The Triad Nocturia, Smoking and Obstructive Sleep Apnea

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In patients with obstructive sleep apnoea (OSA), a consequence of the intermittent hypoxia is nocturia. The frequency of nocturia related OSA is increased because many pathological pathways are present simultaneously. The aim was to assess the prevalence of nocturia among OSA patients and to identify the relationship with OSA and its comorbidities. A transversal study determining the prevalence of OSA's comorbidities and nocturia related OSA and smoking was assessed, from 2011 to 2015, in 2 Romanian centres of Somnology, in Constanta county. All patients suspected of sleep breathing disorders were investigated by polygraphy and all patients diagnosed with OSA were recruited. Demographic and clinical characteristics were assessed, including the onset of nocturia. The comparison between groups with and without nocturia was performed using SPSS software, using Anova for numerical outcomes and χ^2 test for the categorical ones. Nocturia was highly prevalent (62.75 %) among 204 OSA patients, especially in elderly ($p < 0.00001$). High blood pressure (hypertension), obstructive pulmonary disease (COPD), smoking exposure were more frequently reported in the OSA patients presenting nocturia ($p<0.05$). Type 2 diabetes and cardiac failure were also frequent, but did not reach a significant threshold of 95%. In conclusion, the nocturia is a frequent symptom and it is influenced by the OSA severity and comorbidities as hypertension and COPD. A further multidisciplinary approach in these patients is justified, especially in smokers.

Key words: nocturia, obstructive sleep apnoea, smoking, COPD

More than half of the patients with obstructive sleep apnoea (OSA) have nocturia [1], a complaint defined by a void preceded and followed by sleep [2]. Behind the low tract infections, nocturia is classified as a global polyuria, nocturnal polyuria and reduced bladder capacity and all these 3 entities might be present in OSA. Therefore, nocturia is classified as a mixt disorder associated with OSA. Directly related to the pathophysiology of the sleep apnoea is the intermittent hypoxia, with an increase of the sympathetic tonus and a decrease of the parasympathetic one, determining an alteration of the bladder contractility and detrusor instability. The intermittent collapse of the upper airways increases the negative intrathoracic pressure that opposes to the obstruction [2].

Consequently, the transmural left ventricular pressure rises and the afterload increases. So, the negative intrathoracic pressure augments the venous return and right ventricular load, while the hypoxic pulmonary vasocontriction augments the right ventricle afterload. The higher intraventricular pressure triggers the secretion of the natriuretic peptides [3]. Through its extensive influence on metabolic and vascular inflammation, OSA impairs the renal concentration function and induces hormonal changes, which both contribute to the nocturia [4].

Experimental part

In a cohort of new OSA cases, the study proposed to assess the prevalence of nocturia in relation with the OSA's comorbidities. The recruitment methodology included all patients with suggestive sleep breathing symptoms, but not previously diagnosed with OSA, examined by cardio-respiratory sleep polygraph in Constanta Somnology centre, Romania, between October 2011 to April 2015. Patients with central sleep apnoea, obesity-hypoventilation syndrome and upper airways resistance syndrome were excluded from the analysis and 204 OSA patients were included. Using a standard examination protocol interview, all signs and symptoms of OSA, chronic diseases related OSA and smoking exposure were assessed as previous analysis reported [5]. The body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. The apnoea-hypopnea index (AHI) and oxygen desaturation index (ODI) were extracted from the polygraph datasheets. ODI represents the hourly average number of desaturation episodes; a desaturation episode is recorded for each least 4% decrease in saturation from the average saturation in the preceding 2 min that lasts for more than 10 seconds [6]. According to the AHI value, cases were grouped in mild (AHI = 5-14.9), moderate (15-29.9) and severe (AHI>30) forms of OSA. Classes of OSA severity were, also, defined according to the ODI values, as following: mild (ODI: 5-14.9); moderate (ODI = 15-29.9) and severe (ODI>30). Patients were divided in 2 groups: group 1 included the patients with nocturia and group 2 the patients without nocturia. COPD severity was considered as stages I-IV, according to the Global Initiative for Chronic Obstructive Lung Disease [7].The statistical analysis of the data recorded was performed with SSPS software (StatPlus for Mac, Analyst Soft Inc. version V6, 2016). Comparison between categorical and numerical variables was

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performed using chi^2 test and Kruskal Wallis Anova. The threshold for the statistical significance was set at 95%.

Results and discussion.

The prevalence of nocturia among adult OSA patients was high (n=128/204; 62.75%). Nocturia was not reported by 76 patients (37.25 %). Patients with nocturia were older than those without (55.37 + 9.39 years versus 48.59 + 11.22 years; p<0.00001) and the distribution of cases by age revealed the predominance of nocturia among patients older than 50 years (fig. 1). From the total number of 204 OSA patients, mean aged 52.84 + 10.61 years, 160 (78.43%) were men and 44 (21.57%) women, but gender did not influenced the occurrence of nocturia (p<0.7) (table I).

Smoking exposure was higher in OSA patients (67.65%), counting similar values in both groups with and without nocturia (p<0.9) but the distribution of OSA comorbidities among groups was totally different (table 1). A significantly higher prevalence of high blood pressure (p<0.00001) and COPD (p<0.04) was noticed in patients with nocturia compared with no significance among patients with OSA and diabetes (p<0.07) (table I). Considering the stages of high blood pressure (HBP), the majority of cases were in stage 2 in both groups. However, the distribution of the HPB stages in the 2 groups was statistically significant (p =0.024), with more severe cases in group 1. COPD was diagnosed in 28.91% of the patients from group 1 and in 21.06% of the patients in group 2. Almost ¾ of OSA patients were diagnosed with moderate COPD in both groups (28/37 patients in group 1 and 12/16 patients in group 2), without differences of distribution by the severity of lung function decline between groups (p = 0.78). Among 60 patients with ENT disorders, the most prevalent disease in both groups was nasal polyposis (8 cases in group 1 and 7 cases in group 2), followed by the nasal septum deviations (6 cases in group 1 and 7 cases in group 2), the great majority of them with previously surgical treatment (70.58% of cases in group 1 and 85% in group 2). Difference in the distribution of the ENT disorders was not statistically significant (p =0.19), but there were more patients with associated ENT disorders in group 1 (31% versus 20% in group 2). Patients with nocturia had more severe forms of OSA revealed by higher values of AHI and ODI, and lower average saturation with minimal values of O_2 saturation. The distribution of cases among groups, by the severity of AHI, was significantly different (p=0.0012) with a lower proportion of mild OSA (7.08%) in group 1 compared to

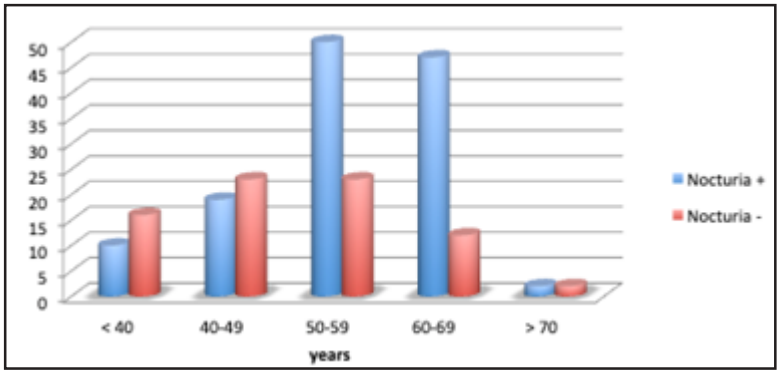

Fig. 1. Age distribution of OSA cases by nocturia

	Total	Group 1	Group 2	P<
Number; %	204 (100%)	128 (62.75%)	76 (37.25%)	
Age (years)	52.84 ± 10.61	55.37 ± 9.39	48.59 ± 11.22	0.00001
Sex (M/F)	160/44	99/29	61/15	0.7
BMI	35.21 ± 6.72	35.77 ± 6.83	34.26 ± 6.44	0.2
Smokers (No/%)	138 (67.65%)	87 (67.97%)	51 (67.1%)	0.9
Current smokers	81	48	33	
Ex smokers	57	39	18	
Non smokers (No/%)	66 (32.35%)	41 (32.03%)	25 (32.9%)	
Comorbidities				
T2D	31	24	7	0.07
HBP	130	95	35	0.00001
Cardiac failure	24	19	5	0.08
COPD	53	37	16	0.04
ENT disorders	60	35	25	0.4
OSA characteristics				
AHI	45.91 ± 23.91	49.82 ± 23.59	39.302 ± 23.12	0.002
ODI	48.04 ± 26.98	51.71 ± 27.10	41.86 ± 25.79	0.002
Av SO_2	91.21 ± 4.001	90.99 ± 4.09	91.59 ± 3.85	0.4
Min SO_2	72.96 ± 7.69	72.52 ± 7.63	73.63 ± 7.82	0.4

Table I
CHARACTERISTICS OF THE STUDY GROUP

Legend: BMI = body mass index; T2D = type 2 diabetes; HBP = high blood pressure; COPD = chronic obstructive lung disease; ENT= Ear Nose Throat; OSA = obstructive sleep apnoea; AHI = apnoea-hypopnea index; ODI = oxygen desaturation index; Av SO_2 = average saturation in O_2; Min SO_2 = minimal level of saturation in O_2

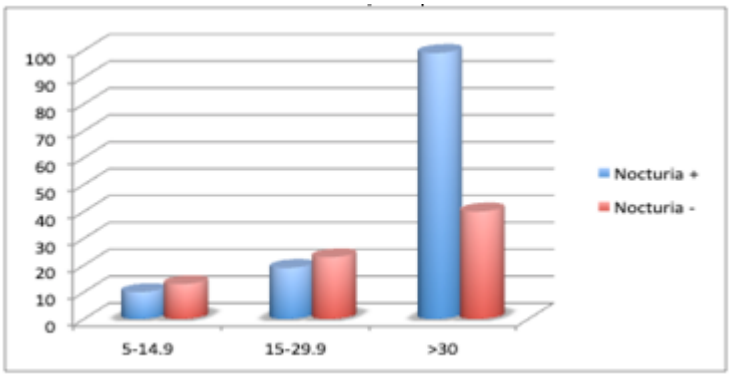

Fig.2. Severity of obstructive sleep apnoea among groups, according to the apnoea hypopnea index (AHI).

17.1% in group 2, and higher proportion of severe OSA in group 1 (77.34%) than in group 2 (52.63%) (fig. 2). These significant differences in evaluating the severity of OSA forms are maintained when using ODI as criteria for severity ($p=0.00196$).

This study found a high prevalence of nocturia in OSA patients, in accordance with other previously reported data [8,9]. Two biases of the reported symptom of nocturia in OSA were described: the awaken time during sleep that could initiate the reflex of voiding and the significant contribution of aging [10]. The influence of age was also confirmed in our study, by mostly cases in their fifth and sixth decade of age having nocturia. Aging is associated with different modifications that can ultimately contribute to nocturia, such as: impairment of the circadian rhythm decreasing the nocturnal arginine-vasopression (AVP) secretion as well as the nephron response to AVP [11], and augmentation of the collagen to smooth muscle ratio of the bladder wall limiting the bladder capacity [12]. Despite these, the intervention by continuous positive airway pressure (CPAP) in reducing the number of the nocturnal voiding [9] is a strong argument for an independent existing relation between nocturia and OSA. Sometimes more efficient measures and therapies have to be associated in OSA patients as smoking cessation, losing weight by exercise and hypocaloric diet, or even dental interocclusal thermoformed appliances for preventing other risk factors of sleep disturbances [13,14]. We also found a significant incidence of comorbidities, as previously reported in other OSA studies [15], some of them having a direct effect on the nocturnal, intermittent obstruction, while others only sharing common pathogenic pathways [16] or being therapy related [17]. Nocturia related to OSA revealed a significant association with HBP and COPD, while other OSA comorbidities as cardiac failure and diabetes were not significantly associated. All of these OSA comorbidities are sharing common pathophysiological mechanisms as activation of the sympathetic neuronal system, of the renin-angiotensin axis (RAA) [18] and a high level of arginin-vasopression (AVP). In late stage of hypertension [19] and cardiac failure, abnormal high atrial and brain natriuretic peptides (ANP and BNP) levels are reported. The triggers of these pathophysiological mechanisms are complemented by specific neurohormonal pattern of OSA. Concerning the RAA axis, it is important to underline that primary hyperaldosteronism is more prevalent in OSA, particularly in the hypertensive patients [19]. A recent meta-analysis found an increased plasma levels of angiotensin II and aldosterone in OSA [20], consistent with a high prevalence. A predominant renal effect of the RAA activation was noticed in OSA; this effect is reflected by a lower effective renal basal flow, a higher filtration fraction and a blunted reno-vascular response to angiotensin II [21]. All these mechanisms can contribute to the progression to the chronic renal disease and accelerate the loss of kidney function [22], explaining the urine concentration impairment and the diminished response to AVP. The subclinical vascular inflammation and the atherogenic process in OSA [23] will also contribute to the impairment of renal flow, eventually leading to nocturia. Aldosterone retention of sodium and water manifested during the daytime expend the body volume of fluid. The nocturnal rostral shift of this fluid towards the neck, increases the severity of OSA [24], but also enhances the secretion of the ANP and BNP. The negative pressure generated to overpass the upper airways obstruction promotes the venous return. Intermittent hypoxia and pulmonary vasoconstriction increases the atrial transmural pressure, aggravating the atrial stretch and the natriuretic peptides release. Indeed, an increased fraction of sodium excretion was recorded, particularly in the hypertension patients [25]. Saturation in O_2 correlates positively with basal and pulse secretion of ACTH and cortisol; the hippocampal damage and sympathetic nervous activation presumably impair the normal control feedback of the hormonal secretion [26]. Nocturia is related to severe forms of OSA ($p<0.002$) as Mansour et al, also, showed [27]. Several factors are referred to the quality of life in OSA patients, among which diurnal somnolence, dyspnoea and nocturia are most frequently cited. Although lung function can be impaired, particularly among the obese patients [28], the quality of life might be earlier affected, as well as for other lung diseases [29,30]. Nocturia affects the quality of life of OSA patients by further decreasing the duration of sleep, the proportion of REM sleep and the sleep efficiency. CPAP therapy provides an important improvement of the symptoms [31], but it does not entirely eliminate the nocturnal voiding.

Conclusions

Nocturia is high prevalent among OSA cases, influenced by OSA severity and its comorbidities as hypertension and COPD. Although smoking exposure is the main risk factor of COPD and it was prevalent among OSA patients. Interdisciplinary collaboration is mandatory in order to explore better the mechanisms of nocturia in OSA and to identify specific biomarkers for severe OSA forms for providing an efficient, individualized and patient-centered treatment.

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Manuscript received:22.08.2018