Relationship between obstructive sleep apnea syndrome and metabolic syndrome in a patient with chronic extrinsic allergic alveolitis

Relația sindrom de apnee obstructivă de somn – sindrom metabolic la un pacient cu alveolită alergică extrinsecă cronică

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Abstract

Obstructive sleep apnea syndrome (OSAS) is a health issue of major importance globally. Although OSAS has a prevalence of 4-10% in the general population, it is less diagnosed, with redoubtable consequences on the quality of life and the professional performance. Observational studies showed that lack of sleep is correlated with weight gain and an increased risk of obesity; this relationship was confirmed by mutually reinforcing pathophysiological mechanisms. We report a case that is relevant for the consequences of the pharmaceutical treatment which proved effective in extrinsic allergic alveolitis, but was not supported by an effective intervention on lifestyle (by proper dietary adjustment and increased physical activity) thus exacerbating the obesity, the OSAS and the metabolic syndrome. We believe that this case exemplifies the relevant pathophysiological interdependence between obesity, metabolic syndrome and OSAS.

Keywords: ***obstructive sleep apnea syndrome, extrinsic allergic alveolitis, metabolic syndrome***

Rezumat

Sindromul de apnee obstructivă în somn (SASO), reprezintă o problemă de sănătate de o importanță majoră la nivel internațional. Deși are o prevalență de 4-10% în populația generală, este puțin diagnosticat, cu consecințe redutabile asupra calității vieții și a performanțelor profesionale. Studiile observaționale au arătat că lipsa somnului se corelează cu creșterea în greutate și creșterea riscului de obezitate, iar această relație a fost confirmată prin mecanisme fiziopatologice care se potențează reciproc. Prezentăm un caz relevant pentru consecințele tratamentului medicamentos care s-a dovedit eficient în alveolita alergică extrinsecă, tratament care nu a fost susținut însă de o intervenție eficace asupra stilului de viață (ajustarea dietetică corectă și creșterea nivelului de activitate fizică) agravând obezitatea, SASO și sindromul metabolic. Considerăm că acest caz exemplifică în mod pertinent interdependența fiziopatologică între obezitate, sindrom metabolic și SASO.

Cuvinte-cheie: ***sindrom de apnee obstructiva de somn, alveolita alergica extrinseca, sindrom metabolic***

Introduction

Obstructive sleep apnea syndrome (OSAS) is a respiratory disorder which occurs during sleep[(1)] and is manifested by repeated episodes of upper airway obstruction which reduce (hypopnea) or stop (apnea) the oro-nasal air flow resulting in shallow and poor quality sleep. OSAS has an influence on the quality of life and the professional activity by affecting alertness and performance, increasing the risk of traffic accidents, and doubling the general risk of work accidents[(2,3)].

Although OSAS affects 4-10 % of the general population and generates numerous co-morbidities, it is an often ignored diagnosis in medical practice. The cardiovascular effects of OSAS were highlighted in many epidemiological studies[(4,5,6)]; the pathophysiological hypotheses that were put forward are the increased sympathetic tone and the endothelial dysfunction, elements common to both disorders. We report below a case of extrinsic allergic alveolitis (EAA) to molds in an obese patient with OSAS and metabolic syndrome, which eloquently illustrates this pathophysiological relationship.

Case report

A 56 year-old patient from an urban setting, non-smoker, retired for medical reasons, with 2nd degree disability for 8 years, came for admission to the Occupational Medicine Clinic complaining of exertional dyspnea, palpitations, occipital headache, tinnitus, polyphagia, polydipsia, polyuria, excessive daytime sleepiness (EDS) and significant weight gain (55 kg in 8 years, of which 33 kg in the last 3 years).

The medical history shows the following: he is in evidence at the Bucharest Occupational Medicine Clinic for 8 years, since he was diagnosed with professional EAA; he had treatment courses of systemic corticosteroids and immunosuppressants for 4 years, and he was

Table 1 Patient evolution between 2008-2016

Parameters	2008	2013	2016
Weight (kg)	90	113	146
BMI (kg/m^2)	35.15	50.29	57.01
Neck circumference (cm)	44	46.5	50
Waist circumference (cm)	139	145	167
Mallampati Score	-	III	IV
Epworth questionnaire (points)	-	19	21
STOP BANG questionnaire (points)	-	8	8
Berlin questionnaire (risk)	-	Increased	Increased
High blood pressure (stage)	Absent	II	III
Blood glucose (mg/dL)	87	116	194
Glycosylated hemoglobin (%)		5,9	7.8
Total cholesterol	213	266.3	295
HDL-C		32.9	30.1
LDL-C		153	193
Triglycerides	176	307	448
VC	69.2%	68.6%	67.3%
FVC	68.3%	67.3	67 %
FEV1	66.5	68%	61.6%

HDL-C = high density lipoprotein cholesterol; LDL-C = cholesterol low density lipoprotein; VC= Vital Capacity; FVC = Forced Vital Capacity; FEV1 = First second Expiratory Volume – Maximum expiratory volume on the first second of a forced maximum expiration;

admitted every 6 months for clinical, biological and functional assessment at the territorial pulmonology department and Occupational Medicine Clinic, respectively. He is known with stage III high blood pressure, high risk group, mixed dyslipidemia, ischemic heart disease, he had a single drug-converted episode of atrial fibrillation one year ago. He is on treatment with 3 classes of antihypertensive agents (diuretics, calcium blockers and angiotensin-converting enzyme inhibitors), statins, and antiplatelet agents.

Current clinical examination reveals morbid obesity (BMI=57.01 kg/m^2), macroglossia, prominent tonsils (Mallampati score IV), short thick neck (neck circumference 50 cm), waist circumference 167 cm, blood pressure 190/100 mmHg under treatment.

The patient worked at a brewery for 26 years, as a machinery maintenance mechanic in the fermentation station and grain silos, with respiratory exposure to molds, amoebas, grain dust, particles of insecticides, raticides. He was diagnosed with professional allergic alveolitis based on the medical history, the imaging exam (standard chest radiography and CT showing changes of pulmonary fibrosis), the functional respiratory exam (restrictive dysfunction with low alveolar-capillary transfer) and the cytology of the bronchoalveolar lavage fluid (increased lymphocyte number, CD4/CD8 ratio below unity, mast cells present).

For about 4 years he complains of excessive daytime sleepiness (EDS), loud snoring, pauses in breathing during sleep, nocturia (3-4 nighttime urination), morning fatigue, morning headaches, decreased alertness. In 2013 he was diagnosed with OSAS, the manual validation of the first polysomnography (2013) revealed an AHI of 33 events per sleep hour, predominant obstructive apneas, a blood oxygen desaturation index of 29 (average SaO_2: 95% with a minimum of 81%) and a pulse variations index of 5 (33 episodes of bradycardia-tachycardia alternation) (Figure 1). He used an automatic continuous positive airway pressure (CPAP) device with 6-10-14 cmH_2O, with good compliance for 1 year, during which symptoms have considerably improved. He discontinued CPAP for the past 2 years and, after discontinuation, he was involved in two traffic accidents, one of which resulted in multiple fractures requiring prolonged hospitalization, and a plaster corset with bed rest for 6 months.

During the current admission he was diagnosed with type II diabetes mellitus, and treatment with antidiabetic oral agents (metformin 1.5 g/day) was initiated. The patient meets all criteria to define the metabolic syndrome (central obesity, diabetes mellitus, high blood pressure, high triglycerides) (biblio IDF). The main clinical and laboratory data of the patient's evolution during the 3 years from the diagnosis of OSAS are presented in Table 1.

During the current admission the patient was reassessed by polysomnography over a period of 6 hours of sleep, which reconfirmed the severe obstructive sleep apnea syndrome, AHI: 85.3 events per sleep hour, predominant obstructive apneas, with average duration of an event of 15-48 sec, with a desaturation index of 106.7 (average saturation of 74%) and multiple pulse alternation episodes with an index of 46.1 which means 402 events (Figure 2).

Recommendations: **1)** reduced calories diet for weight loss; **2)** compliance to the treatment of co-morbidities; **3)** CPAP treatment with constant pressure of 13 cm H_2O.

Discussion

We report the case of a patient with extrinsic allergic alveolitis due to occupational exposure to molds and dust grains, with a favorable evolution for 8 years under prolonged systemic corticosteroid and immunosuppressive treatment, exogenous morbid obesity driven by the corticoid treatment, with severe OSAS and metabolic syndrome. The metabolic syndrome evolved in severe hypertension and type 2 diabetes mellitus.

The main particularity of this case is the effective therapeutic control of the initial respiratory disease, and the occurrence of an adverse reaction to the treatment which triggered another respiratory disease, with consequences at least as severe. The chronic allergic alveolitis had a favorable evolution due to the interruption of the exposure and the anti-inflammatory and immunosuppressive treatment. The duration of the corticoid treatment was about 4 years with intermittent courses of 3 and 6 months with equivalent daily dosage starting from 60 mg prednisone with gradual decrease, during which the patient gained weight, and progressed from stage I obesity to stage III of extreme obesity. A first conclusion of this case is that, in obese patients, the corticoid treatment requires enhanced efforts of intervention on lifestyle (nutrition and increased physical activity).

The morbid obesity, the metabolic syndrome with both major clinical sides (cardiovascular disease and diabetes), and the OSAS create a pathophysiological triumvirate where the co-existence of the three entities worsens the evolution of each condition separately. In severely obese patients the incidence of OSAS varies between 40-90%[7] but OSAS is a predictive factor of metabolic syndrome independently from obesity[8,9]. There are numerous pathophysiological elements common to the three diseases: the subclinical inflammatory syndrome, the oxidative stress and the endothelial dysfunction, also the imbalance of autonomous system, manifested by increased sympathetic nervous tone and loss of baroreceptor sensitivity to pressure variations.

Fat depositing affects airway function and induces changes in the central mechanisms regulating airway tone and ventilation control. Inflammation is activated by the increase of free fatty acids and is maintained also by the release of pro-inflammatory cytokines (leptin, resistin, and others) from the hypertrophied adipose tissue. Leptin, whose level increases gradually in obese patients, exerts a direct effect on the sympathetic tone in the brainstem. As in other pathophysiological contexts, the increase of the sympathetic tone is not uniform; in obese patients the increased sympathetic tone is particularly manifested on the heart[10]. Ghrelin is a neurohormone secreted by gastric and intestinal cells. The main regulating factor of ghrelin secretion is food intake: pre-prandial levels significantly decrease after ingestion of food. Ghrelin is normally secreted during

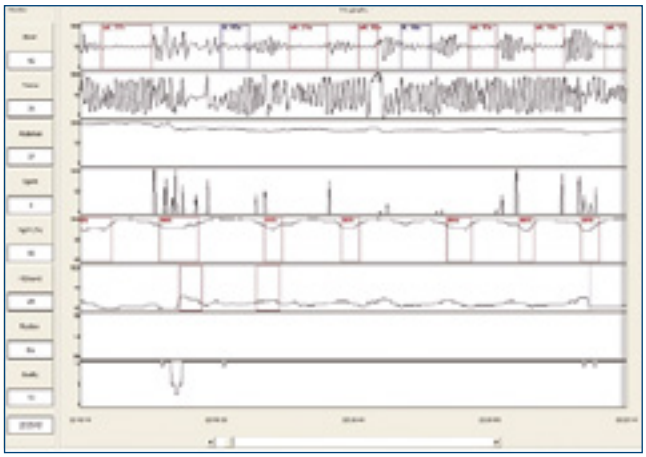

Figure 1. *Graphic representation of a 5-minute interval respiratory recording (8.02.2013)*

periods of slow-wave sleep, and in healthy subjects it has a baroreceptor sensitivity-increasing effect[11]. In obese people the ghrelin level is low[12]). In addition, in obese people with sleep apnea, the 4th period of REM sleep, in which ghrelin is physiologically secreted, decreases[13]. The decrease of ghrelin both by peripheral mechanism (secondary to obesity) and by alteration of sleep architecture in sleep apnea, favors loss of baroreceptor sensitivity to increased blood pressure, a phenomenon that contributes to permanent hypertensive status.

The metabolic syndrome is a major risk factor for chronic heart disease, atherosclerosis and diabetes. The installation of insulin resistance contributes to cardiac remodeling and fibrosis by altering the energy metabolism in the myocardial cell; endothelial dysfunction and atherosclerotic process development maintain an increased peripheral resistance and alter the large vessel walls, increasing blood pressure and afterload. Overtaking the possibilities of the pancreas to synthesize sufficient amounts of insulin to overcome the resistance of target organs to insulin triggers manifest diabetes.

The contribution of OSAS to this triumvirate is mainly by intermittent hypoxia, responsible for oxidative stress, alterations of lipid metabolism in liver cell, decreased baroreceptor sensitivity, impaired nocturnal profile of renin and aldosterone secretion[14] and decreased cardiac performance index[15,16]. High sensitivity C-reactive protein was positively associated with AHI and negatively associated with the nadir SaO_2 (Kim) and the atherogenic risk is higher[17]. The arrhythmogenic risk in OSAS was explained by repetitive Mueller maneuvers performed by patients during sleep that increase intrathoracic pressure and transvalvular gradients, ventricular wall stress and afterload[18,19]. Also, changes have been described for the expression of myocardial potassium channels[20] which may prolong the QT interval with pro-arrhythmogenic effect and an increase in the intra-atrial and interatrial conduction time, favoring the occurrence of atrial fibrillation[21]. The repetitive nocturnal hypoxemia in OSAS is a risk of sudden post-infarction death[22,23].

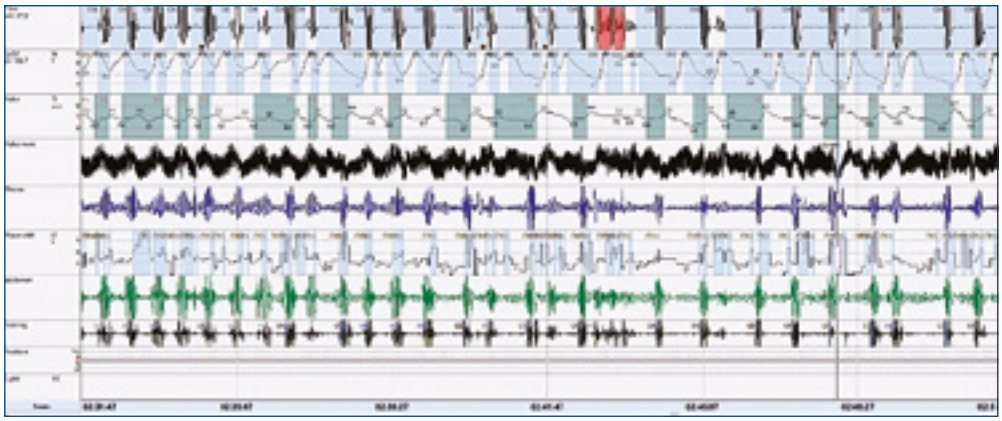

Figure 2. *Graphic representation of a 20-minute interval respiratory recording (20.10.2016)*

The daytime sleepiness and the humoral profile of the metabolic syndrome reduce the energy consumption and aggravate the obesity. All these pathophysiological relationships substantiate the mutual conditioning of the three elements of the obesity, metabolic syndrome and OSAS triumvirate, increasing the severity of each entity[24,25]. A natural corollary illustrated by the reported case is that an interruption of the common pathophysiological chains of the triumvirate is required in order to provide a real therapeutic benefit. In obesity as severe as that of our patient, the only measure having a fast effect would be bariatric surgery and, at this point, respiratory function might allow the intervention. As for the OSAS, resuming the CPAP treatment is mandatory. Both interventions are currently limited by non-medical reasons. The only treatments that the patient can benefit (the treatment of the hypertensive disease and of the diabetes) have limited medium- and long-term effects as they address the effects and not the actual pathogenic mechanisms.

Conclusions

Several conclusions can be drawn from this case, namely: in patients with professional allergic alveolitis, exposure cessation as soon as possible is a positive prognostic factor. The second conclusion is the approach of obese patients requiring cortisone treatment, whose medical treatment must be doubled by a sustained intervention on lifestyle.

Obesity, metabolic syndrome and OSAS are mutually reinforcing pathophysiological conditions, with multiple interferences. Therefore, in morbid obesity associated with vascular disease and diabetes, therapeutic solutions are required, addressing both obesity and the effects of intermittent hypoxia, i.e., bariatric surgery and CPAP treatment. ■

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