

Upper airway resistance syndrome: still not recognized and not treated

Síndrome da resistência da via aérea superior: ainda não-reconhecida e não-tratada

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ABSTRACT

The upper airway resistance syndrome (UARS) is a sleep breathing disorder described by Guillemineault et al., in 1993, to identify patients that present increased respiratory effort and airflow limitation during sleep associated with an increase in the upper airway resistance. Patients usually complain of daytime sleepiness, fatigue, snoring, and difficulty to maintain sleep. Complaints related to cognitive impairment, headache, anxiety, and irritability are also frequent. The physical examination shows nasal obstruction, increase in soft tissue and craniofacial abnormalities associated with decrease in the upper airway space. Nocturnal polysomnography does not show apneas or hyponeas for diagnostic criteria of obstructive sleep apnea syndrome (OSAS), and respiratory abnormalities consist on periods of increase in respiratory effort, sleep fragmentation, presence of respiratory event related arousal (RERAs) and presence of flattening of respiratory curve, which indicates airflow limitation. Controversies exist regarding the characterization of upper airway resistance syndrome as part of a continuum with other sleep breathing disorders, or as a separate entity that may not progress to obstructive sleep apnea syndrome. Treatment of upper airway resistance syndrome is more challenging than obstructive sleep apnea syndrome, since patients have lower tolerance for continuous positive airway pressure (CPAP) use. Other treatment modalities have been investigated, but they are still not established for clinical practice. Recognition of upper airway resistance syndrome is important, since it may prevent long-term consequences or progression to more severe forms of sleep-related breathing disorders.

Keywords: airway resistance; polysomnography; electroencephalography; sleep apnea, obstructive; sleepiness; arousal; respiration.

RESUMO

A síndrome da resistência da via aérea superior (SRVAS) é um distúrbio respiratório do sono, descrito por Guillemineault et al., em 1993, para identificar pacientes que apresentam aumento do esforço respiratório e limitação ao fluxo aéreo durante o sono, associado com aumento na resistência da via aérea superior durante o sono.

Estes pacientes geralmente queixam-se de sonolência diurna, fadiga, ronco e dificuldade para manter o sono. Queixas relacionadas a prejuízo cognitivo, cefaleia, ansiedade e irritabilidade também são frequentes. O exame físico demonstra obstrução nasal, aumento dos tecidos moles e anormalidades craniofaciais associadas à diminuição no espaço aéreo superior. A polissonografia noturna não apresenta apneias e hipopneias suficientes para o diagnóstico da síndrome da apneia obstrutiva do sono (SAOS), e as anormalidades respiratórias consistem de períodos de aumento do esforço respiratório, fragmentação do sono, presença de eventos respiratórios relacionados ao despertar e presença de achatamento da curva respiratória, o que indica limitação ao fluxo aéreo. Controvérsias existem em relação à caracterização da síndrome da resistência da via aérea superior, como sendo parte de um contínuo com outros distúrbios de sono ou como uma entidade clínica distinta que não necessariamente progride à síndrome da apneia obstrutiva do sono. O tratamento da síndrome da resistência da via aérea superior é mais desafiante do que o da síndrome da apneia obstrutiva do sono, uma vez que os pacientes têm menor tolerância ao uso do CPAP (*continuous positive air pressure*). Outras modalidades de tratamento tem sido investigadas, contudo, a resposta a estas modalidades não esta totalmente estabelecida para a prática clínica. O reconhecimento da síndrome da resistência da via aérea superior é importante, uma vez que pode prevenir consequências a longo prazo para formas mais graves de distúrbios respiratórios do sono.

Palavras-chave: resistência das vias respiratórias; polissonografia; eletroencefalografia; apnéia do sono tipo obstrutiva; respiração com pressão positiva; nível de alerta; respiração.

INTRODUCTION

The upper airway resistance syndrome (UARS) is a sleep-related breathing disorder characterized by clinical signs and symptoms, including daytime sleepiness and/or fatigue, and increased upper airway resistance associated with frequent arousals and sleep fragmentation. In 1993, the term 'upper airway resistance syndrome' was first

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used, by Guilleminault et al.¹, to describe a subgroup of patients with conditions that were formerly diagnosed as idiopathic hypersomnia or central nervous system (CNS) hypersomnia. These terms were used to describe excessive daytime sleepiness (EDS), without a clear cause defined by the nocturnal polysomnography (PSG) or the multiple sleep latency test (MSLT). Patients with the UARS demonstrated repetitive increased upper airway resistance episodes defined by increasingly negative inspiratory esophageal pressure (Pes), which occurred concomitantly with decreased oronasal airflow in the absence of frank apneas or oxygen desaturation. These episodes were brief, typically lasting one or three breaths, and resulted in brief electroencephalograms (EEG) arousals (from two to four seconds), followed immediately by decreased upper airway resistance. Since this initial description, several studies have been published demonstrating the importance of recognizing UARS.

Some consider UARS as part of a spectrum that includes benign snoring, obstructive hypopnea, obstructive sleep apnea, and hypoventilation. Others consider the UARS as a distinct entity, since it presents some differences in the clinical presentation and different aspects of the pathophysiology. Furthermore, the progression from UARS to obstructive sleep apnea syndrome (OSAS) is questionable, and there is no data on follow-up to demonstrate the evolution of this condition.

The UARS was described 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 patients must be overweight or clearly obese with a large neck.

Today, more than a decade later after the former initial description, patients with UARS are often not recognized and not treated. These patients come to the sleep clinic complaining of daytime sleepiness or fatigue and have a PSG, which do not demonstrate the presence of OSAS. Symptoms such as fatigue, lack of energy, irritability and decreased memory and concentration presented by these patients may be labeled as depression or as related to stress. PSG patterns indicating increased upper airway resistance are frequently missed. These patients are misinterpreted as not having a sleep-related breathing disorder, treatment is not indicated, and they are told to come back on the future for a follow-up.

UARS need to be suspected by every sleep specialist, so patients can get early treatment and prevent long-term consequences.

PATHOPHYSIOLOGY

The UARS pathophysiology is considered similar to OSAS in some aspects. However, some aspects indicating UARS as a different entity with different pathophysiology have been suggested by some studies. One aspect is regarding different upper airway responses. It has been demonstrated that OSAS and UARS present differences regarding presence or absence of neurogenic lesions, caused by frequent trauma related to abnormal breathing. Data from Friberg² provided evidence of local neurogenic lesions of the upper airway in OSAS, and these lesions are associated with slowing of impulse conduction³. Afifi et al.⁴ demonstrated that OSAS present an abnormal response to respiratory-related evoked potentials, indicating a specific dampening of cortical processing of inspiratory effort related information. They concluded that OSAS patients present neurogenic lesions in the pharynx and upper larynx that interfere with normal control of the upper airway patency, which leads to apneas and hypopneas caused by an abnormal balance between intrathoracic effort and upper airway muscle contractions, created by local sensory impairment. Some studies have demonstrated that UARS patients do not present these local destructions⁵.

The authors suggested that OSAS and UARS may have different pathophysiology with the following conception: the blunting or elimination of sensory input from the upper airway predispose muscle tone to many challenges and this lead to a narrow upper airway at the onset of the inspiration, leading to 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 the point with a variable location, from the external valve of the nose to the base of the tongue⁶.

Differences on the impact and changes observed on the autonomic nervous system (ANS) have also been demonstrated between OSAS and UARS patients. In the OSAS, there is a hyperactivity of the sympathetic tone related to oxygen saturation drops and arousals. UARS subjects present an inhibition of sympathetic tone⁷ related to abnormal inspiratory effort associated with increased airway resistance. The release of the vagal tone is responsible for the observation of mild orthostatism and vagal dominance, during sleep.

In summary, the UARS have upper airway reflexes intact during wake and sleep, while they are impaired in OSAS. Furthermore, in OSAS, the presence of repetitive SaO₂ drops excite the sympathetic tone during sleep, leading to progressive sympathetic tone resetting and hyperactivity, a response that is not present in UARS.

CLINICAL PRESENTATION

By definition, UARS patients have daytime sleepiness or fatigue. Initial studies in adults⁸ included only men; it was later recognized that the syndrome was also present in women, with a roughly equal gender distribution¹. Contrary to what is seen in OSAS patients, UARS patients are typically nonobese, with body mass index (BMI) ≤ 25 kg/m²^{1,8}. They are also frequently younger than OSAS patients.

Patients with UARS have symptoms that overlap with OSAS patients, but recent studies showed some clinical differences⁹. Chronic insomnia tends to be more common in patients with UARS, and many of them report nocturnal awakenings and difficulty in falling back to sleep. They often complain of sleep onset and maintenance insomnia, which is thought to be due to “conditioning”, as a consequence of frequent sleep disruptions¹⁰. Other presentation includes parasomnias, such as sleepwalking and sleep terrors, myalgia, depression, and anxiety. Gold et al. emphasized that UARS patients have complaints more related to functional somatic complaints, such as headaches, sleep-onset insomnia, and irritable bowel syndrome. Their patients had polysomnographic findings of UARS¹¹. It is frequent that UARS is misinterpreted as chronic fatigue syndrome, fibromyalgia, or as psychiatric disorders, such as attention deficit disorder/attention deficit hyperactivity disorder (ADD/ADHD)¹². Patients refer cold hands and feet. Some of them refer lightheadness or tendency to faint upon standing abruptly. This last complaint may be explained by the finding that low-blood pressure (BP) (SBP < 100 mmHg) is more commonly associated with UARS¹³, whereas hypertension is more commonly associated with OSAS (Table 1).

PHYSICAL EXAMINATION

Clinical examination shows low-BP in about one-fourth of subjects, often associated with worsening during orthostatic maneuvers^{13,14}. The physical examination needs to include evaluation of the nose, maxilla, mandible, and soft tissues.

Upper airway examination frequently shows craniofacial abnormalities including low soft palate, long uvula, increased overbites, and high, narrow and hard palate.

Despite the differential clinical features, it is sometimes difficult to dissociate patients with UARS from those with mild OSAS, based on symptoms and clinical signs alone. Diagnosis can only be confirmed by PSG.

PSG

Patients with UARS have symptoms related to daytime alertness impairment associated with PSG parameters,

Table 1. Most important clinical aspects of UARS compared to OSAS.

Aspects	UARS	OSAS
Age	Young	Children, middle age men Menopausal woman
Gender	1:1	2:1
Sleep onset	Insomnia	Fast
Snoring	Common	Almost always
Apneas	Absence	Frequent
Daytime symptoms	Tiredness Fatigue	Daytime sleepiness
BMI	Normal	Increased
Somatic complaints	Fibromyalgia, headache	Rare
ANS symptoms	Cold extremities fainting	Rare
BP	Low or normal	High

BMI: body mass index; ANS: autonomic nervous system; BP: blood pressure.

indicating increase in upper airway resistance. They also must have an indication of increased upper airway resistance and respiratory effort during sleep, in the absence of apneas/hypopneas criteria that fulfill OSAS criteria.

Increased respiratory effort during sleep in UARS patients was initially described using an esophageal pressure monitoring, and it still is considered the gold-standard of diagnosis¹. The use of a pediatric feeding catheter instead of a balloon has made the procedure better tolerable in adults¹⁵. Three abnormal patterns indicative of increased respiratory effort during sleep have been described; *Pes crescendo*, sustained continuous respiratory effort, and *Pes reversal*¹⁶.

Airflow limitation is defined by an increase in respiratory effort without the increase in airflow, it is also an indication of upper airway initial decrease in area. The development of a plateau on the inspiratory flow signal from a nasal cannula can also be used as a marker of increased upper airway resistance and flow limitation and, hence, may be used to indicate presence of periods of increased resistance¹⁷. Flow limitation will appear as a ‘flattening’ of the normal bell-shape curve of normal breath, with a drop in the amplitude of the curve by 2 to 29% compared to the normal breaths immediately preceding. The nasal cannula/pressure transducer is more sensitive than thermistor in picking up respiratory changes and detecting flow limitation, which is demonstrated in respiratory event related arousal (RERAs) (term defined by AASM to describe flow limitation leading to arousal). However, sensitivity comparable with *Pes* measurement has not been demonstrated.

UARS patients have nocturnal PSG with normal apnea hypopnea index (AHI), no significant oxygen desaturation and presence of flow limitation during sleep, as

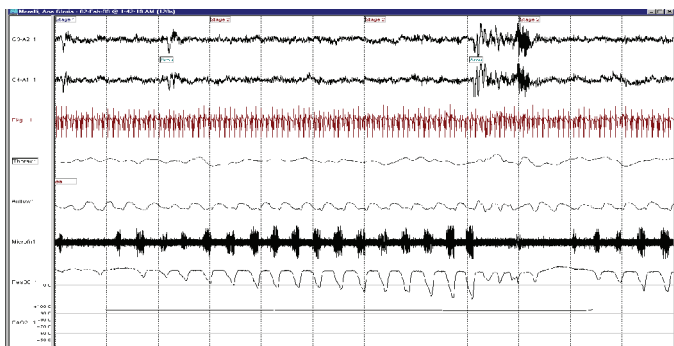


Figure 1. RERA example with increased respiratory effort leading to an arousal.

well as other non apnea hypopnea respiratory events. The American Academy of Sleep Medicine (AASM) task force for sleep-related breathing disorders defined the term RERA to describe events involving the increased respiratory effort and arousal (Figure 1). The event must fulfill the criterion for an abnormal breathing pattern indicated by a progressively more negative esophageal pressure or flattening of the respiratory curve, which last ten seconds or longer leading to an arousal.

Other noninvasive markers of increased upper airway resistance have been proposed, such as: brief arousals accompanying increasing snoring intensity, beat to beat BP measurement¹⁸, forced oscillation technique¹⁹ pulse transit time (PTT)²⁰, and respiratory inductive plethysmography²¹. Although other respiratory measurements have been investigated, the measurement of esophageal pressure remains the gold-standard for detecting increase in respiratory effort.

It has also been demonstrated that, in UARS patients, clinical complaints of fatigue and sleepiness are associated with sleep instability. UARS is a subtype of SDB, which is strongly associated with daytime complaints and sleep disruption²². UARS patients have an increase in alpha EEG rhythm during sleep²³, which is correlated with low-arousal threshold¹⁶. Typically, an arousal can occur associated with flow limitation and abnormal increase in respiratory efforts during sleep. These patients have peaks in Pes measured around -33 ± 7 cm H₂O, in 1993. However, it is often observe Pes reversal (normalization of Pes) without classic ASDA arousal in the end of event (in 2000)²⁴. Flow limitation in nasal cannula can be associated with EEG changes²⁵. Cyclic alternant pattern (CAP) in NREM sleep has been described as a new marker of sleep instability and sleep disruption in adults with several sleep disorders²⁶. This pattern was increased in severe OSAS patients and it was decreased after continuous positive air pressure (CPAP) treatment of OSA patients²⁶. UARS is associated with sleep disruption and insomnia

complaints. Parrino et al. have been calling the insomnia as an internal noise that has an increase in CAP rate in NREM sleep. UARS patients have also an internal noise associated with increase in respiratory effort. The analyses of CAP have been showing that there is sleep instability in NREM sleep in UARS patients²⁷

The MSLT helps to objectively confirm the subjective symptom of EDS²⁸. But, often, the MSLT scores are not very demonstrative. Similarly, the Epworth Sleepiness Scale may not provide a valid impression, and fatigue and visual analog scales have been better tools to investigate the UARS.

CONSEQUENCES

Daytime sleepiness

The increased respiratory effort, due to increased upper airway resistance during sleep, leads to increased arousals lasting only seconds²⁹, heading to sleep fragmentation and daytime sleepiness. However, often subjects will complain more of daytime fatigue, or difficulty to concentrate. The level of negative intrathoracic pressure is the most likely stimulus for arousal, possibly mediated by the mechanoreceptors in the upper airway and chest wall.

Disrupted nocturnal sleep and complaint of 'insomnia'

Subjects may perceive more the repetitive arousal and nocturnal disruption and may develop conditioning secondary to arousal during sleep with fear of poor sleep. If left untreated, the pattern may be one of 'insomnia' with nocturnal arousal, and if secondary conditioning occurs, long sleep latency may give a mixed presentation. The association between insomnia and sleep disorders breathing (SDB) is another important subject. The interaction between insomnia and SDB has been important to better understand the arousal ability process, which can be an important differential factor to recognize subtypes of SDB.

Effect on blood pressure

Several studies have established the association between OSAS and hypertension^{30,31}. A positive correlation between chronic loud snoring and stroke or hypertension has been reported. Patients with UARS have a higher risk for abnormal BP control³². A review by Silverberg and Oksenberg³² showed 30 to 40% incidence of OSAS and 30 to 75% incidence of nonapneic snoring in hypertensive individuals. In a study by Guilleminault³³, 110 UARS patients were evaluated using 48-hour continuous am-

bulatory BP monitoring, before and after treatment with nasal CPAP. Five out of six subjects used CPAP on a regular basis and their chronic borderline BP was completely controlled. No changes were seen in the sixth subject who discontinued his CPAP after three days. In another group of seven normotensive subjects, continuous radial artery BP recording was obtained during sleep along with PSG recording. Increased systolic and diastolic were observed during the breaths with the greatest inspiratory effort, even though there was no associated oxygen desaturation. A further increase was seen accompanying the arousals. Three of these subjects underwent echocardiography during sleep, which demonstrated a leftward shift of the interventricular septum with pulsus paradoxus at the time that the peak end-expiratory pressure was more negative than -35 cm H₂O.

Similar BP changes have been observed by Lofaso et al.³⁴. The authors concluded that undetectable arousals were occurring during these events, and it was the autonomic response to arousal that led to BP rise rather than changes in intrathoracic pressure or intraventricular septal shift. The exact mechanism is still debated. It is likely that both arousal and homodynamic factors are involved in BP changes.

There is also a subgroup of UARS individuals that the BP may be in fact lower than normal. The presence of orthostatic hypotension and intolerance with cold extremities and dizziness at standing upright was documented in these patients¹³. The authors hypothesized that subjects with sleep-disordered breathing, who do not suffer recurrent hypoxemia (UARS), have repetitive episodes of systemic hypotension that eventually lead to sympathetic nerve dysfunction. In contrast, subjects with sleep-disordered breathing, who suffer hypoxemia (OSAS), have repetitive pressure responses that eventually lead to daytime hypertension.

TREATMENT

In the original description of UARS, by Guilleminault et al., in 1993, patients were successfully treated with nasal CPAP. It was used to confirm the diagnosis and to document potential improvement. CPAP was titrated to achieve a Pes pressure of less than -7 cm H₂O. Although most subjects initially accepted it, 98% rejected it as a long-term treatment modality³⁵. Rausher et al. studied the effect of CPAP in patients with RDI <5 and with symptoms of snoring and arousal index of 20 ± 10 /hr. However, esophageal pressure was not followed-up in this study. Out of 11 patients, only 19% accepted the treatment, with a mean daily use time at six months of 2.8 ± 1.5 h. As expected, 73% of those who used it reported a decrease in

daytime sleepiness. The criteria that could predict CPAP compliance could not be determined³⁶. Thus, data suggest that CPAP is an effective form of therapy, but the compliance rate is unfortunately poor.

Recent studies have demonstrated that adding cognitive behavioral therapy (CBT) to CPAP treatment is beneficial for patient's chronic insomnia or psychosomatic symptoms secondary to UARS³⁷.

Septoplasty and radiofrequency reduction of enlarged nasal inferior turbinates can be successful in treating UARS. But, often, anatomical abnormalities involve soft tissue in soft palate and the maxilla and mandible skeletal structures. Correction absence of primary cause of the abnormal breathing, such as crowded airway and narrow jaw, will leave patients untreated and potentially may lead to develop local neuropathy and occurrence of OSAS. The classical surgical procedures have been considered too aggressive to treat UARS. Uvulo-flap as well as distraction osteogenesis have been helpful for management of UARS³⁸.

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-related breathing disorders showed promising clinical improvement. This combined surgical and orthodontic treatment is much less invasive than traditional jaw advancement surgery. However, patients are required to wear braces for an extended time after jaw expansion for orthodontic purposes.

Oral appliances can achieve satisfactory outcomes in UARS³⁹. Further well-documented studies are required, before the exact role of surgery and oral appliances in UARS patients can be established.

In summary, UARS treatment 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, which may consist on aggressive treatment of nasal allergies, usage of palatal soft tissue surgery, orthognatic surgery, or the use of dental devices.

CONCLUSIONS

UARS has been increasingly recognized, but it is still not part of the routine in clinical practice in sleep centers, and several patients remained untreated. The early non-recognition in life of the syndrome and the anatomical

abnormalities surrounding the upper airway responsible for the symptoms will probably lead to complications and perhaps even development of OSAS. Considering that the prevention is much less costly to society than the syndrome's treatment with permanent lesions, recognition and treatment of UARS should also be a priority.

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