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Review Article
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Acromegaly and Sleep Disordered Breathing

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Abstract

Acromegaly is the result of oversecretion of growth hormone and IGF-1 and the disease can affect several organ systems. Sleep Disordered Breathing (SDB) is a frequent disease in acromegaly patients. The mechanism of SDB is somewhat different in acromegaly patients than SDB in normal population. Although central apneas can be seen, obstructive apneas according to structural changes complicate the course of the disease. Treatment of SDB is as important as the treatment of acromegaly. In this review, we searched the medical literature and summarized the etiology, pathogenesis, mechanism of SDB development and treatment of SDB in acromegaly patients.

Keywords: Acromegaly; Sleep disordered breathing; Obstructive apnea; Central apnea; Positive airway pressure

Introduction

Sleep Disordered Breathing (SDB) is a common disorder characterized by fragmented sleep due to recurrent episodes of apnea and hypopnea [1]. Two different kinds of apnea can be seen in patients; obstructive and central. Obstructive Sleep Apnea (OSA) occurs as a result of obstruction at the upper airways but Central Sleep Apnea (CSA) ensues in the absence of rib cage and abdominal movements which is a sign of loss of ventilatory drive [2]. Although SDB affects 2-4% [3] of the normal population its prevalence can increase in specific patient groups or diseases. Especially patients with endocrine diseases like acromegaly, hypothyroidism, diabetes and Cushing's syndrome are more prone to have SDB [2].

Acromegaly is a rare disease (estimated prevalence is 1:140,000-250,000) that affect both sexes and cause abnormal growth of bony structures, visceral organs and soft tissues due to over production of Growth Hormone (GH) and insulin like growth factor (IGF-1) after closure of epiphyseal plates [4,5]. The presence of SDB in acromegaly was described at the 19th century first by Roxburg and Collins [6]. They described heavy snoring and daytime sleepiness in an acromegaly patient. To date, retrospective and prospective studies have shown the presence of SDB in acromegaly patients and reported prevalence roughly 60% [7-19]. High body mass index, neck circumference, GH and IGF1 levels, older age, and increased index-finger circumference are known predictors of SDB in acromegaly [20]. Also, narcolepsy [21], cheyne stokes respiration in sleep [22] and restless leg syndrome [23] were reported in acromegaly patients.

Mechanisms of SDB in Acromegaly

There are different kinds of presumptive mechanisms to cause SDB in acromegaly. These are changes in bony structures and soft tissues (hypertrophy and edema), obesity/overweight, mechanical alterations of the upper airway and alterations at neuromuscular control of ventilation [24]. The main triggering point is the increased levels of GH and IGF-1. Many studies showed higher frequencies of SDB in active acromegalic patients with a positive correlation with GH and IGF-1 levels [9,13,17,24], but van Haute et al. [19] couldn't observe this correlation. The two types of apnea may be seen in acromegaly; obstructive apnea and central apnea. Although obstructive apnea is more frequent, some studies indicate higher level of GH and IGF-1 levels in central apnea [10].

Changes in Bony Structures and Soft Tissues

Because obstructive apneas are more frequent, skeletal abnormalities are initially incriminated. Several anatomical abnormalities can occur in acromegalic patients; Hochban et al. [25] showed a dorsocaudal rotation of the mandible which leads to posterior displacement of the tongue, more vertical bony growth of the face which causes narrowing of the bony frame work of the nasopahrynx. However, these findings were not supported by other investigators. Also, in the study of Dostalova et al. [26] skeletal abnormalities in acromegaly patients with SDB were different from those in apneic patients without acromegaly and they reported the role of soft tissue changes be more important in obstructive apneas of acromegaly [26]. Although anatomical deformities can cause apneas, they are not sufficient to explain the whole course.

Growth hormone and IGF-1 regulates metabolism and body composition [27]. Due to over secretion of these hormones in acromegaly, an increase in body water and lean body mass cause altered body composition [28]. These changes in soft tissue can occur locally or generally. Local changes are deposition of glycosaminoglycan and collagen, and tissue edema [1]. Also, Kamenicky et al. [29], showed that tissue edema is due to increased renal sodium reabsorption, by direct stimulation of epithelial sodium channel by GH and IGF-I, which causes generalized edema. Patients with generalized edema also have a high prevalence of SDB, and this may be related to repositioning of the fluid from the lower extremities to the neck while the patient is lying, casing pharyngeal obstruction [30,31]. The soft tissue swelling of the upper airways leads to obstruction in acromegalic patients [16,27,32]. Edematous and polypoid nasal mucosa can block nasal passages and can cause altered sleep quality [33].

The increase in the size of the pharyngeal structures either due to depositions or edema can be shown by Magnetic Resonance Imaging (MRI). MRI, compared with radiographs, has the advantage

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of more precise delineation of the tongue volume [34]. Herrmann et al. [14], studied tongue volume by use of MRI and reported 36% greater in acromegalics than control patients and showed decrement in the signal intensity of the tongue after acromegaly treatment which indicates water/edema resolution. van Haute et al. [19] showed serious downsizing in thickness of the tongue, soft palate, pharyngeal walls and the opening of oropharyngeal space after treatment in one patient with MRI.

Rosenow et al. [20] reported a relatively high frequency of SDB in patients with acromegaly, with a positive correlation with GH/IGF1 levels, age, neck and index-finger circumference as measures of soft tissue hypertrophy. Interestingly, in this study, index finger circumference greater than or equal to 8.5 cm was associated with frequency of desaturations [35].

Mechanical Alterations

Changes in the structural component of the pharynx, tongue and bones with hypertrophy of parapahryngeal and retropharyngeal soft tissue deteriorate the patency of the upper airways. Isono et al. [36], compared acromegaly patients with and without OSAS, and found that the former group have more collapsible airways. Patients in this study were not obese and body mass indices were lower than 27 kg/m^2. Also, our study [37] revealed similar findings that acromegaly patients with and without OSAS have similar BMIs.

Obesity/Overweight

Some studies reported that excessive weight is associated with SDB in acromegaly patients [1,24], but also SDB can manifest independent of weight in acromegaly [35]. Although there are not sufficient evidence in the studies, increase of weight can be a risk factor of SDB development in acromegaly.

Central Nervous System Changes

The frequency of central apnea is increased in acromegaly patients. Grunstein et al. [10] reported central apnea in 20% of the 54 acromegalic patients. The suspected mechanism for increased central apnea was GH and IGF-1 induced central chemosensitivity to hypercapnia. Somatostatin, also known as growth hormone-inhibiting hormone, is a peptide hormone which controls the secretion of GH and affects neurotransmissions. Grunstein et al. [38] postulated that the loss of the inhibitory pathway of somatostatin causes loss of regulation on the central respiratory control in the brainstem and hypothalamus [10]. On the other hand, upper airway closure with inhibition of ventilation and increased ventilatory gain are other potantial etiologies for central sleep apnea development [39].

Consequences of SDB in Acromegaly

Cardiovascular complications

Cardiovascular complications are the major cause of mortality and morbidity in acromegaly. The risk of cardiovascular complications increases even in mild OSAS [40,41]. These complications may occur both due to the direct affect of acromegaly on myocardium (hypertrophy, myopathy or arrhythmias) and affect of SDB on cardiovascular system. Repeated hypoxia/reperfusions cause oxidative stress, inflammation, tissue injury and eventually lead to hypertension, coronary artery disease, arrhythmia and heart failure [42]. Also, SDB affects the limbic system (amygdala and hippocampus) and leads to dysregulation of blood pressure [43]. Coronary artery disease prevalence changes between 3 to 37% in different series, arrhythmias were present in 40% of subjects and arterial hypertension was reported in 30-405 of patients [24].

Neurocognitive complications

The frequency of SDB (between 20 and 80% of patients) in acromegaly is greater than in normal population. Owing to fragmented sleep, these patients suffer from daytime sleepiness, poor memory, loss of concentration, irritability, increased risk of accidents and depression [24,44-48].

Endocrine complications

The relationship between endocrine disease and SDB is complex. While some endocrine problems can cause SDB, also SDB can lead to endocrine diseases with probable mechanisms of hypoxemia, hypercapnia, and fragmented sleep [2]. Nocturnal awakenings cause cortisol and catecholamine release and eventually hormonal axis alteration. Increased cortisolemia is a risk factor for metabolic syndrome [49]. Moreover, GH exhibits lipolytic and insulin resistance effects and IGF-1 cause anti-lipolysis and insulin sensitivity [28]. Dysregulation of glucose and lipid metabolisms, due to excessive GH and IGF-1, are present in acromegaly patients with SDB. In the study of van Haute et al. [18], AHI was significantly higher in diabetic acromegaly patients. Davi et al. [11], had similar findings; in their study, AHI of diabetic patients was higher than non-diabetics, and hormonally uncontrolled acromegalic patients were overweighed, IGF-1 levels and diabetes frequency were higher than hormonally controlled patients.

Treatment

Treatment of acromegaly patients with SDB should be directed towards both acromegaly and sleep problem. It is postulated that if the acromegaly can be controlled, due to hormonal and structural changes, SDB will regress. But the effect of acromegaly control on the course of SDB is controversial [11,18,34,50]. Some studies have shown that SDB can remain even after complete hormonal treatment of acromegaly because of permanent structural changes [1,11,24]. In our study, we have shown some regression in the severity of SDB but there was no reduction in the necessity of positive airway pressure (PAP) therapy [37]. Consistent with our results, ACCP Sleep Medicine Board advice respiratory specialists to remain vigilant for evaluating the patients for PAP therapy [51].

Acromegaly treatment

Control of GH and IGF-1 secretion is the currently available main goal of the treatment in acromegaly. Optimal treatment should normalize GH/IGF-1 levels, preserve normal pituitary functions, prevent recurrence, be effective for long term, and relieve comorbidities (cardiovascular and metabolic complications) [24]. Although there is no single perfect treatment modality to control the disease, three treatment options for acromegaly are present; medical, surgical or radiotherapy.

- Surgery allows removal of the adenoma or reduction of the tumoral mass. It is cost effective and most of the patients are treated with surgery due to rapid initiation. However, large tumor size and invasive tumors, high levels of circulating GH during preoperative period, are harbingers of surgical failure [18, 24,52,53]. Overall cure rate of transsphenoidal surgery is 44-76% [54].

- Radiotherapy reduces tumor volume and GH/IGF-1 values but onset of action is slow and hypopituitarism may develop. After improvements in surgical techniques popularity of radiotherapy decreased [55-57].

– Pharmacotherapy can be started as first line therapy, especially in patients with contraindications to surgery, or can be applied following surgery or radiotherapy. Dopamine agonists, somatostatin receptor ligands and GH receptor antagonist (pegvisomant) are the currently available drugs for pharmacotherapy [24].

SDB treatment

Treatment strategies of acromegaly may help to relive the symptoms of SDB. Surgical treatment of acromegaly can improve sleep-disordered breathing. Cadieux et al. [58] treated two acromegaly patients with tracheostomy, successfully. In the study of Mickelson et al. [59] they reported that transsphenoidal hypophysectomy or transsphenoidal hypophysectomy and radiation treatment of acromegaly improved SDB, but also reported that uvulopalatopharyngoplasty did not improve SDB. Some studies showed significant improvement or cure after adenomectomy [18,60], while others found persisting nocturnal problems [61].

Many studies reported that SDB symptoms and severity in acromegaly patients improved with pharmacotherapy [13,62,63]. Octreotide and pegvisomant treatments have demonstrated improvement in patients with acromegaly and SDB [13,35,50,58,63]. Although hormone control strategies may reduce the severity, SDB does not completely disappear in acromegaly patients. In our recent study, 14 acromegaly patients had SDB and 12 of the cohort had indication of PAP therapy. After 6 months of acromegaly remission, 11 of 12 patients remained to be indicated for PAP therapy [37].

Conclusion

SDB may develop in acromegaly patients due to direct excessive hormonal activity on central nervous system (inhibition of somotostatinergic pathways), structural changes (soft tissue and bony structure) or aberration in the regulation of metabolism. Treatment of acromegaly may relieve SDB course but does not cure. In all acromegaly patients with SDB, treatment strategies for SDB must be planned concomitantly with acromegaly treatment.

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