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Upper Airway Resistance Syndrome – A Twenty-Five Years Experience

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1. Introduction

This paper will review the prevalence, pathophysiology, clinical picture, diagnostic advances, natural history, morbidity and management of upper airway resistance syndrome (UARS). The aim is to improve our knowledge about this disease and help to identify patients with UARS.

2. Background

UARS was initially used to describe a group of patients who were sleepy but did not meet the polysomnography diagnostic criteria of obstructive sleep apnoea syndrome (OSAS) (Guilleminault 1993). The first mention of the term was used about children by Guilleminault (Guilleminault 1982) in 1982 and years later also in women (Guilleminault 1995). Is UARS really a disease?. Twenty-five years after first being described, there is still significant controversy among experts as to whether UARS is a specific syndrome.
Some authors consider it to be part of the spectrum of obstructive disorders affecting the upper airway (Douglas 2000; Jhonson 2008; Cracowski 2001), while others believe that OSAS and UARS are separate entities (Gold 2008; Bao & Guilleminault 2004;Lindberg & Gislason 2000).
Normally, it is up to the clinician practitioner to screen for this syndrome. Due to its diagnostic difficulty, currently UARS is significantly under diagnosed and no standard management strategy in place in sleep labs. However, great interest exists in the literature for this entity, and many revisions have been carried out (Exar & Collop 1999; Monserrat & Badia 1999; Bao & Guilleminault 2004; Velamuri 2006; Ramar & Guilleminault 2008; Giblin 2009; Guilleminault & de los Reyes 2011).

3. Epidemiology

Epidemiologic studies estimate that SAHS affects 1–5% of adult men in western countries (Young 2002). Sleep apnoea hypopnoea syndrome is the most common form of sleep

disordered-breathing. Limited data is available on the prevalence of UARS in the general population in both children and adults. Some authors consider it an uncommon disease in clinical practice. In earlier descriptions, the estimated prevalence was 6% in men and 11% in women (Votteri 1994; Guilleminault 1995). Kristo found a prevalence of 8.4% in a one year polysomnography review (Kristo 2005). In an epidemiological study conducted in Brazil, the prevalence of UARS was 18.7%, being more common in women and young people (Tufik 2009).

4. Pathophysiology

The upper airway is a very complex structure. In SAHS patients, apneas during sleep are caused by upper airway obstruction, wich leads to progressive asphyxia and awakening. The inspiratory efforts to overcome occlusion lead to arousal, sleep fragmentation, and oxyhemoglobin desaturation. From a physiological standpoint, both UARS and OSAS present intermittent upper airway collapse. This increase in upper airway resistance occasionally accompanies airflow limitation and arousals, with little desaturation. Johnson, found that even minimal airflow limitation could produce arousals that occur before alterations in gas exchange (Johnson 2005). These episodes are of short duration, about four breaths, and present negative intrathoracic pressure increases.

Another interesting difference from OSAS is that UARS patients do not present neuropathological lesions in the upper airway (Friberg 1998; Guilleminault 2002a; Boyd 2004), which could explain why these patients tend to respond more rapidly to treatment and do not develop OSAS over the long-term. Early studies did not seem to reveal differences in sleep architecture between UARS and OSAS (Loube & Andrada 1999). However, today UARS patients are considered to have unstable sleep, characterized by a cyclic alternating pattern in nonREM sleep (Guilleminault 2005a), which predisposes to the occurrence of arousals. These findings correlate with symptoms such as tiredness and fatigue, for which these patients are often referred to sleep labs. The cyclic alternating pattern has been described in many other situations (Ferré 2006), such as fibromyalgia, chronic fatigue syndrome, and OSAS (Terzano 1996). Current research suggests that nearly 50% of fibromialgia syndrome patients experience intrusive alpha wave periods. Patients with UARS present an increase in the number of cyclic alternating patterns, with a decreased phase 1 and an increased phase A2 and A3 (Guilleminault 2005c) In recent years, polysomnography has revealed that UARS patients present nonREM-sleep instability. Alpha-delta sleep is characterized by an intrusion of alpha EEG waves into slow delta waves during deep sleep, which also occurs in insomnia and non-refreshing sleep (Guilleminault 2001a).

5. Symptoms

Although OSAS and UARS share common symptoms, in most cases the clinical manifestations are different (Stoohs 2008). The most common symptoms of SAHS patients include chronic loud snoring, excessive daytime sleepiness, personality changes, depression and deterioration of quality of life (Pichel 2004). Hypersomnolence is the principal daytime manifestation of sleep disordered breathing. Excessive sleepiness resulting from increased breathing effort and sleep disruption is the guide symptom of UARS patients (Guilleminault 1993, 2001a). Drowsiness related to general exhaustion has a negative impact on quality of

life. As in OSAS, snoring is a common symptom, predominantly in males, although the absence of snoring has also been described in this syndrome, the so-called silent UARS (Kristo 2005). In recent years, several studies have demonstrated strong associations between UARS and functional somatic syndromes, such as chronic fatigue syndrome, chronic insomnia, chronic pain, irritable bowel syndrome, fibromyalgia, depression, parasomnias and posttraumatic stress disorders (Gold 2003, 2011). Due to its association with chronic somatic diseases, UARS has been postulated to activate the hypothalamic-pituitary-adrenal axis (HPA) (Gold 2010), although not all studies support the association of sleep disordered breathing with these somatic functional disorders. (Vgontzas & Fernandez-Mendoza 2011, Trakada 2007).

A number of studies compare the clinical characteristics of UARS patients to those of SAHS subjects. Patients with UARS are usually younger than those with SAHS and have a lower level of obesity. There is no major difference in terms of gender prevalence, although UARS appears to be more frequent in postmenopausal women. An overall ratio of prevalence for men to women of 3.3 has been reported in SAHS patients (Bixler 2001).

UARS patients report both onset and maintenance insomnia (Guilleminault 2002b). A state of physiologic hyperarousal in UARS patients with chronic insomnia is accepted (Gold 2008). Some authors have reported complex insomnia, which paradoxically involves nighttime insomnia and daytime sleepiness (Krakov 2001; Gold 2008). This type of insomnia has been associated with parasomnias (Guilleminault 2006a), which mainly occur in young patients together with sleepwalking and night terrors. Insomnia is more common in UARS than in OSAS.

Powers (Powers 2009) found a tendency to hypersomnia in UARS patients. These patients showed altered results on the maintenance of wakefulness test that were not correlated with the Epworth scale. This author considered non-obese premenopausal women, who often consult for chronic insomnia and parasomnias, to represent a specific attention group.

Approximately half of UARS patients present symptoms of increased vagal tone such as orthostatic hypotension and coldness of the extremities (Guilleminault 2001b). Disturbances in heart rate variability have also been reported along with a decrease in the HF component (associated with increased vagal tone). In contrast, OSAS patients have an increase in the LF/HF ratio, associated with increased activity sympathetic. (Guilleminault 2005).

SAHS is widely associated with cardiovascular risk. Long-term effects can lead to severe cardiovascular and cerebrovascular diseases. However, there is little data regarding the association of cardiovascular disease and UARS. Some studies have found an association between hypertension and UARS, with a good response to CPAP treatment (Guilleminault 1996), but this association has been put into question. Notably, this controversy sheds light on the importance of hypoxia and sympathetic activation (which are not present in UARS) in OSAS as intermediary mechanisms associated with cardiovascular events.

The diagnosis of UARS is often delayed becasue of the absence of respiratory events in polysomnography. Sometimes the symptoms of UARS have been confused with other medical conditions, such as asymptomatic habitual snoring, sleep deprivation, chronic fatigue syndrome, idiopathic hypersomnia, psychiatric disorders (Lewin & Pinto 2004) and asthma (Guerrero 2001).

Some authors report a greater likelihood of traffic accidents in UARS patients (Stoohs 1994). Among drowsy drivers, UARS is associated to a higher frequency of accidents. Thus, identification of this syndrome is of great practical importance.

6. Physical examination

UARS patients differ anthropometrically from patients with SAHS. They are generally thin, young, and predominantly female. The recommended physical examination is similar to that for OSAS patients. As in OSAS, craniofacial abnormalities such as elongated face and reduced mouth opening are frequent. Guilleminault described an increase in nasal resistance, excessive pharyngeal tissue, mild retrognathia, narrowing of the oropharynx and ogival hard palate (Guillemianult 1995), with high scores on the Mallampati scale.

7. Diagnosis

UARS is defined as daytime sleepiness associated to a sleep disordered breathing and arousals related to respiratory effort (RERA) but without sufficient apneas/hypopneas for OSAS. The diagnosis is based on the association of clinical symptoms and polysomnographic findings.

Nocturnal polysomnography, which is the gold standard for diagnosing SAHS, sometimes demonstrates the presence of apneic events and non apneic breathing (hypopneas), but does not definitively diagnose UARS. Nevertheless, an increased number of RERA may lead to suspicion of UARS. Simplified polygraphic studies are not useful in this disease because they do not provide arousal information. Some laboratories have used the split-night technique followed by CPAP titration successfully. These situations require an index of over 20 RERA during the first three hours of sleep (Kristo 2009).

The continuous recording of esophageal pressure throughout the night is the gold standard for the diagnosis of UARS (Kushida 2002; Iber 2007). Esophageal manometry is a complex technique which may be affected by the placement of the probe and the position of the catheter. Moreover, it is time-comsuming, may affect patient's sleep, and is not widely available (Johnson 2008). The correct positioning of the esophageal catheter requires a lot of experience and clinical practice. The use of a small catheter has improved tolerance of the procedure. The analysis of esophageal pressure can be quantitative or qualitative, though the latter approach is more common in clinical practice (Watanabae 2000). Gold et als used the critical pressure criteria to differentiate between SAHS and UARS patients [Gold 2002].

The esophageal pressure reading may present three different patterns: a crescendo pattern that ends in arousal without achieving 3% desaturation, continuous sustained effort for at least four breaths, and finally 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 patterns (Pes reversal).

Although esophageal manometry is indicated mainly for the diagnosis of UARS has also demonstrated its usefulness in studying the Cheyne-Stokes syndrome as it allows to differentiate obstructive from central apneas. However, it is a laborious technique, disruptive for patients and normal values remain to be established. The utility in the clinic is unclear and have been confined its use to research.

Indeed, the presence of RERA in the absence of apneas and hypopneas is the key polysomnography finding for diagnosing UARS (Bonnet 2007). However, the difficulty of registering respiratory effort has prompted the search for other non-invasive methods that can provide similar information (Hosselet 1998; Loube 1999; Badia 2001; Mosler 2002; Kenach 2005; Popovic 2009)(Table 1). Most systems try to develop a reliable non-invasive tecnique for respiratory effort and upper airway resistance that could represent a non-invasive alternative to esophageal pressure measurement. Of these, the most widely used and accepted by the American Academy of Sleep Medicine are nasal pressure cannulas, inductance plethysmography or diaphragmatic/intercostal EMG. The nasal cannula is the tool of choice for monitoring respiratory airflow during sleep in both clinical and research sleep studies. Nasal cannula is more sensitive than thermistor for detecting RERA The use of new technologies such as pressure probes have made it possible to identify signs of UARS in patients with high levels of arousal and airflow limitation (Krakow 2001).

The diagnostic criteria for UARS have not been established. At present, the diagnostic polysomnography of UARS is based on careful analysis of the esophageal pressure reading and nasal cannula (Guilleminault 1995, 2001; Black 2000), together with an AHI under 5 and the presence of desaturation of no more than 92%. Visual identification of intermitent flow limitation is cumbersome, subjective and trought with variability and potential error. Some authors recommend determining the length of airflow limitation episodes as well as the total percentage of airflow limitation with respect to total sleep time. Termination of flow limitation was indicated either by respiratory events related to arousal or with essofageal pressure reversal (Guilleminault 1995; 2001) without alpha EEG arousal (Guilleminault 2005b). In UARS patients these episodes of airflow limitation that is not accompanied by desaturation, are of varying lengths, and are not always associated with an increase in esophageal pressure. The coincidence of EEG arousals and Pes events is well documented. A percentage of Pes events terminate without coincident EEG activity. However, Guilleminault describes that, in patients with UARS, apnoeas accompanied by arousals have a greater tachycardic effect, even if there is only a small reduction in blood oxygen saturation (Guilleminault 2005). The shape of the inspiratory flow contour has been proposed as a noninvasive predictor of increased upper airway obstruction, increasing the potential for erroneous classification of respiratorye events (Hosselet 1998; Rees 2000; Ayyapa & Rapoport 2003). Various definitions of airflow limitation exist (Norman 2007; Mansour 2004; Kaplan 2000;Aittokallio 2001)(Table 2).

RERA is the most important event in UARS patients. In early studies, the definition of UARS included the presence of frequent arousals, indicating an RERA index >10/h as a diagnostic criteria. Owing to their relation, treating RERA tends to improve excessive daytime sleepiness. This index was established as a treatment criterion. UARS has not found its way into the International Classification of Sleep Disorders Diagnostic and Coding Manual, which is one of the main problems for the acceptance of UARS as a specific entity (AASM 1999; Iber 2007). RERA has been accepted by the American Academy of Sleep Medicine Task Force (AASM, 1999) but it has yet to be standardized. According to the AASM and a number of authors (Cracowski 2001), RERA episodes are rare and their encoding need not be mandatory. However, others consider it to be a key element, with an identifiable pathophysiology. RERAs have been incorporated into normal clinical practice, and the respiratory disturbance index used to quantify OSAS severity takes them into account together with apneas, and hypopneas.

- Pneumotachygraphy
- Nasal cannula pressure
- EMG signals
- Resistive Inductance Plethismography
- Pulse Transit Time
- Neural network
- Forced oscillation technique
- Suprasternal pressure transducer
- Presence ofalteringcyclicpattern(EEG)
- Forehead venous pressure signal
- Snore signals

Table 1. Techniques to assess respiratory effort.

Periods of high esophageal pressure swings with associated inspiratory flow limitation
Lack of increase in airflow despite increasing respiratory effort.
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
Abnormal inspiratory air flow shape during partialupper airway obstruction
Abnormal contour in the nasal/presure transducer signal waveform
Presence of an inspiratory plateau or reduction in inspiratory flow independent of any increase in inspiratory efforts.
Pressure waveflattening<30% is associated with a physiological event (arousal, CAP complex, variabilidad RR, etc)
Two or more breaths (10 sec) without sinusoidal appearance and without hypopnea criteria, end abruptly, taking on the sinuidal flow aspect
At least four successive breaths reduction in amplitude simultaneously with the development of an inspiratory plateau (loss of a sinusoidal inspiratory waveform)

Table 2. Inspiratory flow limitation: Definitions.

From the standpoint of polysomnography in recent years has gained great interest to consider these patients have instability in their sleep nonREM. OSAS and UARS patients have different brain activity during sleep. Thus, in patients with UARS have described alterations in sleep architecture, such as sleep fragmentation, consequent to the presence of respiratory arousals, the presence of an alpha-delta pattern, characteristic modifications in the EEG spectral analysis and the existence of an increase of cyclic alternating pattern. Alpha-delta sleep is characterized by an intrusion of alpha EEG waves into slow delta waves during deep sleep, which also occurs in insomnia and non-refreshing sleep. It appears that cyclic alternating pattern could be a valid indicator for the persistence of some degree of sleep disturbance and instability of NREM sleep. With respect to the EEG spectral analysis in patients with UARS have less activity in slow wave sleep (delta) and a higher prevalence in the range of 7-9 Hz consequent to a different cortical activity. The development of slow wave sleep is also abnormal, with persistence of a large number of "power delta" at the end of sleep cycles. Both abnormalities may explain the symptoms of daytime sleepiness, insomnia and fatigue in patients with UARS (Guilleminault 2001a).Black et als found that visually undetectable EEG alterations may occur during breathing disturbances in the absence of arousal (Black 2000).

8. Follow up

Te long time evolution of UARS patients, within the overall spectrum of sleep disordered breathing disorders, is an area of interest. RERA may be intermediate event between snoring and hypopnea. RERA predominate in younger and thinner people than apnea and hypopnea episodes. Hypopneas becoming true apneas with increasing age and weight. Few existing studies on the matter. In a five years follow-up study of untreated UARS patients, Guilleminault report that only 10% developed a OSAS and always in the context of weight gain (Guilleminault 2006b). Jonzak, in a retrospective study,also report that obesity as an aggravating factor of severity in follow up six years (Jonzak 2009).

9. Treatment

Treatment options for UARS include lifestyle changes, Continous Positive Airway Pressure (CPAP), oral appliance therapy and surgery. All patients with UARS should be counseled about the potential benefits of therapy and the risks of going without therapy.

Obesity is a modifiable risk factor associated with OSAS so weight loss should be recommended to all overweight or obese. However, patients with UARS are often not obese, so this recommendation has less value in them. As in the treatment of OSAS, within conservative measures are recommended sleep hygiene and avoiding the supine position. Just like in OSA is advisable to multidisciplinary treatment.

Continous positive airway pressure (CPAP) is the treatment of choice for SAHS patients. CPAP was the gold standard for UARS. Initial studies described a good response to CPAP treatment which was considered to be a diagnostic criteria for the syndrome (Messner & Pelayo 2000; Guerrero 2001; Guilleminault 2006). As in mild to moderate OSAS, CPAP compliance and adherence are low. Regarding CPAP titration, it is recommend a similar protocol that for OSAS.After reaching the optimal CPAP, the esophageal peak pressure at the end of inspiration must be higher than-7 cm H_2O or the RERA index <10. If this is not achievable, CPAP may be applied at an empirical pressure level of between 8 and 10 cm of

H2O (Kristo 2009). CPAP ususally improves symptomatology and parasomnias. Some reports exist of worsening after CPAP treatment.
No studies exist about the usefulness of positional treatment or electrical stimulation of the muscles of the upper airway in patients with UARS. With respect to drug treatment, as with OSAS, the evidence on the usefulness of pharmacological treatment in UARS is scarce.
Given the poor adherence to CPAP treatment, oral devices may be a good alternative for UARS, although little research has been published (Loube 1998; Guerrero 2001; Yoshida 2002; Rose 2000). Predictable efficacy of oral appliances treatments has yet to be demonstrated.
Surgical option include laser-assisted uvulopalatoplasty,uvulectomy, snoreplasty injection, radiofrequency submucosal needle therapy and somnoplasty (Newman1996; Powell 1998; Newman 2002; Pirelli 2004). Existing data on treatment of UARS are scarce, which together with the difficulty of diagnosis makes it a priority disease research in the future.

10. Conclusions

Despite the time elapsed since its initial description, UARS remains controversial as it has yet to be accepted as its own entity. However, the literature continues to reflect interest in this disorder. Perhaps SAHS and UARS share the same pathophysiological mechanism, although their clinical expression and pathophysiologic consequences are different. We could say that UARS and OSAS are distinct entities in the spectrum of sleep-disordered breathing.
SAHS is one of the most common sleep disorders in clinical practice. It is associated to cardiovascular morbidity, and has become regarded as a public health problem. UARS is an underdiagnosed disorder with low prevalence of sleep units. It has special implications on sleep structure, especially sleepiness and tiredness, and is associated to chronic somatic diseases such as chronic fatigue syndrome, fibromialgia, irritable bowel syndrome, and tension headache. The correct diagnosis of this syndrome is essential to allow the best choice of therapy.
The identification of UARS, although not recognized by the AAMS as an entity, has improved our understanding of respiratory events and arousals, as well as increasing the search for non-invasively ways of assessing respiratory effort. Today, terms such as airflow limitation or RERAs are widely used in the polysomnographic reports.

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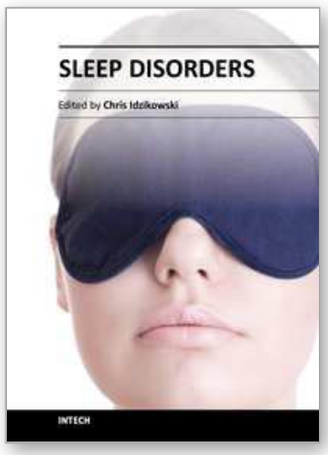

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For progress to be maintained in a clinical field like sleep medicine, unimpeded, unrestricted access to data and the advances in clinical practice should be available. The reason why this book is exciting is that it breaks down the barriers to dissemination of information, providing scientists, physicians, researchers and interested individuals with a valuable insight into the latest diverse developments within the study of sleep disorders. This book is a collection of chapters, which can be viewed as independent units dealing with different aspects and issues connected to sleep disorders, having in common that they reflect leading edge ideas, reflections and observations. The authors take into account the medical and social aspects of sleep-related disorders, concentrating on different focus groups, from adults to pregnant women, adolescents, children and professional workers.

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