Upper airway resistance syndrome-one decade later

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Purpose of review

The term *upper airway resistance syndrome* (UARS) was coined to describe a group of patients who did not meet the criteria for diagnosis of obstructive apnea–hypopnea syndrome and thus were left untreated. Today, most of the patients with UARS remain undiagnosed and are left untreated.

Recent findings

Today, the clinical picture of UARS is better defined. We have learned that patients usually seek treatment with a somatic functional syndrome rather than sleep-disordered breathing or even a disorder of excessive daytime sleepiness. Therefore, most of these patients are seen by psychiatrists. In addition, recent technologic advances have allowed a better recognition of the problem. We have learned that obstructive apnea–hypopnea syndrome is associated with a local neurologic impairment that is responsible for the occurrence of the hypopnea and apneas. In contrast, patients with UARS have an intact local neurologic system and have the ability to respond to minor changes in upper airway dimension and resistance to airflow. New treatment options including internal jaw distraction osteogenesis are used and are promising for treatment of patients with UARS.

Summary

The clinical presentation of patients with UARS is similar to the presentation of subjects with functional somatic syndrome. To diagnose UARS, nocturnal polysomnography should include additional measurement channels.

Keywords

upper airway resistance syndrome, obstructive sleep apnea syndrome, polysomnography, power spectral EEG analysis, distraction osteogenesis

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Abbreviations

AHI	apnea–hypopnea index
CAP	cyclic alternating pattern
OSAHS	obstructive apnea–hypopnea syndrome
OSAS	obstructive sleep apnea syndrome
Pes	measurement of esophageal pressure
RERA	respiratory related respiratory arousal
SDB	sleep-disordered breathing
UARS	upper airway resistance syndrome

Introduction

Upper airway resistance syndrome (UARS) was first recognized in children in 1982 [1]. The term *UARS*, however, was not used until adult cases were reported in 1993 [2]. The description of UARS brought clinicians' attention to a group of patients left undiagnosed and untreated despite severe impairment. Since the original description, the syndrome has been recognized in patients with clinical and polysomnography presentations different from that of obstructive sleep apnea syndrome (OSAS). However, controversies exist regarding the syndrome. Some have rejected it as a distinct clinical entity or even doubted its existence [3]; others have considered it part of a spectrum that includes benign snoring, UARS, obstructive hypopnea syndrome, OSAS, and hypoventilation. The term *sleep-disordered breathing* (SDB) is used widely today, often without clear definition by the authors. Supposedly it includes all these breathing abnormalities in sleep, including central apnea and hypoventilation. Clinically, the disease entity of SDB is often called *sleep-related breathing disorders*. In clinical practice, a label of SDB or sleep-related breathing disorders is applied when a breathing abnormality is found in sleep but no clear distinction between UARS and obstructive apnea–hypopnea syndrome (OSAHS) is attempted or can be made. In the past few years, there have been at least two review articles published on UARS in general [4] and in children [5]. This review is aimed at coverage of recent progress progresses in recognition and understanding of UARS, with greater emphasis on data published over the period of the past 2 years.

Since the first description of a polygraphic pattern called *obstructive sleep apnea* in the Pickwickian syndrome in 1965 [6,7], sleep medicine has undergone an evolution. UARS was born as part of the efforts to describe a generally unrecognized patient population that is nonobese with clinical features not matching those reported with OSAHS. Unfortunately, many sleep breathing abnormalities are still ignored because of the belief that SDB is synonymous with OSAHS and that patients must be obese. Such limited views have already led to the underdiagnosis and undertreatment of OSAS in women (the forgotten sex) [8]. With use of new techniques, such as the esophageal catheter for esophageal pressure measurement (Pes) [9] and nasal cannula/pressure transducer

[10], it has become more convenient to identify subtle changes in breathing patterns during sleep. Recently, UARS has been linked to many somatic, psychiatric, or psychosomatic conditions, including parasomnias, attention deficit disorder or attention deficit hyperactivity disorder, fibromyalgia, and chronic insomnia. Also, to many clinicians, the distinction between UARS and OSAS lies in the clinical severity, such as apnea–hypopnea index (AHI) and level of oxygen desaturation, but research in recent years supports the presence of a different pathophysiology in the two syndromes.

Pathophysiology

The upper airway consists of the nasal passage, nasopharynx, oropharynx, hypopharynx, and supraglottic larynx. The histologic changes associated with OSAHS have been investigated extensively. Edstrom *et al.* [11] studied biopsies of palatopharyngeal muscle samples from eight patients with OSAHS compared with those from normal controls. Only biopsies from patients with OSAHS showed atrophy with a fascicular distribution, and an abnormal distribution of fiber types in many muscle fascicles corresponding to type grouping. All changes pointed to a neurogenic alteration. These authors suggested that the neurogenic lesion might be a primary phenomenon or secondary to the trauma of repetitive and prolonged stretching of the pharyngeal structures during apneas. Friberg *et al.* [12••] performed further histologic and electron microscopic investigations of the palatopharyngeal muscles in patients with OSAHS. Their results show progressive lesions consistent with a polyneuropathy. The degree of the abnormalities correlates with the severity of obstructive events. Using immunohistochemical staining and peptide localization, the same group further demonstrated increased density in sensory nerve terminals of the soft palatal mucosa, indicative of afferent nerve lesions [13••]. These authors coupled their studies with palatal stimulation and investigations of reflex responses to thermal and electrical stimulation. Recently, using functional magnetic resonance, Henderson *et al.* [14] demonstrated attenuated signals in certain areas of the brain in patients with OSAHS. Woodson *et al.* [15] and Series *et al.* [16] provided further histologic evidence. Kimoff *et al.* [17•] and the authors [18••] used the two-point discrimination technique to investigate further the local abnormal sensory response to palatal stimulation. Afifi *et al.* [19••] showed the presence of a blunted cortical response to inspiratory occlusions in NREM sleep, but the absence of significant differences in evoked responses to auditory stimuli, supporting the concept that the sleep-related differences seen in patients with OSAS are specific to the processing of inspiratory effort-related stimuli. There is an accumulation of evidence showing that in OSAS, dilator muscles in the upper airway may undergo an adaptation and remodeling process in response to changes in airway dynamics, which may be beneficial or harmful [20]. Patients with OSAS have receptor dysfunctions causing hyporesponsiveness or nonresponsiveness. The afferent receptors in OSAS are blunted as a result of repetitive airway closures, with a delay in perception of the abnormal collapse and an absence of adjustment of upper airway dilators. The failure of immediate response leads to a profound degree of collapse of the upper airway. We have shown a similar two-point discrimination in the palate of patients with UARS and control subjects, which supports a sensory difference between UARS and OSAHS [18••]. Another study showed that minor breathing impairments can lead to UARS, such as in patients with collapse of the nasal valves, enlargement of inferior nasal turbinates, and a deviated septum, or any combination of these [21•]. Patients with UARS may have increased airway collapsibility, as suggested by Gold *et al.* [22], because of abnormal inspiratory airflow dynamics [23] or increased collapsibility of the upper airway during expiration [24], all related to abnormal anatomy. However, perception of the

Table 1. Clinical differential features in upper airway resistance syndrome (UARS) and obstructive sleep apnea-hypopnea syndrome (OSAHS)

Feature	UARS	OSAHS
Age	All ages	Children Male > 40 y old Female after menopause
Male:female ratio	1:1	2:1
Sleep onset	Insomnia	Fast
Snoring	Common	Almost always
Apnea	No	Common
Daytime symptoms	Tiredness Fatigue	Sleepiness (less common in children)
Body habitus	Slim or normal	Obese
Somatic functional complaints	Fibromyalgia Chronic pain Headaches	Rare
Orthostatic symptoms	Cold hands/feet Fainting Dizziness	Rare
Blood pressure	Low or normal	High
Neck circumference	Normal	Large

Table 2. Polysomnography and power spectral analysis in upper airway resistance syndrome (UARS) and obstructive sleep apnea-hypopnea syndrome (OSAHS)

	UARS	OSAHS
Sleep onset latency	Long	Short
AHI	< 5	≥ 5
Minimum O_2 saturation	> 92%	Often < 92% (rare in children)
Respiratory effort-related arousals	Predominant	Minimal
Cyclic alternating patterns	Frequent	Less common
Power spectral EEG analysis	Higher α power	Less α or δ
	Higher δ in rapid eye movement	

AHI, apnea-hypopnea index as events per hour.

change in airway size is much faster and can trigger a much faster response and better adaptation than shown by patients with OSAS. This fast response may be a reflex leading to a subcortical activation, appearing on EEG as phase A1 of the cyclic alternating patterns (CAPs). With stronger and broader activation, phases A2 and A3 of CAPs occur [25••], called an α *EEG arousal* according to the ASDA nomenclature [26].

Clinical presentation

Although many of the symptoms in UARS overlap with those in OSAS, recent studies found some important differences [27•]. Chronic insomnia tends to be more common in patients with UARS than with OSAS. Many patients with UARS report nocturnal awakenings and soon find it difficult to fall back to sleep. Adult patients with UARS are more likely to complain of fatigue than sleepiness. They often complain of sleep onset and sleep maintenance insomnia, which is thought to be a result of conditioning as a consequence of frequent sleep disrup-

tions [28•]. Other presentations include confusional parasomnias including sleepwalking and sleep terrors [29], myalagia, depression, and anxiety. Gold *et al.* [30••] recently emphasized that patients with UARS have complaints more related to functional somatic problems such as headaches, sleep-onset insomnia, and irritable bowel syndrome; their patients had polysomnographic findings for UARS. Not infrequently, UARS is misinterpreted as chronic fatigue syndrome, fibromyalgia, or psychiatric disorders, such as attention deficit disorder/attention deficit hyperactivity disorder [31]. Patients report cold hands and feet. A quarter of them have lightheadedness or a tendency to faint on standing or bending abruptly (the latter is more common in teenagers and young adults). This last complaint may be explained by the finding that low blood pressure (SBP < 100 mm Hg) is more commonly associated with UARS [32,33•], whereas hypertension is commonly associated with OSAS [34]. A clinical case report of UARS has also presented symptomatology mimicking nocturnal asthma [35]. Despite the differential clinical features, it is sometimes difficult to dissociate patients with UARS from those with mild OSAHS based on symptoms and clinical signs alone. Moreover, patients could be missed or mislabeled with a different diagnosis [36].

Diagnosis

The key clinical features for UARS include presentations of atypical symptoms for OSAS, especially functional somatic complaints; clinical examinations often show craniofacial abnormalities. Polysomnography reveals AHI < 5, oxygen saturation > 92%, and the presence of respiratory related respiratory arousals (RERAs) and other nonapnea/hypopnea respiratory events (Tables 1 and 2). Although quantitative respiratory plethysmography [37], pneumotachograph [2], and most commonly

Figure 1. Continuous sustained effort

Note presence of flow limitation on nasal cannula, -pressure transducer tracing. Note on Pes tracing a continuous increase in respiratory effort with peak end inspiratory Pes reaching always an increased negativity (approximately −15 cm H_2O) compared with −6 during nonobstructed breathing.
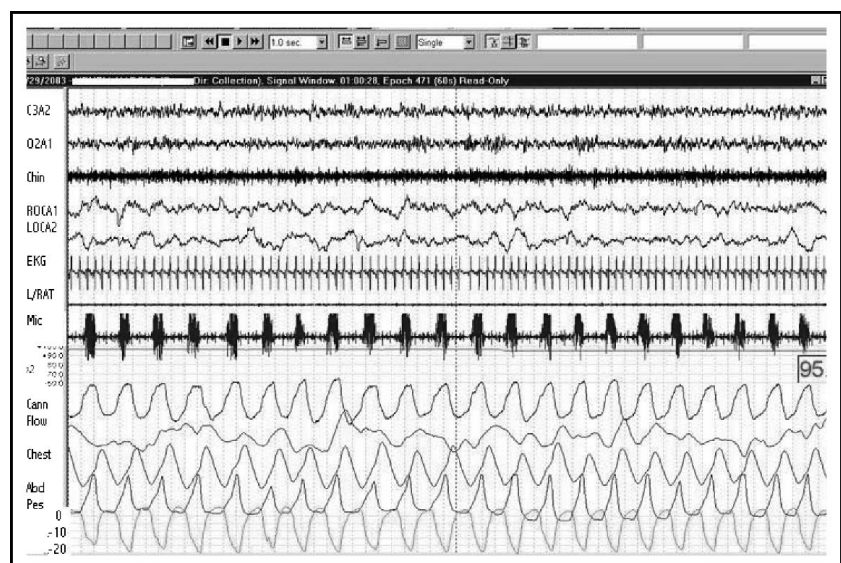
nasal cannula/pressure transducer have been tried to measure subtle respiratory alterations [38•,39•], Pes remains the gold standard for detecting respiratory abnormalities. The use of a pediatric feeding catheter instead of the esophageal balloon has made the procedure more tolerable in both adults [38•] and children [40•]. The nasal cannula/pressure transducer is more sensitive than thermistors in picking up respiratory changes and has been used to detect RERAs. However, it has not been demonstrated to have sensitivity comparable with Pes measurement. Three abnormal forms of Pes tracing have been described [41•,42••]. First, Pes crescendo is a progressively increased negative peak inspiratory pressure in each breath that terminates with an α-wave EEG arousal or a burst of δ-wave. This is not associated with a drop in oxygen saturation of 3% as used for the definition of hypopnea. The second form is a sustained continuous respiratory effort (Fig. 1). Pes tracing shows a relatively stable and persistent negative peak inspiratory pressure, which is more than the baseline and nonobstructed breaths. This lasts longer than four breaths. The third form is Pes reversal, an abrupt drop in respiratory effort indicated by a less negative peak inspiratory pressure after a sequence of increased respiratory efforts independent of the EEG pattern seen (Fig. 2). The disadvantage of Pes measurement is the need to insert a small catheter from the patient's nostril down to the esophagus. Despite validations of good tolerability and a low complication rate in adults and children, Pes measurement is not widely applied because of patients' fear of discomfort and sleep technologists' hesitancy, except in centers in which the technique has been well adapted, or in an academic and research setting. Recently, the authors applied a new algorithm using intercostal EMG signals to detect the respiratory variations. The results are quite promising [43••]. Another technique using pulse wave signals was developed in Japan and was recently patented in the United States for commercial de-

Figure 2. Flow limitation monitored with a pneumotachograph
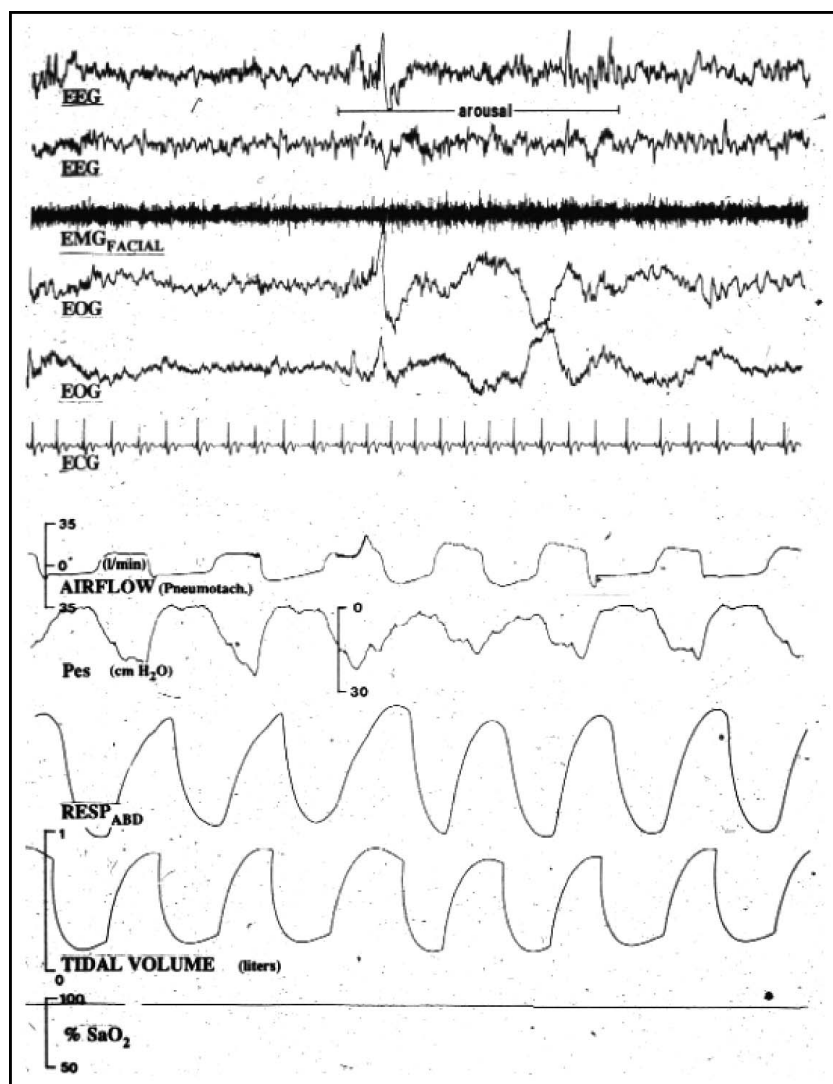
The flow limitation is associated with abnormal peak end inspiratory Pes on the first 2 breaths on the left side of figure. With occurrence of an EEG arousal (underline EEG), there is an abrupt decrease in effort indicated by esophageal pressure monitoring. This pattern is called *Pes reversal*; it begins with the third breath from left. It is associated with a change in the EEG indicative of the EEG arousal.

velopment [44••]. It is expected that in the near future, new techniques will be available for measuring even subtle changes in respiratory efforts without the need of an esophageal pressure catheter placement.

Polysomnographic findings and power spectral EEG analysis

The typical polysomnographic findings for UARS include AHI < 5, minimum oxygen saturation > 92%, an increase in α rhythm, and a relative increase in δ sleep, which persists in the later cycles of sleep. Recent studies also confirm that patients with UARS may have more α EEG frequency time [45•,46•] and more RERAs [46•] during sleep than patients with OSAHS. Scoring of CAPs is another novel approach evaluating the quality of sleep in UARS (Fig. 3). A higher frequency of CAPs is noted in sleepwalkers with UARS [29]. The comparison of the sleep EEG of UARS, OSAS, and normal control subjects using power spectrum analysis shows a higher amount of high θ and low α powers (*ie*, 7–9 Hz bandwidth) during NREM sleep and more δ powers during rapid eye movement sleep compared with OSAHS and normal subjects [45•]. The new analytic approach design by Chervin *et al.* [47] that quantifies so-called *respiratory cycle-related electroencephalographic changes* breath by breath and correlates δ, θ, and α in EEG powers with respiratory cycle variations may allow detection of more subtle sleep EEG changes related to abnormal respiratory efforts.

Treatment

In the original description of UARS in 1993, the authors treated patients successfully with nasal CPAP. Since then, other therapeutic alternatives have been used.

CPAP is still widely tried as the first line therapy. It is often used as a therapeutic trial to demonstrate improvement of symptoms [28•]. Recent studies have demonstrated that adding cognitive behavioral therapy to CPAP treatment is beneficial for patients with chronic insomnia or psychosomatic symptoms [28•,48•] secondary to UARS. In a randomized study conducted on postmenopausal women with UARS and chronic insomnia, radiofrequency reduction of nasal turbinates or turbinectomy or a trial of CPAP showed better relief in daytime fatigue than behavioral treatment alone at 6 months [28•]. Krakow *et al.* [48•] reported that 1-night CPAP titration improved objective measures of insomnia, arousal, and sleep in patients with chronic insomnia and SDB, and in their retrospective study of a small sample, validated measures of insomnia, sleep quality, and sleep impairment achieved clinical cures or near-cures after combined cognitive behavioral therapy and SDB therapies. Oral appliances can also achieve satisfactory outcomes in UARS [49•]. Septoplasty and radiofrequency reduction of enlarged nasal inferior turbinates can be successful in treating UARS. However, anatomic abnormalities often involve palatal soft tissues and the maxilla and mandible skeletal structures. Absence of correction of the primary cause of the abnormal breathing, such as crowded airway and narrowed jaws, will leave patients with a complaint of worsening functional symptoms and potentially may lead to development of local polyneuropathy and the occurrence of OSAS. The classic surgical procedures have often been considered too aggressive for treatment of UARS. Treatment must address the cause of the syndrome and avoid progression of untreated anomalies. Uvulo-flap [50•] and distraction osteogenesis have been helpful for

Figure 3. Cyclic alternating pattern (CAP)

The EEG tracing presents alternatively a burst of high-amplitude waves (phase A) and low-amplitude waves (phase B). This pattern is seen during nonrapid eye movement sleep. It indicates an instability of the state. The high-amplitude waves are formed by burst of δ waves, or a mixture of δ-α waves. The tracing also shows a nasal cannula-pressure transducer curve indicative of flow limitation.
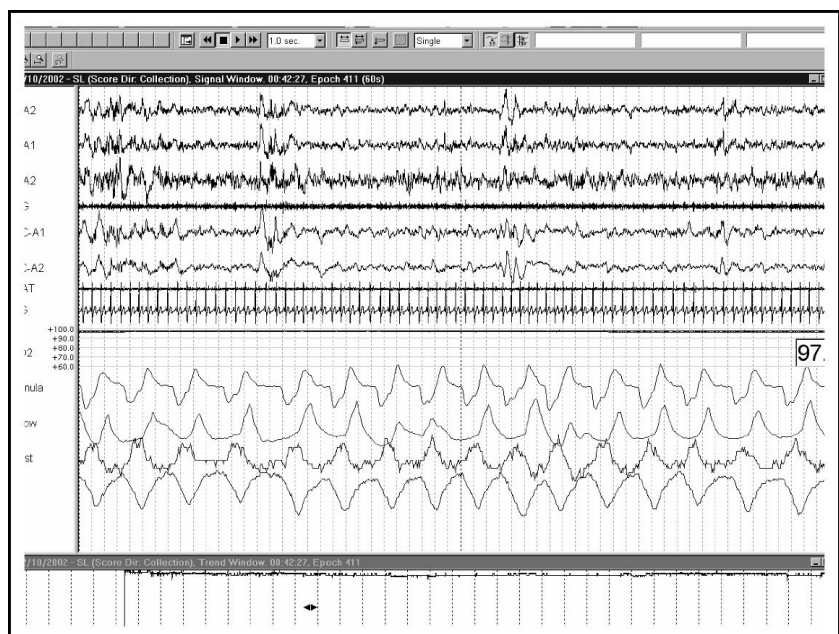
management of UARS. Orthodontic approaches such as rapid maxillary distraction, which are easily performed in children and teenagers, are not directly applicable in adults. This is caused by complete ossification of the maxilla and mandible. In adults, midline incisions of the maxilla and mandible are necessary before the placement of internal jaw distractors. Distraction osteogenesis applied to patients with SDB showed promising clinical improvement [51••,52•]. This combined surgical and orthodontic treatment is much less invasive than the traditional jaw advancement surgery. However, patients are required to wear braces for an extended time after jaw expansion for orthodontic purposes.

Conclusion

More and more clinicians recognize UARS as a clinical syndrome that has differential features from OSAS. It is critical to recognize the associated symptoms with UARS that are not traditionally related to OSAS. Considering the obesity epidemic in the United States and other industrialized countries, it is easy to miss UARS, but nonrecognition early in life of the syndrome and the anatomic abnormalities surrounding the upper airway responsible for its symptoms will lead to complications and perhaps even development of OSAHS. With better understanding of breathing during sleep and better monitoring technology, it becomes clear that the existence of benign snoring should be questioned. We should evaluate for snoring not only children, as emphasized by the American Academy of Pediatrics [53••], but also adults, because many will prove to have UARS. Considering that prevention is much less costly to society than treatment of a syndrome with permanent lesions, recognition and treatment of UARS should also be a priority.

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