SPECIAL ISSUE 1: INVITED ARTICLE

Upper Airway Resistance Syndrome

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International Journal of Head and Neck Surgery (2019): 10.5005/jp-journals-10001-1364

Case Description

A 35 years female with BMI of 23 kg/m^2, came with complaints of excessive daytime fatigability and sleepiness. Her husband gave history of snoring while sleep. She suffered with depression and had excessive sweating issues. Her limited channel study was normal. Complete overnight polysomnography showed lowest SpO_2 of 92%, AHI—2.5/hr, RDI—15.5/hr with RERAs—13/hr. No positional variation noted in AHI.

Upper airway resistance syndrome (UARS) was first recognized in children in 1982, though the term UARS was not used until 1993, when adult cases were reported for the first time.[1] The term UARS was devised to delineate a group of individuals who did not meet the criteria for obstructive sleep apnea (OSA) and therefore were not diagnosed or not treated, despite severe impairment.[2] Pioneering work of Guilleminault and others in past three decades paved the way for UARS in the broader umbrella of disorders called sleep-disordered breathing (SDB) (Fig. 1). UARS is characterized by frequent arousals in response to increased respiratory effort as a result of upper airway narrowing without overt apnea or hypopnea. Global prevalence is around 10–15% when definition is applied to adults who suffer from snoring and excessive daytime somnolence (EDS).

The existence of UARS is still a matter of controversy with no clear-cut standardized diagnostic criteria. The lack of education about UARS in the medical community, and also the controversies related to its position within SDB results in health practitioners accepting the decisions from medical insurance companies and eventually no specific treatment is provided to UARS subjects.

Pathophysiology

The pharyngeal collapse depends on the balance between collapsible factors like UA narrowing, pharyngeal collapsibility and protective factors like UA-dilating muscle activity and the protective pharyngeal reflexes (Fig. 2). Patients with UARS exhibit typical craniofacial abnormalities (Fig. 3) leading to size reduction of the pharynx.

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How to cite this article: Pandey A, Vala B, Shah M. Upper Airway Resistance Syndrome. Int J Head Neck Surg 2019;10(1):18–21.

Source of support: Nil

Conflict of interest: None

Dematties et al.[4] and Guilleminault et al.[5] showed that UA sensitivity in UARS subjects is close to normal subjects. Due to unimpaired UA sensitivity, these patients have intact ability to activate the protective reflexes. They rather have very high levels of dilator muscle activity in response and lower arousal threshold making arousals frequent and impactful.

Clinical Presentation

Typically, patients with UARS are less obese, heavy snorers with excessive daytime sleepiness (Table 1). UARS patients do not have severe oxygen desaturation during sleep. Few patients also present with functional somatic syndrome, a form of complex presentation due to presence of psychological factors (depression), neurologic factors (increased pain sensitivity), hormonal factors (orthostatic hypotension and alterations in hypothalamo-pituitary-adrenal axis) and sleep-related factors (frequent arousals and alpha frequency intrusion into sleep).[8] UARS generally remains stable over time. However, it may progress to OSA if there is an increase in body mass index (BMI) of patient.

Cardiovascular Sequelae

UARS has known to cause cardiovascular and metabolic consequences, attributed to snoring, increased respiratory efforts throughout the night and sleep fragmentation. Lee et al.[9] in an observational cohort of 101 snorers and non-snorers with mild non-hypoxic OSAS, noted that heavy snoring (>50% night snoring) was

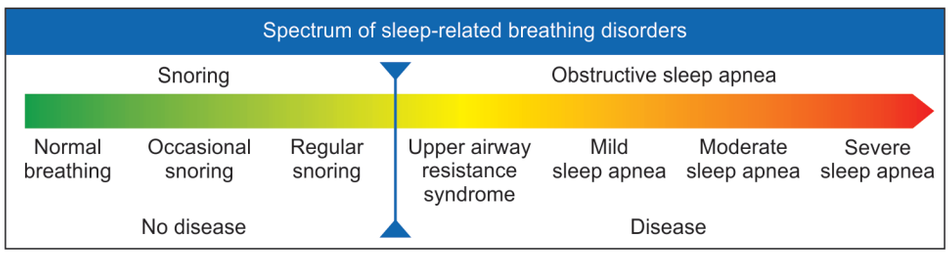

Fig. 1: Spectrum of SDB

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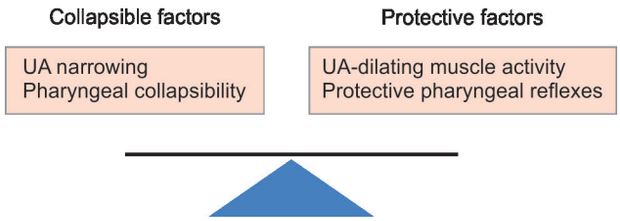
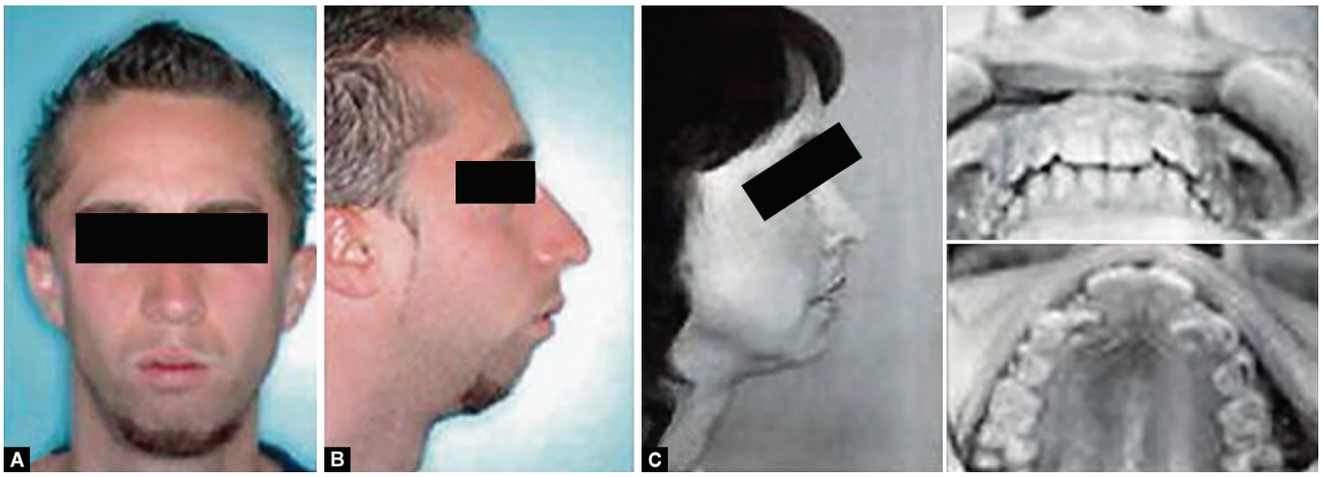


Fig. 2: Balance between UA collapsible and protective factors[3]



Figs 3A to C: Typical craniofacial features of UARS. (A and B) Long face syndrome with a short and narrow chin and with retrognathic chin; (C) Dental overjet and ogival hard palate in UARS. *Courtesy:* Dallas Center for Sleep Disorders.

Table 1: Clinical presentation of UARS

Symptoms	*Signs[6] (shown in figure)*
• Snoring • Nocturia/nocturnal awakening/Sleep inefficiency • EDS • Daytime fatigue • Headache/vasomotor Rhinitis/Irritable bowel syndrome • Decreased performance/ Anxiety/depression	• Classical long face syndrome with short and narrow chin and reduced mouth opening • Presence of classical 'Click' and subluxation while opening Temporomandibular joint as evidenced by palpation • Mandible in back position and palate is high and narrow • Low resting arterial blood pressure or orthostatic intolerance[7]

an independent risk factor for carotid atherosclerosis. Convincingly, the prevalence of carotid atherosclerosis was found to increase progressively with severity of snoring. In UARS, the second key mechanism responsible for cardiovascular consequences is the occurrence of repetitive microarousals evident in the form of Respiratory effort-related arousals (RERA) episodes and consequent rise in airway resistance which in turn leads to repetitive increase in blood pressure in these patients.[10] Therefore, UARS-induced sleep fragmentation and prolonged episodes of inspiratory flow limitation might lead to a chronic increase in sympathetic outflow that could explain the secondary occurrence of cardiovascular and metabolic consequences.

Diagnosis

Diagnosis of UARS depends upon the presence of supportive clinical presentation as explained above, accompanied with following positive findings on diagnostic evaluation.

- Increased respiratory effort on esophageal pressure monitoring (Gold standard). Three abnormal patterns are seen:
  1. Pes crescendo
  2. Sustained continuous respiratory effort
  3. Pes reversal
- Polysomnography (PSG) findings:
  - RERA event which is defined as sequence of breaths lasting for atleast 10 seconds and characterized by series of respiratory cycles of increasing/decreasing effort or flattening, recorded by nasal manometry and resulting in arousal, not defined by apnea or hypopnea.
  - Normal AHI, i.e., no significant apnea or hypopnea
  - No significant oxygen desaturation
  - Air flow limitation evident as flattening of normal bell-shape curve of normal breath, with a drop in the amplitude of the curve by 2–29% compared to normal breaths immediately preceding.

In our case patient is young with normal BMI with suggestive symptoms of sleep disordered breathing and autonomic features. Her PSG has distinct RERAs but in significant AHI with normal oxygen levels. Thus, classical for UARS. UARS despite being on the same spectrum as SDB, has many contrasting features when compared to OSA as shown in Table 2.

Treatment

Treatment of UARS should be given due importance in view of its established consequences in form of cardiovascular and metabolic compromise. As snoring has been a major risk factor for the same, this domain can be handled with surgical intervention promisingly than other disease of SDB.[11]

Table 2: Comparison of features in UARS and OSAS

Parameters	*UARS*	*OSAS*
Age	All ages	Children Male >40 years Female after Menopause
M:F ratio	1:1	2-3:1
Sleep onset	Insomnia	Fast
Snoring	Common	Almost always
Apnea	No	Common
Daytime symptoms	Tiredness and fatigue	Sleepiness
Body habitus	Slim or normal	Commonly Obese
Somatic dysfunction	Fibromyalgia Chronic pain and headache	Rare
Orthostatic symptoms	Cold hands/feet Fainting and dizziness	Rare
Blood pressure	Low or normal	High
Neck circumference	Normal	Large

Adapted from Guilleminault et al. Upper airway resistance syndrome—one decade later. Curr Opin Pulm Med 2004

- Continuous positive airway pressure (CPAP) therapy—It is the mainstay of treatment though the patients have difficulty in tolerating CPAP and which is better evaluated in various studies.[12,13]
- *Surgery*—Surgical modality is helpful in patients who either do not tolerate CPAP or are not willing to adhere to CPAP. The choice of surgical procedure is usually based on the site of upper airway obstruction, with the understanding that multiple levels of increased airway resistance or collapse may exist.
  - Uvulopalatopharyngoplasty (UPPP) and laser-assisted Uvulopalatopharyngoplasty (LAUP) are the most commonly performed surgeries for UARS, with good success rates; LAUP can be more cost-effective approach.
  - A multilevel, pharyngeal surgical approach consisting of UPPP, mandibular osteotomy with genioglossus advancement (GA), and Hyoid myotomy with advancement (HM) proposed by Riley et al.[14,15] They reported a success rate of 60–65% postoperatively and a result equivalent to CPAP.
  - Septoplasty with bilateral inferior turbinate resection should be reserved as an adjunct to pharyngeal surgery or to improve the tolerance of CPAP.
- *Orthodontic approaches*—Mandibular advancement devices and rapid maxillary distractionare easily performed in children and teenagers. These devices act by repositioning the lower jaw forward and reduce upper airway resistance.
- *Oral Appliances (OA)*—these are the devices inserted into the mouth to modify the position of tongue and mandible, relieving obstruction during sleep. These devices have shown to improve snoring, transient arousals and EDS.[16]
- Cognitive behavioral therapy (CBT) in conjunction to CPAP in patients with chronic insomnia or psychosomatic symptoms can be helpful.
- *Hormonal therapy*—as an adjunct to CPAP and surgical modality is also helpful as shown in some studies, especially in menopausal women.[13]

UARS is a structural problem caused by smaller-than-normal jaw structures, leading to narrowed air-passages which eventually results in the pathophysiological changes and clinical features. Eventually some proportion of patients will either not tolerate or adhere to CPAP therapy.

The two most common reasons for non-compliance with CPAP are obstruction within the nose and pharynx and lack of subjective improvement with treatment. Studies showed that CPAP did not improve sleep efficiency and sleep stages in these patients.[13] UARS patients do not tolerate CPAP very well, due to highly sensitive upper airway unlike OSAS patients where there is diminished upper airway muscle tone and neurology, as seen by Guilleminault et al in a long term outcome study in UARS subjects.[17]

Pearls of Wisdom

- UARS is a separate established entity which needs early diagnosis with level 1 study
- Functional Somatic syndrome with EDS and snoring should raise suspicion for UARS
- UARS needs treatment in view of cardiovascular consequences
- Close monitoring is needed in view of possibility of incipient OSA in some
- Surgical intervention has a role in UARS

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