuronal cholinergic systems in males and females.

Here we hypothesize that in OSA patients the impairment of α7nAChR expression contributes to exacerbate inflammatory conditions making these patients more susceptible to comorbidity development. To the best of our knowledge, this is the first study to show the outcome of cholinergic and inflammatory system modulation in OSA patients. The complete mechanism through which OSA may be linked to impaired cholinergic pathway and if it could influence immune functions and metabolic or cardiovascular disease risk is not completely clarified. Thus, the results of this study can pave the way for new studies on the role of both inflammatory and cholinergic markers in OSA prognosis, comorbidities and related treatments in men and women.

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