Upper Airways Resistance Syndrome (UARS) - The underdiagnosed syndrome

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Classification

In the International Classification of Sleep Disorders (2005) and current ICSD[3] classification, UARS is classified under obstructive sleep apnea (OSA).

Guilleminault et al originally proposed UARS to explain the sleepiness/fatigue involved in the fragmentation of sleep by arousal, resulting from increased respiratory effort associated with inspirational airflow limitation (IFL) that is milder than the IFL of hypopnea.[2]

UARS is understood as a form of sleep disordered breathing (SDB) characterized by IFL during sleep with excessive sleepiness/fatigue, but without the recurrent apnea/hypopnea or oxyhemoglobin desaturation that characterizes OSA.[2]

The significance attributed to these arousals gave rise to a new term, respiratory effort related arousals (RERA).[2]

UARS is traditionally diagnosed when Apnea/Hypopnea index (AHI) is fewer than 5 events per hour and the simultaneous calculated Respiratory Distress index (RDI) more than 5 events per hour, the difference being the RERA.

The use of nasal cannula pressure transducers/catheters, to measure esophageal/supraglottic pressure, has given better understanding of IFL, apneas/hypopneas and RERAs.

Definition

RERAs are defined, using nasal pressure (they were originally defined using esophageal pressure) as:

- "a sequence of breaths lasting at least 10 seconds characterized by increasing respiratory effort or flattening of the nasal pressure waveform leading to an arousal from sleep when the sequence of breaths does not meet criteria for an apnea or hypopnea." or
- Arousals preceded by three or more breaths with an inspiratory airflow plateau that was above 50% of waking airflow[3] or
- AASM panel defined a RERA as "a sequence of breaths characterized by increasing respiratory effort leading to an arousal from sleep, but which does not meet criteria for an apnea or hypopnea."

Oxygen desaturation does not drop below 92% or more than 3%-4% from baseline.

In UARS it is important to differentiate between an upper airway problem, e.g. pharyngeal collapse in obstructive sleep apnea (OSA) and IFL in sleep disordered breathing (SDB). RERAs are considered the diagnostic hallmark for UARS.

Younger patients report parasomnias, of which the most common is sleepwalking, with or without sleep terrors, and persons with parasomnias and UARS show an increase in cyclical alternating patterns (CAP) indicating NREM sleep instability.

Parasomnias/NREM arousal disorder include sleep talking, sleep eating, grinding of teeth, sexsomnia and confusional arousal.

Treatment of UARS usually eliminates parasomnias and abnormal CAP rates, which is not seen with pharmacologic and psychiatric treatment of the parasomnias alone.

Clinical features

UARS patients report nocturnal awakenings and find that it is difficult to return to sleep. Sleep-onset and sleep-maintenance insomnia have been reported with UARS.

Studies indicate that chronic insomnia tends to be more common with UARS than OSA.

Symptoms of OSA can overlap with UARS. UARS patients are more likely to complain of daytime fatigue rather than sleepiness.

Postmenopausal women with UARS have higher fatigue scale scores than premenopausal women. Treatment of UARS return these abnormal scores to within normal range.

Up to half of the UARS patients complain of cold hands and feet, usually during teenage years. A third of the UARS patients have lightheadedness upon standing or bending abruptly. This complaint can be related to the observation of systolic blood pressure less than 105mm Hg and often below 90 mm Hg. OSA is commonly associated with hypertension.

Autonomic response to abnormal breathing in UARS showed a dominance of vagal response compared to a more dominant sympathetic response in OSA.

UARS patients have a different electroencephalogram (EEG) spectra and also different CAP rate at visual scoring. This indicates more sleep disturbance compared with OSA patients.

In a comparative study of the pathophysiology of UARS by Rees and associates, comparing the inspiratory flow dynamics during sleep between eight UARS patients and eight controls (normal asymptomatic subjects), they found considerable IFL in both groups. [2] The UARS patients had larger esophageal pressure swing during IFL (greater inspiratory effort) with a greater number of arousals from sleep.[2] This suggest that UARS patients differ from asymptomatic individuals not in having IFL, but in having increased inspiratory effort during sleep associated with arousals.[2]

This supported Guilleminault et al's paradigm that sleepiness/fatigue of UARS is related to sleep fragmentation caused by RERAs.[2]

It has since been recognized by clinicians that UARS patients experience not only sleepiness/fatigue, but also a variety of symptoms of the central sen-

sitization syndromes (CSS) such as insomnia, body pain, headache, irritable bowels (IBS) and other functional somatic syndromes (FSS).[2] These symptoms are less frequent in patients with severe OSA.

Table 1 - CSS/FSS[6]

- Chronic fatigue syndrome
- Hypersomnolence
- Fibromyalgia
- Migraine/Tension headache syndrome
- Irritable Bowel Syndrome (IBS)
- Gastrointestinal hyper/hypomobility
- Temperomandibular joint syndrome
- War-related illness/Gult war illness (GWI)
- Multiple chemical sensitivity/Sick house syndrome
- Restless leg syndrome (RLS)
- Mitral valve proplapse syndrome
- Joint hypermobility syndrome
- Insomnia
- Problems with concentration and memory

As the apnea/hypopnea index increases the prevalence of FSS decreases. Patients with FSS and anxiety disorders tends to have low apnea/hypopnea index <10.

The paradigm of sleep fragmentation by RERAs giving rise to sleepiness fatigue gives no explanation for the insomnia, body pain, head ache, and IBS observed frequently by UARS patients and less frequently by patients with severe obstructive sleep apnea/hypopnea.[2] The aetiology of FSS is unknown but usually occurs in individuals who have undergone physical or emotional trauma leading to the activation of the HPA or sensitisation of the limbic system altering the brain response to internal or external stimuli. **(See Fig 1,2 and 3)**.

Underdiagnoses of UARS

UARS is a multidisciplinary disease but by the time the patient is sent for a sleep study, in some cases as a last resort, they have been treated by many in the medical field, usually with persistence of their problems e.g. anxiety, depression, insomnia, ADHD, FSS, etc.

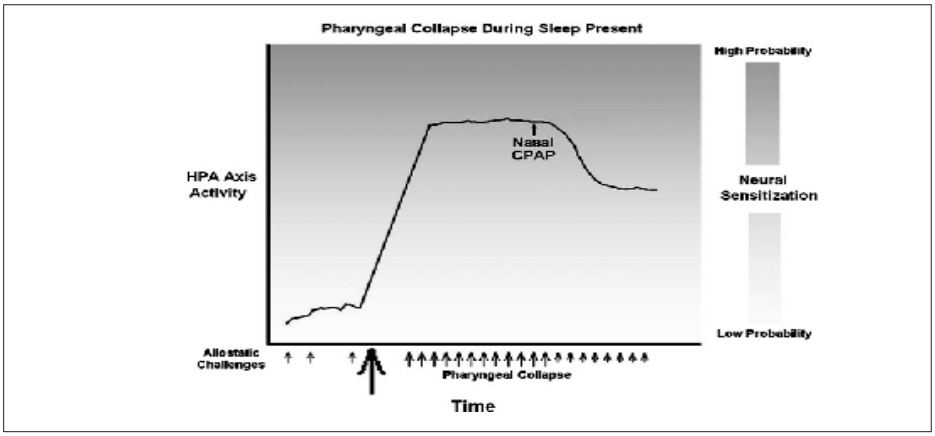

Fig. 1. This figure illustrates a model of neural sensitization of the limbic system in an individual with sleep disordered breathing. The sensitization occurs when a strong allostatic challenge (an emotional or physical trigger factor; represented as a large arrow beneath the abscissa) leads to marked activation of the hypothalamic-pituitary-adrenal (HPA) axis. Higher levels of HPA axis activity increase the probability of neural sensitization predisposing to the recognition of previously benign stimuli such as odorants and pharyngeal collapse during sleep as allostatic challenges. Following neural sensitization, the nightly occurrence of snoring or hypopnea leads to chronic stimulation of the HPA axis (a perpetuating factor represented as a chain of smaller arrows beneath the abscissa) and the symptoms of chronic stress, the functional somatic syndromes and anxiety disorders. Using nasal CPAP during sleep (black arrow above), by preventing pharyngeal collapse during sleep, lessens the allostatic challenge and lowers HPA axis activity ameliorating the symptoms of chronic stress.[6]

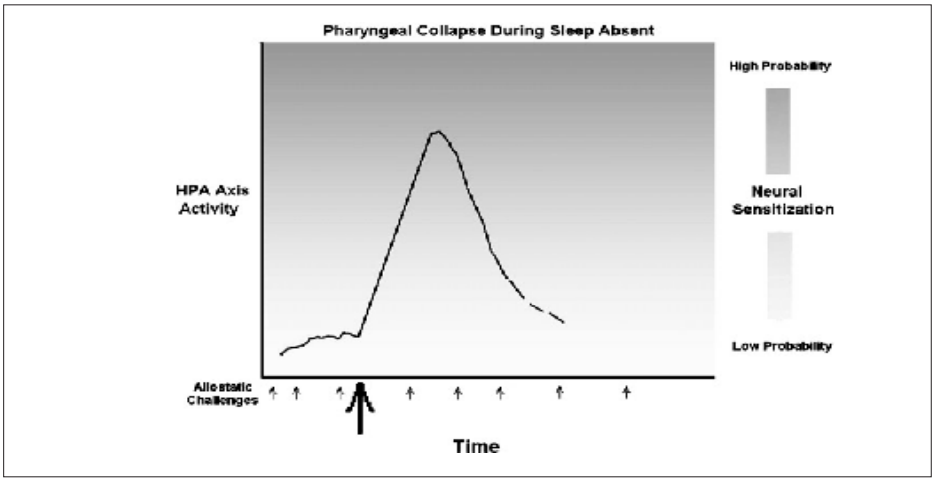

Fig. 2. This figure illustrates the model of neural sensitization of the limbic system in an individual without sleep disordered breathing. As in Fig. 3, this individual also undergoes a marked allostatic challenge which triggers neural sensitization as detailed in the legend for Fig. 3. In this individual without pharyngeal collapse, the chronic, nightly activation of the HPA axis is absent (the perpetuating factor of pharyngeal collapse during sleep is absent) and there is a return toward baseline levels as the allostatic challenge subsides. The figure shows that although episodic allostatic challenges continue, they are not sufficient to lead to the symptoms of chronic stress in the absence of pharyngeal collapse during sleep.[6]

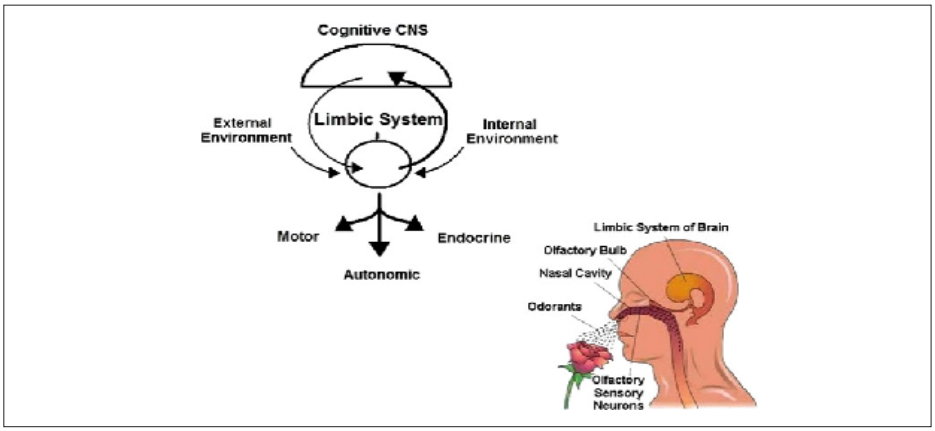

Fig. 3. This figure illustrates, schematically, the inputs and outputs of the limbic system. The thin arrows indicate the inputs to the limbic system from the external and internal environments and from cognition. The thick arrows indicate the output of the limbic system initiating responses that involve motor function, the autonomic nervous system and activation of the hypothalamic-pituitary-adrenal axis (endocrine). The lower right hand portion of the figure demonstrates that odorants (external environment) input directly into the limbic system through the olfactory nerve.[6]

UARS

- IFL/RERA
- AHI<5
- Limited oxygen desaturation
- Insomnia
- Sleep Parasomnias NREM/ disorders of arousal
- Parasympathetic autonomic activation
- Vagus response
- Hypotensive/lower heart rate
- Low BMI
- Urinary frequency, regular trickle
- Gastro intestinal tract- Increase mobility
- Anxious, depressed, Bipolar Mood Disorder, ADHD
- Don't tolerate CPAP treatment
- Tolerate MAD treatment

OSA

- Pharyngeal collapse/Apnea
- AHI>5
- Severe oxygen desaturation
- Sleeplike a log
- REM behavioral disorders
- Sympathetic autonomic activation
- Fight and flight response
- Hypertensive/increased heart rate
- High BMI/overweight or obese
- Full Bladder
- Gastro intestinal tract-Decrease mobility
- Cardiovascular and metabolic symptoms
- Tolerate CPAP treatment
- Tolerate MAD treatment

If the patient is sent for polysomnography (PSG) which is usually within the bounds of normal for OSA, with an AHI < 5, and limited oxygen desaturation, the patient is told that they do not suffer from OSA and therefore have no SDB problem. This occurs if an automated analysis of PSG is done and no RERAs are noted or looked for therefore PSG studies should be manually analysed.

Polysomnography (PSG) has been promulgated as the "gold standard" for the diagnosis of SDB as it can quantify both the abnormal breathing events and neurophysiology of sleep. Currently, if the recommended criteria by which sleep studies are scored are followed precisely, computer programs that are used in many laboratories around the world run on erroneous software algorithms that omits legitimately scored respiratory events and underestimate AHI.[5]

In a study comparing manual analysis of PSG recordings of patients with chronic obstructive pulmonary disease (COPD) to automated analysis by two sleep specialists it was found that the automated analysis, does not produce reliable outcomes and should, therefore, not replace the manual analysis of PSG recordings in patients with and without COPD.[7]

This suggest that all PSG studies should be manually scored and one should not rely on automatic scoring.

Much of the current confusion and controversy surrounding UARS probably reflects the lack of standardized definitions and recording techniques.

Sleep Medicine physicians and others treating patients, overlooking the role of SDB in FSS and anxiety disorders, limits the ability to help patients and limits the growth of the understanding of the relationship between the disorders.[6]

Sleep breathing complaints were extremely common among a large sample of treatment-seeking, self-identified, adult chronic insomnia patients.[8]

Indications for PSG should be handled less restrictively in the diagnostic workup of middle-age women and older patients with chronic insomnia since they have a high risk of comorbid sleep disorders even in the absence of clinical signs of sleep apnea syndrome or periodic limb movement

Treatment

Treatment of UARS, by utilizing CPAP or mandibular advancement device (MAD), must be seen as long term and multidisciplinary. The treatment is aimed at deactivation of the chronically activated limbic system and HPA axis and therefore the initial trigger/ traumatic event must be identified to successfully treat the patients with SDB. There will be little success if the patient continues to suffer emotional/physical stress. It is not an overnight quick fix treatment!

References available on request.

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