Researchers Work to Define Phenotypes of Obstructive Sleep Apnea

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Obstructive sleep apnea (OSA) is a complex disease that is characterized by the collapse of the pharyngeal airway, resulting in recurrent episodes of airway closure, oxygen desaturation, and disrupted sleep. The pathophysiological mechanisms of OSA are heterogeneous, resulting in diverse clinical phenotypes. In recent studies, researchers have sought to define multiple phenotypes on the basis of local and distant anatomy, sleep breathing and arousal patterns, and response to treatment. In this session, experts in sleep-disordered breathing discussed the spectrum of OSA phenotypes and their implications for therapy.

Upper Airway Phenotypes

Certain anatomical features can predispose patients to airway obstruction and sleep apnea. The specific combination of upper airway soft tissue and craniofacial risk factors influences the clinical features of OSA, as well as symptom severity. Richard J. Schwab, MD, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania, USA, described how variations in upper airway anatomy can affect the diagnosis and treatment of OSA.

In a landmark study of OSA risk factors, Schellenberg and colleagues evaluated oropharyngeal abnormalities in 420 patients who presented to a sleep disorders center with suspected OSA. In a multivariate analysis, several anatomical features were associated with a significantly increased likelihood of OSA, including narrowing of the airway by the lateral pharyngeal walls (OR, 2.5; 95% CI, 1.6 to 3.9), tonsil enlargement to >50% lateral impingement of the oropharyngeal airspace (OR, 2.0; 95% CI, 1.0 to 3.8), enlargement of the uvula to >1.5 cm in length or >1.0 cm in width (OR, 1.9; 95% CI, 1.2 to 2.9), and tongue enlargement (OR, 1.8; 95% CI, 1.0 to 3.1) [Schellenberg JB et al. *Am J Respir Crit Care Med* 2000]. Thus, enlarged soft tissue structures of the oropharynx appear to be important anatomical determinants of OSA.

Alterations in other craniofacial structures are also associated with OSA. In 2011, Chi and colleagues used 3-dimensional magnetic resonance imaging (MRI) to characterize additional anatomical risk factors for OSA (Table 1). The study included 55 patients with OSA and 55 controls who were matched for age, race, height, visceral fat in the neck, and skeletal type. Increased mandibular length and depth were associated with a decreased risk of OSA for men but not women. Regardless of gender, greater hyoid-to-nasion distance and greater supramentale-to-hyoid distance were associated with an increased risk of OSA. However, the more inferior and posterior positioning of the hyoid in patients with OSA was largely explained by increased tongue volume in these patients. Therefore, the primary craniofacial risk factor for OSA was a small and shallow mandible in men [Chi L et al. *Eur Respir J* 2011].

Table 1. Craniofacial Risk Factors for Obstructive Sleep Apnea.

Parameter	Odds Ratio (95% CI) for OSA	
	Men	Women
1-SD increase in mandibular length	0.52 (0.28–0.99)	NS
1-SD increase in mandibular depth	0.46 (0.23–0.91)	NS
Greater hyoid-to-nasion distance	2.64 (1.19–5.89)	5.01 (2.00–12.52)
Greater supramentale-to-hyoid distance	2.39 (1.12–5.14)	3.38 (1.49–7.68)

CI=confidence interval; NS=nonsignificant; OSA=obstructive sleep apnea; SD=standard deviation.

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Why are the soft tissue structures of the upper airway enlarged in patients with OSA? Genetic factors certainly play a role, Dr. Schwab said. Medical comorbidities (for instance, acromegaly) and trauma (secondary to recurrent apneic events) can also enlarge these structures, resulting in increased risk for OSA. In obese patients, the deposition of fat in tissues (in particular the parapharyngeal fat pads and the tongue) that surround the upper airway increases the risk and severity of OSA. Changes in blood flow, edema, and tissue injury can also adversely affect the geometry and size of the soft tissues that surround the oropharynx. Even the vibration that is associated with snoring can result in soft tissue enlargement.

For patients with suspected OSA, a thorough diagnostic assessment should include an evaluation of upper airway soft tissue and craniofacial risk factors. The combination of enlarged soft tissue structures and reduced craniofacial morphology may be the most important anatomical predictor of OSA. By assessing the oropharyngeal features in patients with suspected OSA, physicians can better risk-stratify these patients and determine the best options for treatment on the basis of individual anatomical risk factors.

Distant Anatomical Risk Factors

Beyond variations in upper airway anatomy, several other anatomical features can predispose patients to OSA. Amy S. Jordan, PhD, University of Melbourne, Melbourne, Australia, described the relationship between distant anatomical features and clinical phenotypes of OSA.

Distant anatomical factors that influence the natural history of OSA include abdominal compression due to central obesity or pregnancy. Chronic edema due to heart failure and other comorbidities also adversely affects lung volume (LV) in patients with OSA. Given that LV is known to influence airway size, resistance, and collapsibility, researchers have hypothesized that altered LV may also contribute to the development and severity of OSA.

In 2010, Stadler and colleagues evaluated changes in end-expiratory LV (EELV) and diaphragm muscle activity at sleep onset in healthy individuals and in obese patients with OSA. Compared with control subjects, obese patients with OSA experienced a greater fall in diaphragm muscle activity following sleep onset ($p<0.001$) and a greater decrease in EELV ($p=0.007$). However, the difference in EELV on the third breath after sleep onset was very small at only 27 ml, and it is not known whether absolute EELV differed between the groups before sleep. Furthermore, diaphragm activity and EELV decreases at the onset of sleep are greater when accompanied by respiratory events in patients with OSA. Thus, decreasing EELV appears to contribute to increased risk of upper airway collapse at sleep onset in patients with OSA [Stadler DL et al. *J Appl Physiol* 2010]. These findings, and others, suggest that decreased LV is one of the pathological mechanisms by which obesity increases the risk and severity of OSA. Further research may explore the therapeutic potential of raising LV in obese and normal-weight patients with OSA.

Epidemiologic and clinical studies demonstrate that OSA is a multifactorial disease that is still only partially understood. By studying the spectrum of anatomical risk factors that are associated with OSA, researchers are moving toward identifying distinct phenotypes of this disease. The identification of OSA phenotypes will facilitate the development of new approaches to treatment and the selection of treatments that are best suited to individual patients. Identifying OSA phenotypes will also lead to improved clinical trial design and the evaluation of phenotype-specific therapy, Prof. Johnson said.