INTRODUCTION

Upper-airway resistance syndrome (UARS) was first recognized in children in 1982 (Guilleminault et al., 1982). The term UARS, however, was not used until adult cases were reported in 1993 (Guilleminault et al., 1993). The description of UARS brought the attention of clinicians to a group of patients that was left undiagnosed and untreated despite severe impairment. The authors indicated that they had to identify this clinical entity as many had been denied proper treatment based on subjects’ symptoms and polysomnographic (PSG) features that differ from those of obstructive sleep apnea syndrome (OSAS). However, controversies exist regarding UARS. Some have rejected it as a distinct clinical entity or even doubted its existence (Douglas, 2000). In the past few years, however, there has been greater acceptance of this entity, and review articles have been published on UARS in general (Exar and Collop, 1999) and in children (Guilleminault and Khramtsov, 2001).

Since the first description of a polygraphic pattern called obstructive sleep apnea in the pickwickian syndrome in 1965 (Gastaut et al., 1965; Jung and Kuhlo, 1965), sleep medicine has undergone an evolution. UARS was introduced as part of the efforts to describe a generally unrecognized patient population that is nonobese and whose clinical features do not match those reported with OSAS. Unfortunately, many sleep-breathing abnormalities are still ignored due to the belief that sleep-disordered breathing is synonymous with OSAS and that patients must be overweight or clearly obese. Such limited views have already led to the underdiagnosis and undertreatment of OSAS in women, “the forgotten gender” (Guilleminault et al., 1995). With the use of new techniques, such as the esophageal catheter for esophageal pressure ($P_{es}$) measurement (Flemale et al., 1988) and nasal cannula/pressure transducer (Norman et al., 1997), it has become more convenient to identify subtle changes in breathing patterns during sleep.

In the past few years, UARS has been linked to many somatic, psychiatric, or psychosomatic conditions, including parasomnias, attention deficit disorder (ADD) or attention deficit hyperactivity disorder (ADHD), fibromyalgia, as well as chronic insomnia. It has been shown that the consequences of the syndrome on the autonomic nervous system are different compared to those linked to OSAS. Some considered UARS as part of a spectrum that includes benign snoring, UARS, obstructive hypopnea, obstructive sleep apnea (OSA), and hypoventilation. However, despite the fact that some patients may present such progression, it is too simple to link all these entities together.

The first issue is whether to believe that there is a “benign” chronic snoring. Our studies support that chronic snoring is not “benign” and is part of UARS. The American Academy of Pediatrics recognized such possibility when it recommended exploring chronic snoring in all children (American Academy of Pediatrics, 2002), but such a recommendation has never been made in adults. The second issue is whether to consider that UARS is systematically associated with chronic snoring, as even the initial description of the syndrome indicated that snoring was absent in about one-third of reported patients (Guilleminault et al., 1993). Finally, the progressive evolution from UARS is questionable. The only longitudinal study performed on about 100 UARS subjects seen again without treatment about 5 years later reported that fewer than 10% had such evolution (Guilleminault et al., 2006b). In these cases, it was associated with clear weight gain, leading to fatty infiltration of both neck and abdomen, with secondary restrictive chest bellows impairment; this was particularly obvious during rapid eye movement (REM) sleep and became worse by
physiologic development of the REM sleep-related muscle atonia that eliminates usage of respiratory accessory muscles.

Our understanding of OSAS and its underlying lesions has improved in recent years, and the two syndromes can be understood as related to the presence of either normal or impaired capability to respond to specific upper-airway airflow challenges during sleep.

**EPIDEMIOLOGY**

There is no investigation of UARS in the general population. In children, it has been reported that 9–12% of children are chronic snorers (Guilleminault et al., 2005a). Chronic snoring without OSA in children has been shown to be associated with different health problems, mostly behavioral, such as hyperactivity, inattention, poor school performance, anxiety, or depressive effects. Unfortunately, most chronic snorers have not been studied with PSG. When studied, however, absence of apnea–hypopnea and presence of increased respiratory effort, indicative of UARS, and documented by $P_{es}$, were shown during sleep. In children, prevalence of OSAS has been calculated at between 4 and 5%, compared to the reports of chronic snoring, at 9–12% (Guilleminault et al., 2005a).

**CLINICAL SYMPTOMS**

Although some of the symptoms in UARS overlap with those in OSAS, studies have found some important differences (Guilleminault and Bassiri, 2005). Chronic insomnia tends to be much more common in patients with UARS than those with OSAS. Many UARS patients report maintenance insomnia characterized by frequent nocturnal awakenings and difficulty falling back to sleep, but sleep-onset insomnia is also present, and is thought to be caused by “conditioning” as a consequence of frequent sleep disruptions (Guilleminault et al., 2002a). Adult patients with UARS are also more likely to complain of fatigue rather than sleepiness. They may have difficulty getting up in the morning and may shift their sleep schedule, evolving toward a delayed sleep phase disorder. Other presentations include parasomnias with sleepwalking and sleep terrors (Guilleminault et al., 2006a), myalgia, depression, and anxiety. Gold and colleagues (2003) emphasized that UARS patients have complaints related more to functional somatic syndromes, such as headaches, sleep-onset insomnia, and irritable bowel syndrome. Not infrequently, UARS is misinterpreted as chronic fatigue syndrome, fibromyalgia, or psychiatric disorders such as ADD/ADHD (Lewin and Pinto, 2004) or depressive disorders. A clinical case report of UARS has also presented symptomatology mimicking nocturnal asthma (Guerrero et al., 2001). Symptoms related to chronic nasal allergies are often seen.

The clinical interview reveals the presence of light-headedness with abrupt positional changes, sometime more pronounced on awakenings, and subjects may have learned early to avoid “jumping out of bed” and having a two-step approach when getting up. History of fainting mostly during teenage years may also be elicited. Between one-fifth and one-fourth will report the presence of cold hands and/or cold feet and sometimes other mild signs associated with vagal hyperactivity such as orthostatic hypotension and cold extremities. The other reported health problems are related to the most common cause of UARS, i.e., small maxilla and/or mandible manifested as impaction of wisdom teeth with need for removal between 15 and 25 years, history of orthodontic treatment often with teeth removal, usage of dental retainer or other dental device during childhood, or presence of bruxism. A history of chronic nasal allergies sometimes associated with chronic sinus infection or a history of repetitive upper-airway infection or earaches may occur during the first years of life.

**PHYSICAL EXAMINATION**

Clinical examination will show low blood pressure in about one-fourth of subjects, often associated with moderate worsening with orthostatic maneuvers (Guilleminault et al., 2001a, 2004). Indications of anatomic narrowing of the upper airway have to be evaluated:

1. evaluation of nose: asymmetrical external valve, collapse of internal valve at inspiration, narrow and long nose, enlargement of inferior nasal turbinates due to allergy, presence of deviated septum
2. evaluation of maxilla: high and narrow hard palate, presence of overlapping teeth, short intermolar distance
3. evaluation of mandible: retroposition indicated by important (>2.2 mm) overjet, presence of indentation on lateral sides of tongue, presence of scars related to lateral biting of cheek
4. evaluation of face: elongation of lower anterior third of face, steep mandibular plane, narrow and elongated chin.

Soft tissues should also be evaluated with determination of tonsil size using standard scales and placement of the tongue in relation to the uvula, using the Mallampati scale (Mallampati et al., 1985). Cephalometric X-rays may confirm this information. Although the clinical evaluation allows one to suspect UARS and its potential relationship to anatomical factors impacting the upper airway, the diagnosis can only be confirmed by PSG.
Polysomnography

PSG reveals an apnea–hypopnea index (AHI) < 5, oxygen saturation > 92%, and presence of respiratory effort-related arousals (RERAs) as well as other nonapnea/hypopnea respiratory events. Although inductive respiratory plethysmography (Loube et al., 1999), pneumotachograph, and most commonly nasal cannula/pressure transducer have been tried to measure subtle respiratory alterations (Ayap et al., 2000; Epstein et al., 2000; Virkula et al., 2002), measurement of $P_{es}$ remains the gold standard for detecting respiratory abnormalities. The use of a pediatric feeding catheter instead of an esophageal balloon has improved tolerance of the procedure in both adults (Epstein et al., 2000) and children (Serebrisky et al., 2002). The nasal cannula/pressure transducer is more sensitive than thermistors in picking up respiratory changes and has been used to detect RERAs. In addition to the nasal cannula/pressure transducer system, respiratory channels, mouth thermistor (mandatory to recognize mouth breathing with nasal obstruction), thoracic and abdominal piezoelectric bands or inductive respiratory plethysmography, neck microphone and $P_{es}$ are important to allow proper diagnosis. Calibration of different channels, particularly $P_{es}$, before the beginning and at the end of monitoring, is mandatory. The other PSG channels all have to be present in these cases, particularly several electroencephalogram (EEG) leads that will allow monitoring not only C3–A2 and C4–A1 but also frontal and occipital derivations, that will help in the investigation of the presence of American Sleep Disorders Association (1992) arousals of 3 seconds’ or more duration as well as the calculation of cyclic alternating pattern (CAP) during non-REM (NREM) sleep.

Analysis of PSG will not only recognize apnea and hypopnea as classically defined, but will also determine the presence of flow limitation based on the analysis of the nasal cannula curve. Flow limitation will appear as flattening of the normal bell-shaped curve of normal breath with a drop in the amplitude of the curve by 2–29% compared to the normal breaths immediately preceding (Figures 26.1–26.3). The nasal cannula/pressure transducer is more sensitive than thermistors in picking up respiratory changes and detecting RERAs. However, sensitivity comparable with $P_{es}$ measurement has not been demonstrated. Three abnormal forms of $P_{es}$ tracings have been described (Black et al., 2000; Guillemaintault et al., 2001b). First, $P_{es}$ crescendo is a progressively increased negative peak inspiratory pressure in each breath which terminates with an alpha-wave EEG arousal or a burst of delta wave. This is not associated with a drop in oxygen saturation of 3%, as used for definition of hypopnea. The second form is a sustained continuous respiratory effort, wherein the $P_{es}$ 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 $P_{es}$ reversal, wherein there is 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. This indicates the end of an abnormal breathing sequence, independent of the EEG pattern.

The disadvantage of $P_{es}$ 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, $P_{es}$ measurement is not widely applied, due to patients’ fear of discomfort and sleep technologists’ hesitancy, except in centers where the technique has been well adapted, or in academic and research settings. We have applied a new algorithm using intercostal EMG signals to pick up the respiratory variations. The results are quite promising (Stoohs et al., 2004). Another technique using pulse wave signals was developed in Japan and patented in the USA for commercial development (Nanba et al., 2002). It is expected that, in the near future, new techniques will be available for measuring even more subtle changes in respiratory efforts without the need of a $P_{es}$ catheter placement.

Polysomnographic findings and power spectral EEG analysis

The typical PSG findings for UARS include AHI < 5, minimum oxygen saturation > 92%, an increase in alpha rhythm, and a relative increase in delta sleep, which persists in the latter cycles of sleep. Recent studies also confirm that UARS patients may have more alpha EEG frequency time (Guilleminault et al., 2001c; Poyares et al., 2002) and more RERAs (Poyares et al., 2002) during sleep than patients with obstructive sleep apnea-hypopnea syndrome (OSAHS). Scoring of CAPs is another novel approach evaluating quality of sleep in UARS. A higher frequency of CAPs is noted in UARS compared to age- and gender-matched controls (Guilleminault et al., 2005a; Lopes and Guilleminault, 2005). The comparison of the sleep EEG of UARS, OSAHS, and normal control subjects, using power spectrum analysis, shows a higher amount of theta and alpha powers (i.e., 7–9 Hz bandwidth) during NREM sleep, and more delta powers during REM sleep compared with OSAHS and normal subjects (Guilleminault et al., 2001c). The new analytic approach design by Chervin et al. (2004) that quantifies the so-called respiratory cycle-related electroencephalographic changes breath by breath, and correlates delta, theta, and alpha EEG...
powers with respiratory cycle variations, may allow the
detection of more subtle sleep EEG changes related to
abnormal respiratory efforts.

**PATHOPHYSIOLOGY**

**Difference between OSAS and UARS**

The idea that OSAS involves the presence of a local
neuropathy at the pharyngeal region was first proposed
by Swedish investigators and is based on neurophysio-
logic, electron microscopic, and clinical investigations
(Edstrom et al., 1992; Friberg et al., 1997, 1998a, b).
The presence or absence of these neurogenic lesions
is the basis for the existence of the two syndromes.

Data obtained by Friberg et al. (1997, 1998a, b)
provided evidence of local neurogenic lesions of the
upper airway in OSAS and these lesions are asso-
ciated with slowing of impulse conduction (MacKenzie
et al., 1977). Their data are in accordance with those
shown by Woodson et al. (1991), Series et al. (1996),
Kimoff et al. (2001), and Guilleminault et al. (2002a).
Friberg (1999) compared the findings observed in
the “vibration-induced white finger” syndrome with
those noted in clinical neurophysiologic and histologic
tests in OSAS patients. The clinical and histologic
findings secondary to long-term use of low-frequency
hand-held vibrating tools include decreased sensitivity
to vibration and temperature, hypertrophied muscle
cells, and a demyelinating neuropathy in the periph-
eral nerves. There is marked loss of nerve fibers
and myelin sheaths and relatively smaller axons with-
out myelin. Similar findings have been reported with

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**Fig. 26.1.** Example of flow limitation in a patient with upper-airway resistance syndrome during slow-wave sleep. From top to
bottom the following channels were recorded: channel 1–4 electroencephalogram (EEG) (C3/A2, C4/A1, O1/A1, Fp1/A2); channel 5: chin electromyogram (EMG), channels 6 and 7: left and right electro-oculogram (LOC and ROC), channel 8: electrocardiogram (EKG), channels 9 and 10: leg EMG, channel 11: pulse oximetry, channel 12: neck microphone, channel
13: nasal cannula/pressure transducer, channel 14: oral thermistor, channels 15 and 16 thoracic and abdominal movements.
Bottom: time during the night. During this 120 seconds’ monitoring during slow-wave sleep, the presence of flow limitation
can be seen without apnea, hypopnea, snoring, or oxygen saturation drop. The flow limitation is seen on the nasal cannula
channel. Presence of cyclic alternating pattern can also be seen when looking at the EEG leads.

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**Patient Name:** 100029 Example, 1

**Subject Code:** X

**Study Date:** 02/17/2006

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clinical testing and with the Swedish group’s histologic studies in the oropharyngeal region (Friberg, 1999). Heavy snoring produces low-frequency vibration, and these similarities support the hypothesis that a vibration trauma may be involved in the development of lesions (Nguyen et al., 2005). Furthermore, human receptors located in the upper airway respond to oscillations similar to snoring simply by increasing the EMG activity in the genioglossus and other respiratory muscles.

Nguyen et al. (2005) used an endoscopic sensory testing technique (Aviv et al., 1993, 1999) in OSAS and an air pulse stimulator in control patients. Using such a technique, no difference in sensory thresholds was seen in patients and matched controls when air pulse was delivered on the lips, but clear differences were seen at the oropharyngeal and laryngeal levels, more particularly at the level of the aryepiglottic eminence, indicating that OSAS patients have lesions not only in the oral-pharyngeal but also laryngeal regions, with disturbance of an aryepiglottic reflex due to sensory lesions. The importance of the sensory lesions in the larynx correlates with the AHI (Nguyen et al., 2005). In OSAS the presence of local sensory lesions does not allow passage of information concerning airflow to induce motor response.

An investigation performed by Affifi et al. (2003) also supports this conclusion. Simultaneous investigation of auditory evoked responses and respiratory-related evoked potentials were performed in OSAS and controls during wakefulness and sleep. An abnormal evoked response to inspiratory occlusion stimuli during NREM sleep was demonstrated in OSAS patients compared to matched normal controls. However, normal responses in the same OSAS subjects occurred with auditory stimulation. This study therefore supports the presence of a sleep-specific dampening of cortical processing of inspiratory effort-related information but presence of otherwise normal stimuli response. In summary, OSAS patients have local

Fig. 26.2. Example of flow limitation during stage 2 nonrapid eye movement sleep in a patient with upper-airway resistance syndrome. Montage is the same as for Figure 26.1. Note the presence of flow limitation during 30 seconds of recording, well shown on the nasal cannula channel: the normal upper round shape of each breath has been replaced by a flattening of the curve, indicative of the flow limitation.
neurogenic lesions in the pharynx and upper larynx that interfere with normal control of upper-airway patency and lead to slow modulations of airway patency. Apneas and hypopneas occur due to the abnormal balance between intrathoracic effort and upper-airway muscle contractions created by local sensory pathway impairment.

UARS patients do not present these local sensory destructions, or at least not in a sufficient amount to impair reflexes adjusting the upper-airway patency continuously during sleep. The studies supporting the absence of local neurogenic lesions in UARS are more limited: one study compared the responses between age- and gender-matched OSAS and UARS patients and normal controls, involving 20 subjects per group (Guilleminault et al., 2002a). The results showed similar two-point discrimination responses between UARS and controls while OSAS had abnormal responses. This study matched the results obtained by Dematteis et al. (2005) in patients with low AHJ scores (5–10 events/hour).

The pathophysiological difference between OSAS and UARS is conceptualized as follows. The blunting or elimination of sensory input from the upper airway in OSA does not allow an appropriate adjustment of upper-airway muscle tone to many challenges and this leads to a too narrow upper airway at onset of inspiration, causing airway collapse. In UARS, however, the absence of neurogenic lesions in the upper airways and the persistence of sensory input lead to a faster arousal and changes despite the presence of a narrow airway related to anatomical changes at a point with variable location, from the external valve of the nose to the base of the tongue (Guilleminault et al., 1993; Bao and Guilleminault, 2004).

The presence or absence of an important decrease in the size of the airway in relation to the importance of the local neurogenic lesions will lead to variable changes in blood gases and the need to call upon other stimuli to reopen a collapsing airway. Drops in oxygen saturation ($\text{SaO}_2$) and arousal responses related to these blood gases changes will have a direct impact on the
autonomic nervous system. UARS and OSAS will lead to different autonomic nervous system stimulations.

Investigation of UARS patients with low blood pressure (Guilleminault et al., 2001a; Guilleminault et al., 2004) and studies of heart rate variability using fast Fourier transformation (Guilleminault et al., 2005c) have shown that UARS subjects present an active vagal tone compared to sympathetic tone during sleep.

In contrast, hyperactivity of the sympathetic tone has been well shown in OSAS patients. This sympathetic hyperactivity, initially during sleep but quickly seen during wakefulness, has been well demonstrated in OSAS using different techniques, but the most demonstrative is the continuous recording of muscle nerve sympathetic activity in the leg. This technique shows an abnormal resetting of sympathetic tone, with hyperactivity as the first sign in the development of lesions of the vascular endothelium and of hypertension.

In UARS, the inhibition of sympathetic tone during sleep is related to the abnormal inspiratory effort associated with increased airway resistance. The liberation of the vagal tone left alone as the autonomic regulator during sleep is responsible for the observation of mild orthostatism and vagal dominance during sleep and sometimes during wakefulness. The absence of a clear $S\Delta O_2$ drop in UARS also eliminates one of the important stimuli of the sympathetic tone activity during sleep, as seen in OSAS.

In summary, UARS patients have upper-airway reflexes intact during wakefulness and sleep, while they are impaired in OSAS. Furthermore, in OSAS, the presence of repetitive $S\Delta O_2$ drops excite sympathetic tone during sleep, leading to progressive sympathetic tone resetting and hyperactivity, a response not present in UARS.

**TREATMENT**

In the original description of UARS by Guilleminault et al. (1993), patients were treated successfully with nasal continuous positive airway pressure (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 (Guilleminault et al., 2002b). Studies have demonstrated that adding cognitive behavioral therapy to CPAP treatment is beneficial for patients with chronic insomnia or psychosomatic symptoms secondary to UARS (Guilleminault et al., 2002b; Krakow et al., 2004). On the other hand, 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 (Guilleminault et al., 2002b).

Oral appliances can also achieve satisfactory outcomes in UARS (Yoshida, 2002). Septoplasty and radiofrequency reduction of enlarged inferior nasal turbinates can be successful in treating UARS. Anatomical abnormalities also often involve soft tissues in the soft palate and the maxilla and mandible skeletal structures. If the primary cause of the abnormal breathing, such as crowded airway and narrowed jaws, is not corrected, patients will be left with the complaint of worsening “functional” symptoms, which potentially may lead to the development of local polyneuropathy. 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. Uvulopalatal flap (Powell et al., 1996) and distraction osteogenesis (Guilleminault and Li, 2004) have been helpful in the management of UARS. Orthodontic approaches, such as rapid maxillary distraction, which are conveniently performed in children and teenagers, are not directly applicable in adults. This is due to complete ossification of the maxilla and mandible. In adults, midline incisions of the maxilla and mandible are necessary prior to the placement of internal jaw distractors. Distraction osteogenesis applied to sleep-disordered breathing patients showed promising clinical improvement (Pirelli et al., 2004). 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.

In summary, the treatment of UARS may be more demanding than OSAS, as patients usually tolerate nasal CPAP less and become quickly noncompliant. Treatment of the underlying causes of the upper-airway anatomical problems is the usual approach that may consist of aggressive treatment of nasal allergies, usage of palatal soft-tissue surgery, orthognathic surgery, or the use of dental devices.

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