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Obstructive sleep apnea and dermatologic disorders

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Abstract Obstructive sleep apnea (OSA) is present in at least 2% of women and 4% of men, and its prevalence is increasing, because a major predisposing factor for OSA is a high body mass index. Psoriasis has the most strongly substantiated link with OSA, where the relationship may be bidirectional. Dermatologic disorders may be comorbid with OSA due to several factors: (i) the heightened proinflammatory state in OSA, which can occur independent of body mass index, and may exacerbate inflammatory dermatoses; (ii) intermittent hypoxemia may promote neovascularization and tumor growth in certain cancers, such as melanoma; (iii) obesity, present in majority of OSA patients, can be associated with a heightened proinflammatory state; (iv) upper airway obstruction due to local tumors or soft tissue swelling due to physical urticaria or angioedema; (v) acute nasal congestion in the atopic patient with allergic rhinitis; (vi) dermatologic disorders associated with other OSA risk factors (eg, acanthosis nigricans and metabolic syndrome); and (vii) a high sympathetic tone (eg, in atopic dermatitis) and resultant sleep fragmentation contributing to upper airway instability during sleep. In many instances, the dermatology patient with OSA may have other medical and psychiatric comorbidities that are also associated with increased OSA risk.

Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder[1] that is characterized by upper airway narrowing or closure during sleep, while respiratory effort continues. OSA is characterized by repetitive episodes of partial (resulting in a *hypopnea*) or complete (resulting in an *apnea*) upper airway obstruction during sleep.[1] Conservative estimates indicate a 4% prevalence of OSA in men and 2% prevalence in women[1]; however, the true prevalence of OSA is likely higher.[1] Apneas and hypopneas are believed to have similar underlying pathophysiology and consequences, and therefore there is little clinical value in distinguishing patients with predominantly apneas versus predominantly hypopneas.[1] By definition, the obstructive respiratory events (hypopnea or apnea) last for at least 10 seconds and are associated with a decrease in the blood oxygen saturation and typically terminated by brief arousals from sleep,[1] which result in sleep fragmentation and manifest as cortical arousals on the electroencephalogram. *Central apneas* are caused by the failure of ventilatory control centers in the central nervous system to initiate ventilatory effort during sleep.[1] Central apneas are typically present in conjunction with other medical comorbidities such as congestive heart failure, stroke, and neurologic disorders, or secondary to substances that have a respiratory depressant effect such

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as opioids, and in high altitudes.[1] Patients with central sleep apnea have predominantly central events; OSA patients may also have variable amounts of central apneas even though they have predominantly obstructive events.[1] *Mixed apneas* have features of both obstructive and central apneas. OSA is associated with sympathetic nervous system activation, systemic inflammation, metabolic dysregulation, increased coagulation, and endothelial dysfunction.[2] Positive airway pressure is a mainstay of OSA therapy.[3]

Table 1 has summarized the diagnostic criteria for OSA. In adults, OSA is diagnosed, when ≥5 apneas or hypopneas per hour of sleep (or an apnea-hypopnea index [AHI] of ≥5 events per hour) are present in conjunction with sleep-related complaints or if an AHI ≥15 is present.[1]

A major predisposing factor for OSA is excess body weight,[1] and it is estimated that about 60% of moderate to severe OSA is related to obesity.[1] Alternately, OSA may augment insulin resistance and exacerbate the metabolic dysfunction of obesity.[2] OSA in patients with normal or below normal body mass index (BMI) is more likely to be related to localized obstruction due to soft tissue growth (eg, adenotonsillar hypertrophy or less commonly a local malignancy), nocturnal nasal congestion (eg, due to rhinitis), or structural abnormality, such as maxillomandibular malformation[1]or sleep fragmentation leading to increased upper airway collapsibility during sleep. Hypothyroidism and acromegaly are risk factors for OSA.[1]

The prevalence of OSA in children is estimated to be 1-4% but may be higher due to the obesity epidemic in children.[1] Pediatric OSA (Table 1) can present with apneas and hypopneas or a pattern of obstructive hypoventilation (associated with hypercapnia) and behavioral problems, hyperactivity, attention problems, or learning difficulties.[1] Patients with obstructive hypoventilation typically present with continuous snoring without the pauses or arousals that common in adult OSA patients.[1] Children with OSA therefore may experience hypercapnia, hypoxemia, or both.[1] Children have a higher threshold of arousal from sleep, and in contrast to adults, do not typically experience cortical arousals as a result of the upper airway obstruction in OSA; however, they may have body movements or autonomic arousals (eg, tachycardia).[1] Diaphoresis may be observed as a feature of OSA in children.[1] Adenotonsillar hypertrophy and obesity are the most common predisposing and precipitating factors for OSA in children.[1] Other commonly encountered risk factors in the pediatric age group include craniofacial abnormalities, especially midfacial hypoplasia or micrognathia, neuromuscular disorders that increase the risk of upper airway collapse, or spastic disorders that may affect breathing due to weakness or incoordination of the upper airway muscles.[1] Secondhand tobacco smoke exposure has also been associated with snoring and OSA.[1]

Several factors may contribute to the association of OSA and dermatologic disease, and this relation may be bidirectional in the case of some inflammatory disorders, such as psoriasis.[4] Some of the factors include the following: (i) The heightened proinflammatory state caused by OSA, which can occur independently of BMI,[5] may be a predisposing and/or precipitating factor for inflammatory dermatoses in patients, who are at increased risk for developing these disorders. For example, a study of OSA patients found that serum levels of inflammatory mediators interleukin (IL)–23 and C-reactive protein were significantly elevated in OSA patients in contrast to controls without OSA[6]; a 3-month course of continuous positive airway pressure (CPAP) was associated with a significant decrease in serum levels of IL-23 and C-reactive protein in the OSA patients, and changes in IL-23 levels were positively correlated with improvement in the AHI and C-reactive protein levels.[6] (ii) Intermittent hypoxemia may promote neovascularization of certain cancers, such as melanoma, and thereby promote tumor growth and expansion. (iii) Obesity is a significant risk factor[1] for both adult and pediatric OSA, and visceral adipocytes release proinflammatory cytokines that can explain the relation between central obesity and OSA via a feed-forward mechanism.[5] The heightened proinflammatory state in the patient with visceral adiposity may also be a predisposing or precipitating factor for inflammatory dermatoses in some patients.[7] (iv) Upper airway obstruction due to tumors can affect the upper airway (tongue, nasopharynx, oropharynx). (v) Episodic nasal congestion in the atopic patient with allergic rhinitis could be associated with OSA; however, a study of 150 adult OSA patients[8] reported no significant difference in polysomnographic findings, including indices of OSA, in patients (55 of 150) who had persistent allergic rhinitis versus the remaining 95 OSA patients without nasal problems. (vi) When the dermatologic disorder is associated with other OSA metabolic risk factors (eg, acanthosis nigricans in a patient with metabolic syndrome and diabetes who also has OSA). (vii) A high sympathetic tone and resultant sleep deprivation and sleep fragmentation may further exacerbate OSA by contributing to upper airway instability during sleep[9]; a high sympathetic tone may be present in certain dermatologic disorders such as atopic dermatitis (AD)[10] where a high level of arousal during sleep, unrelated to scratching, may be present, even when the AD is in remission. Psychiatric comorbidities[11] in dermatologic disease such as a major depressive disorder and posttraumatic stress disorder, which are associated with a high sympathetic tone, are also more commonly associated with OSA.[12]

The interface between sleep and dermatologic disease can be complex and multifactorial.[13] In this paper we have reviewed the literature on the association of OSA and dermatologic diseases. OSA may be a factor in complex medical patients (eg, diabetic patient with complications) with treatment-resistant dermatologic problems.[14] The possible role of OSA in dermatologic manifestations of systemic diseases, which may also be comorbid with OSA, are not discussed in this chapter.

Studies from the Danish National Patient Registry have evaluated overall dermatologic morbidity before and after OSA diagnosis.[15,16] OSA patients representing all age groups from the Danish National Registry (1998-2006) had a higher

frequency of disorders of the skin and subcutaneous tissue at least 3 years before their OSA diagnosis (odds ratio [OR] = 1.18, 95% confidence interval [CI] 1.07-1.30)[16] and were about twice as likely (OR = 2.12, 95% CI 1.33-3.38) to develop a disorder of the skin and subcutaneous disorder in the 3 years after diagnosis.[16]

The analysis was repeated in the pediatric OSA population (aged 0-19 years) and revealed an OR of 1.32 (95% CI 1.02-1.71)[15] of having a skin and subcutaneous disorder before OSA diagnosis and an OR of 1.42 (95% CI 1.06-1.89) after OSA diagnosis.[15] These results indicate that there is an overall, and possibly a bidirectional, relationship between OSA and dermatologic disorders but do not help in determining if the relationship of OSA with certain dermatologic disorders is stronger and driving the relationship.

Specific disorders

Acanthosis nigricans

There is a single case study[17] of a 15-year-old girl presenting with progressive worsening of OSA between ages 13 to 15 years, with severe acanthosis nigricans of the neck and axillae in conjunction with severe obesity (body mass index [BMI] = 46.7 kg/m^2) and multiple other medical comorbidities. The patient had evidence of insulin resistance, hypertension, dyslipidemia, polycystic ovary syndrome, and nonalcoholic fatty liver disease. In this case, multimorbidity, likely mediated by severe obesity, appears to underlie the acanthosis nigricans and OSA, but acanthosis nigricans and OSA were likely unrelated.

Acne vulgaris

A single-arm, open-label trial evaluated 0.5 mg/kg isotretinoin in participants with severe acne vulgaris.[18] Participants were assessed for acne severity, depression, excessive daytime sleepiness (EDS), and sleep variables via polysomnography (PSG) before and after 1 month of treatment. Participants experienced improved sleep latency and sleep efficiency but no change in the AHI. Polycystic ovary syndrome, which affects 6-7% of reproductive-aged women, can be associated with acne, hirsutism, and male-pattern alopecia, and one of the complications of polycystic ovary syndrome is OSA.[19]

Atopic dermatitis (eczema)

There are several studies[20–22] of OSA and AD (also identified as eczema) in pediatric populations. One study examined the prevalence of atopic disease in children referred for PSG. They found that children with OSA did not have an increased risk of dermatitis (OR = 0.95, 95% CI 0.63-1.43), after adjusting for tonsillar hypertrophy, obesity, gender, and age.[20] The authors confirmed this finding in an additional pediatric population, where there was no association of dermatitis with OSA (adjusted OR = 0.82, 95% CI 0.56–1.21).[21] In a study of 21 children aged 6 to 16 years with dermatitis attending an allergy and dermatology clinic and 20 controls without dermatitis recruited by advertising,[22] the children with dermatitis, who had greater sleep fragmentation on PSG, had a mean (standard deviation [SD]) AHI of 0.23 (0.65) versus a mean (SD) AHI of 0.31 (0.45) in the controls. The children with dermatitis had greater neurocognitive deficits than controls.[22] There was no clear association between the PSG findings and the neurocognitive parameters.[22] It was previously reported that children with AD had increased arousals and awakenings, compared with control children with mild snoring.[10] There does not appear to be sufficient evidence to substantiate a relationship between the apneas and hypopneas characteristic of OSA and AD in children.

In contrast to the pediatric population, there appears to be an association of OSA and AD in adults.[23,24] A retrospective cohort study of 1222 newly diagnosed OSA patients between 2000 to 2005 from Taiwan's National Health Insurance database examined the incidence of AD in 1222 patients with newly diagnosed OSA between 2000-2005 and matched non-OSA comparison group recruited from 2000-2006.[23] All patients were tracked for 5.5 years from the index date. OSA patients were 1.5 times more likely to develop AD than the non-OSA controls (adjusted hazard ratio [HR] = 1.5, 95% CI = 1.15-1.95) after controlling for age, gender, hypertension, coronary heart disease, obesity, allergy, allergic rhinitis, asthma, monthly income, and geographic location. The HR was elevated in male patients (HR = 1.53, 95% CI 1.14-2.06) and patients diagnosed as children ≤18 years of age (HR = 4.01, 95% CI 1.57-10.26). A case study[24] of a 62-year-old man with dyshidrosis (pompholyx) affecting the palms and severe OSA, marked oxygen desaturation in conjunction with the apneas, and severe sleep fragmentation reported complete resolution of the hand dermatitis, which had been previously refractory to steroids, after successful treatment of the OSA with nasal continuous positive airway pressure therapy. The authors discuss that the sleep loss, hypoxemia, and autonomic arousal associated with OSA may have promoted tissue inflammation in dyshidrosis.[24]

Allergic contact dermatitis

One study evaluated the effect of CPAP mask composition in adult participants undergoing CPAP treatment for OSA comparing individually molded masks (71%) versus industrial silicone masks (28%).[25] Participants with a mean respiratory disturbance index of 53 ± 25/hr and a mean CPAP treatment time of 19 ± 17 months had a mask-related treatment-emergent adverse event (TEAE) rate of 50%. Individually molded masks reduced nasal abrasions and red eyes and had fewer allergic contact reactions than silicone masks (13% vs 5%). The presence of a humidifier did not change the rate of TEAEs between groups. A case study of a 50-year-old nonatopic patient who was using nasal CPAP for OSA[26] describes

the development, after about 1 year, of an erythematopapular vesicular eruption under the black neoprene attachment bands, followed by hair loss and then regrowth of pigmented hair. Patch testing confirmed contact allergy to thiourea derivatives, which is used in the manufacturing of neoprene.[26] The authors discuss the occurrence of depigment hair suggesting contact leukoderma; however, this had not been previously described with thiourea derivatives.[26] The mask straps were covered in cotton, allowing the patient to continue CPAP. Allergic contact dermatitis (ACD) may be a TEAE for OSA patients.

Cicatricial pemphigoid

A case series of 142 patients with cicatricial pemphigoid, a chronic mucosal blistering disorder with a predilection for subsequent scarring, found that 24% had nasal manifestations with nasal obstruction in 79% of participants with nasal lesions.[27] Of these patients, two were diagnosed with OSA. Lesions were found in the larynx in 9% and in the oropharynx and hypopharynx in 8% of patients.[27] Cicatricial pemphigoid may be a direct cause of OSA due to upper airway obstruction.

Diabetic foot ulcers

A case series[28] of three men aged 57 to 63 years with type 2 diabetes examined the association of severe OSA and acutely infected diabetic foot ulcers. A single study examined the association of OSA and diabetic foot ulcers.[28] Two patients had not been previously diagnosed with OSA, and one had a prior diagnosis of severe OSA but was noncompliant with CPAP therapy. The two undiagnosed patients had AHI of 41 and 49, respectively, and were successfully treated with CPAP and standard wound care for the ulcers. Both had marked improvement in wound granulation and healing after CPAP therapy. The third patient refused to consider CPAP therapy and experienced poor wound healing and *Pseudomonas* infection despite aggressive wound therapy.[28] OSA and diabetes often coexist, and untreated OSA may impair the healing of diabetic foot ulcers.

Hyperpigmentation

A case study described a young man presenting with obesity (BMI 50 kg/m^2) and severe OSA, whose weight increased from 293 pounds to 525 pounds over the course of 5 years.[29] The patient could only sleep by sitting upright and leaning his head against the wall. He had developed hyperpigmentation and lichenification on his forehead as a result. The patient had been prescribed nasal CPAP, which had not been effective due to the significant weight gain. The patient's CPAP was retitrated to an increased pressure to adjust for weight gain. Hyperpigmentation may be a TEAE for patients with OSA, who adopt unusual sleeping positions due to insufficient OSA treatment.

Hypertrophic burn scars

Case studies of two boys, aged 10 and 14 years, with hypertrophic burn scars after severe facial and upper body burns, describe the onset of severe OSA (most likely due to restriction of chest wall movement due to a constrictive garment) with significant oxygen desaturation, as a result of wearing pressure garments for the treatment of hypertrophic burn scars.[30] Both children experienced improvement in OSA symptoms after removal of the pressure garments. The authors stress that long-term use of pressure garments, as is sometimes recommended, could lead to significant hypoxemia-related complications.[30] OSA may be a TEAE from the treatment of hypertrophic burn scars.

Malignancies

In a 20-year follow-up study of 397 OSA patients from a town in western Australia (OSA diagnosed with a single night of sleep recording using a four-channel portable home monitoring device in November-December 1990), moderate to severe OSA was significantly associated with all-cause mortality (HR = 4.2, 95% CI 1.9-9.2), cancer mortality (HR = 3.4, 95% CI 1.1-10.2), and incident cancer (HR = 2.5, 95% CI 1.2-5.0).[31] In a prospective cohort study of approximately 5.6 million individuals with OSA from an employee-sponsored health insurance database, the risk of melanoma (HR = 1.14, 95% CI 1.10-1.18) was significantly higher in OSA patients, along with the adjusted risk of pancreatic and kidney cancer.[32] Among individuals with a cancer diagnosis, the presence of OSA was not associated with an increased risk for metastases or death.[32] A study examined the relation between the severity of sleep-disordered breathing and the aggressiveness of cutaneous malignant melanoma (CMM) in 56 CMM patients.[33] OSA with an AHI $\geq$5 was present in 60.7% of CMM patients, and severe OSA (AHI $\geq$30) was present in 14.3% of patients.[33] In a fully adjusted multivariate analysis, the AHI (OR = 1.08, 95% CI 1.02-1.14) was significantly and independently associated with increased melanoma growth rate, as were other indices of sleep-disordered breathing, such as the oxygen desaturation indices (ODI) of 3% ($ODI_{3\%}$) and 4% ($ODI_{4\%}$) (OR = 1.08, 95% CI 1.02-1.11; OR = 1.1, 95% CI 1.02-1.2). The severity and frequency of sleep-disordered breathing (as measured by the AHI, $ODI_{3\%}$, and $ODI_{4\%}$) were independently associated with a higher growth rate of melanoma, greater CMM thickness (Breslow index), higher mitotic rate, and more frequent ulceration, factors that are all associated with worse CMM prognosis.[33] The authors propose the possible role of intermittent hypoxemia in the formation or spread of the malignancy, via intermediate molecules such as hypoxia-inducible factor 1, a carcinogenesis-related molecule, and vascular endothelial growth factor, which promotes neovascularization of the cancer and therefore its expansion.[33] Other factors implicated include oxidative stress and a high degree of systemic inflammation in OSA.[34]

Table 1 Diagnostic criteria for obstructive sleep apnea (OSA)[1]

Adults (criteria A + B or criterion C must be present)	Pediatric (<18 years; may use adult criteria for ages 13-18 years; criteria A + B must be present)
A. Presence of one or more of the following: o Complaints of sleepiness, nonrestorative sleep, fatigue, or insomnia o Awakenings from sleep with choking, breath holding, or gasping o Habitual snoring and/or breathing interruption during sleep reported by another person (eg, bed partner) o Diagnosis of hypertension, mood disorder, cognitive dysfunction, stroke, coronary artery disease, congestive heart failure, atrial fibrillation, or type 2 diabetes	A. Presence of one or more of the following: o Snoring o Labored, paradoxical, or obstructed breathing during sleep o Daytime sleepiness, behavioral problems, hyperactivity, or learning problems
and	B. Overnight polysomnography demonstrates one of both of the following: o One or more obstructive apneas, mixed apneas, or hypopneas per hour *or* o A pattern of obstructive hypoventilation defined as ≥25% of the total sleep time with hypercapnia (partial pressure of oxygen in arterial blood >50 mm Hg) in association with snoring, other signs of upper airway resistance, or paradoxical abdominal motion during breathing
B. Sleep study (in laboratory polysomnography or out-of-center sleep testing) demonstrating five or more predominantly obstructive or mixed apneas and hypopneas per hour	
or	
C. Sleep study (in laboratory polysomnography or out of center sleep testing) demonstrating ≥15 predominantly obstructive or mixed apneas or hypopneas per hour	

A single case of mycosis fungoides (MF) associated with severe OSA has been reported.[35] A 38-year-old woman with a 9-year history of MF presented with snoring and observed apneas. The patient had a BMI of 24.6 kg/m^2. PSG confirmed a diagnosis of severe OSA (AHI = 67.5), and MRI had neoplastic infiltration of the tongue base and posterior pharynx wall, causing a marked reduction in posterior airways space and predisposing to upper airway collapse during sleep.[35] The authors discuss that although the association of OSA with tumors of the neck is not common, in all reported cases (including this patient) the neck tumor caused a reduction of posterior airway space (defined as the distance between the tongue base and posterior pharynx wall), which is the most important predictive metric for OSA.[35] OSA symptoms were treated with CPAP. The MF was treated with chemotherapy followed by radiotherapy. At 1-year follow-up, there were no new MF lesions and previous lesions had been reduced in size. A follow-up PSG revealed a marked improvement in OSA with an AHI = 2, with no CPAP. MF may be a direct cause of OSA due to infiltration of the posterior airway space.

In a retrospective chart review[36] of 56 patients with tumors in the head and neck region who underwent PSG, the majority (68%) had squamous pathologic conditions and 84% met the criteria for OSA. Prior radiation increased the risk of OSA to 88%; it was 67% in patients without prior irradiation.[36]

We found three case reports concerning OSA as a direct result of cancer.[37–39] The first case report[39] concerned a rapidly progressive OSA in a 71-year old man after irradiation of his neck for squamous cell carcinoma of the tonsillar pillar and vocal cord; supraglottic edema and development of hypothyroidism after neck irradiation were factors responsible for the OSA. The second case study[38] described a 20-year-old man with basal cell nevus syndrome (Gorlin-Gorlitz syndrome), who complained of snoring, daytime hypersomnolence, and poorly controlled hypertension. He was diagnosed with OSA; his OSA symptoms were successfully treated with nasal bilevel positive airway pressure.[38] The third case report was of a 71-year-old woman who presented with obesity, snoring, daytime hypersomnia, and nasal bleeding and had severe OSA with an AHI of 73.5.[37] A mass on the nasal septum was identified, and biopsy revealed malignant melanoma. Palliative radiation therapy reduced the tumor size, decreased her AHI to 13.5, and assisted in reducing daytime hypersomnia and snoring. Cancer appears to predominantly be a direct cause of OSA due to infiltration of the upper airway. In certain cases, it may be a TEAE for certain forms of surgical interventions and irradiation.

Nails

Three case reports discussed nail disorders in adult patients with OSA.[40,41] In one report of the association of OSA with yellow nail syndrome a 40-year-old man with 20 markedly discolored yellow nails with onychodystrophy presented with edema of the lower extremities, facial puffiness, and excessive daytime somnolence.[42] PSG findings were consistent with OSA, with some apneic episodes lasting 60 seconds. The OSA had to be treated with a tracheostomy, with significant improvement in daytime sleepiness and nail discoloration; however, the generalized lymphedema and onychodystrophy persisted. In another case of a 60-year-old man who presented with yellow nail syndrome and OSA, CPAP improved the OSA symptoms but not the yellow nail syndrome.[40] There is a case study of a man with sleep-related onychophagia and finger mutilation.[41] A 47-year-old man presented with quadriplegia, severe snoring, daytime hypersomnolence, and depression, in addition to the nail disorder and finger damage. A PSG indicated an AHI of 65. After 8 weeks of bilevel positive airway pressure therapy, there was complete resolution of the onychophagia. There was also improvement in his mood. At 1 year after evaluation, the patient had no further nail dystrophy. OSA may increase the likelihood of additional parasomnias that result in onychophagia as a result of sleep fragmentation.

Nocturnal hyperhidrosis

Sweating is controlled almost entirely by the sympathetic nervous system, and its main function is to increase heat loss and maintain thermoregulation.[43] Habitual snoring in children is associated with OSA.[44] In a study of 1760 German third-grade children, habitual snoring was more often associated with sleep hyperhidrosis (OR = 3.6, 95% CI 1.2-10.8).[45] Two Icelandic studies have examined the relationship between OSA and sleep-related sweating in adults.[43,46] One study of 15 patients with moderate to severe OSA evaluated skin and core body temperature and electrodermal activity (an index of sweating) in men with untreated OSA (mean AHI 45.3 ± 3.9).[43] At baseline, electrodermal activity was correlated with increased morning and evening systolic blood pressure and lower rapid eye movement sleep. After treatment with CPAP for 107 ± 19 days reducing mean AHI to 4.5 ± 0.9, electrodermal activity decreased from 131.9 ± 22.4 to 78.5 ± 17.7. Treatment also correlated with decreases in evening systolic and diastolic blood pressure. CPAP effectively reduced nocturnal sweating and blood pressure, while increasing rapid eye movement sleep. Another study evaluated the efficacy of CPAP on sleep-related sweating in 700 participants in the Icelandic Sleep Apnea Cohort at 2-year evaluation.[46] Frequent (three or more times per week) nocturnal sweating was reported by 30.6% of men and 33.3% of women with OSA compared with 9.3% of men and 12.4% of women in the general population ($P < .001$).[46] The prevalence of frequent nocturnal sweating decreased with full PAP treatment (from 33.2% to 11.5%, $P < 0.003$, compared with the change in nonusers).[46] Sleep hyperhidrosis may be an index of the sympathetic activation and autonomic nervous system dysregulation in OSA.

Psoriasis

Psoriasis has the most strongly substantiated link with OSA.[47–49] Eleven observational studies[4,50–64] and one randomized controlled trial[65] have evaluated the relationship between OSA and psoriasis.[47] Psoriasis patients were more likely to have OSA than matched controls, with the OR for OSA reported to be 1.27 (95% CI 1.08-1.49)[64] and a risk ratio of 3.89 (95% CI 2.26-6.71).[60] The converse relationship is also strong, with a study of 2258 OSA patients from the Taiwanese Longitudinal Health Insurance database reporting a hazard ratio of 2.30 (95% CI 1.13-4.69) for the development of psoriasis or psoriatic arthritis in patients with OSA during a 3-year follow-up period.[63] A study from the Danish National Patient Register reported a bidirectional relationship between OSA and psoriasis, where psoriasis was associated with an increased risk of OSA and OSA was associated with an increased risk for psoriasis.[4] The incidence rate ratios (IRR) for OSA in patients with psoriasis were as follows: mild psoriasis IRR = 1.30 (95% CI 1.17-1.44), severe psoriasis IRR = 1.65 (95% CI 1.23-2.22), and psoriatic arthritis IRR = 1.75 (95% CI 1.35-2.26).[4] Alternately, the IRR for different grades of psoriasis severity in patients with OSA without CPAP therapy (ie, less severe OSA) were as follows: mild psoriasis IRR = 1.62 (95% CI 1.41-1.86), severe psoriasis IRR = 2.04 (95% CI 1.47-2.82), and psoriatic arthritis IRR = 1.94 (95% CI 1.34-2.79). The IRR for different grades of psoriasis in patients with CPAP therapy (ie, the more severe OSA patients) were as follows: mild psoriasis IRR = 1.82 (95% CI 1.43-2.33), severe psoriasis IRR = 3.27 (95% CI 2.03-5.07), and psoriatic arthritis IRR = 5.59 (95% CI 3.74-8.37). The reported prevalence of OSA in participants with psoriasis ranged from 2.7% to 81.8%.[50,51,56,59,62,64] OSA and psoriasis have a well-substantiated complex positive relationship mediated by underlying factors and a high risk for multimorbidity.

A randomized placebo-controlled trial of tumor necrosis factor α antagonist adalimumab 40 mg every other week, involving 20 patients with chronic plaque psoriasis and OSA (AHI ≥15),[65] examined the efficacy of adalimumab in the treatment of sleep parameters in psoriasis and OSA.[65] At 8 weeks, adalimumab did not improve AHI compared with the placebo group. The authors conclude that additional studies using higher adalimumab doses are necessary before concluding that tumor necrosis factor α blockade does not improve OSA.[65]

Urticaria and angioedema

A single case study of a 70-year old woman with vibratory edema, a rare form of physical urticaria, due to snoring and OSA is discussed.[66] The patient presented with episodic itching and swelling of the hands when driving as well as significant snoring. Complement factor 4 and C1 esterase inhibitor

levels were within normal limits. CPAP therapy eliminated the oropharyngeal vibration from snoring and was associated with successful symptom control.[66]

A 47-year old patient with a confirmed diagnosis of hereditary angioedema (presence of C1 esterase inhibitor or C1-INH and complement factor 4 deficiency) presented with a history of 11 episodes of edema of the soft palate and uvula (EU), which always occurred between 3:00 AM to 3:15 AM. The patient would be woken with a feeling that his pharynx was swollen, and swallowing was barely possible and painful. According to the patient's wife, all 11 episodes occurred only after he had been snoring severely, after the consumption of alcohol the previous night. There was no associated tongue swelling. The acute episodes were treated with intravenous C1-INH, and danazol was used for prophylactic treatment. In this patient, severe vibration of the soft palate during snoring induced local swelling of the soft palate, and the swollen soft palate acted as a one-way valve and allowed only inhalation, significantly restricting exhalation.[67]

In a study of 58 patients with EU,[68] 75.9% presented with isolated EU, and no clear etiology could be identified in 55.1% (n = 32), who were therefore classified as idiopathic, and snoring and a high BMI were more prevalent in this group. The remaining 44.9% (n = 26) were identified as having urticaria (n = 8), angioedema (n = 10), and anaphylaxis (n = 3), and there was also a higher prevalence of atopy (7 out of 32 in idiopathic group versus 16 out of 26 in the group with probable cause, $P < .0001$).

Discussion

The association of dermatologic disorders and OSA has a multifactorial basis, and possible underlying factors should be evaluated in each dermatology patient when OSA is suspected. OSA behaves differently in adults versus children (especially <13 years age group), because pediatric OSA presents with obstructive hypoventilation and periods of hypercapnia and much fewer apneas and hypopneas. Psoriasis has the most strongly substantiated link with OSA, where the relationship between psoriasis and OSA may be bidirectional; factors implicated include the heightened proinflammatory state and comorbidities, such as obesity and metabolic syndrome, that are present in both psoriasis and OSA. An association between AD and OSA has not been substantiated in children; however, it may be present in adults. Dermatologic disorders may be comorbid with OSA due to several factors: (i) The heightened proinflammatory state in OSA, which can occur independent of BMI, may exacerbate inflammatory dermatoses; (ii) intermittent hypoxemia may promote neovascularization and tumor growth in certain cancers such as melanoma; (iii) obesity, present in majority of OSA patients, can be associated with a heightened proinflammatory state; (iv) upper airway obstruction due to local tumors (eg, squamous cell carcinoma), scarring (eg, cicatricial pemphigoid, postradiotherapy), or soft tissue swelling due to physical urticaria or angioedema may be precipitated by the soft tissue vibration caused by snoring; (v) acute nasal congestion is common in the atopic patient with acute allergic rhinitis, even though persistent rhinitis in adults has not been associated with OSA; (vi) the dermatologic disorder may be associated with other OSA risk factors (eg, acanthosis nigricans and metabolic syndrome); and (vii) a high sympathetic tone (eg, in atopic dermatitis) and resultant sleep fragmentation may contribute to upper airway instability during sleep. In some instances, the dermatology patient with OSA may have a complex presentation with more than one psychiatric and/or medical comorbidity that may also be independently associated with OSA.

Conclusions

It is important to recognize OSA in the dermatology patient, especially in the otherwise treatment-resistant patient with risk factors (such as obesity and metabolic syndrome, polycystic ovary syndrome) that are common to both OSA and certain dermatologic disorders (such as psoriasis and acne), because the heightened proinflammatory state associated with OSA may adversely affect the course of inflammatory skin disorders. The strongest substantiated link between OSA and dermatologic disease in the literature is for psoriasis, where the association may be bidirectional, suggesting that treating OSA in a patient who may be at a high risk for developing psoriasis or have psoriasis should have a beneficial effect on the overall course of psoriasis. There are multiple case studies of OSA as a result of upper airway obstruction secondary to localized tumors and urticaria or angioedema affecting the uvula, and the dermatologist should maintain an index of suspicion for lesions affecting the upper airways in the dermatology patient with OSA. The dermatologist is most likely to encounter OSA in the complex dermatology patient who has one or more medical or psychiatric condition that is also associated with increased OSA risk. It is important for the dermatologist to be aware of the possible impact of OSA on the course of dermatologic disorders, especially those associated with primarily inflammatory pathophysiology.

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