UPPER AIRWAY RESISTANCE SYNDROME
THE UNDERDIAGNOSED SYNDROME

In the International Classification of Sleep Disorders (2005) and current ICSD3 classification UARS is classified under obstructive sleep apnea (OSA).

Guilleminault et al originally proposed UARS to explain the sleepiness/fatigue of the syndrome 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 being included in the RDI.

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

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 were quantified as RERAs(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 not more than 3%-4% from baseline.

In UARS it is important to differentiate what is related to an upper airway problem, e.g. pharyngeal collapse in obstructive sleep apnea (OSA), from IFL in sleep disordered breathing (SDB).

RERAs, including phase A2 of the cyclic altering pattern (CAP) scoring system, 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 in increase CAP, phases A2 and A3 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, response not seen with pharmacologic and psychiatric treatment of the parasomnias in these subjects.

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 and suffer from chronic fatigue and myalgia’s.

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 as seen in UARS compared to OSA patients, showed a dominance of vagal response in UARS abnormal breathing pattern compared to a more dominant sympathetic response in OSA.

UARS patients have a different electroencephalogram (EEG) spectra and also different CAP rate (an abnormal increase in phase A2 CAP rate) at visual scoring, This indicate 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 sensitization syndromes (CSS) such as insomnia, body pain, head ache and irritable bowels (IBS) (symptoms also related to functional somatic syndromes FSS). (2)

These symptoms are less frequent in patients with severe OSA.

As the apnea/hypopnea index increase the prevalence of FSS decrease.
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)

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Criteria for exclusion for healthy controls

Any medical condition

Being of disability

Taking medications other than birth control, vitamins and non prescription analgesics

Post-menopausal(12 months without a period) or pregnant status

Heartburn

Any current pain on regular basis

Fatigue during the past month>2/10 (0=no fatigue; 10=extreme fatigue)

• Any history of the following syndromes
  • Muscle or joint pain lasting several months not due to any injury or arthritis
  • Chronic fatigue
  • Pre-menstrual symptoms
  • Temporomandibular joint disorder
  • Chemical sensitivity
• Sick building syndrome
• Side effects of silicone breast implants
• Chronic whiplash
• Undiagnosed chest pain
• Chronic pelvic pain
• Chronic head ache
• Chronic low back pain
• Chronic insomnia
• Hyperventilation and dizziness

CSS/FSS\(^{(6)}\)

Anxiety disorders\(^{(6)}\)

The UARS patients had a minimal increase in AHI and only slightly increased IFL during supine, stage 2 sleep in comparison to the healthy controls.\(^{(2)}\)

They did find some healthy controls with high frequencies of IFL. \(^{(2)}\)

It seems therefore unlikely that symptoms observed by UARS patients are caused specifically by the high prevalence of IFL. \(^{(2)}\)

There was no difference in standard sleep architecture and fragmentation between UARS patients and healthy controls. \(^{(2)}\)

This does not support Guilleminault et al's findings. \(^{(2)}\)

In developing a new paradigm of UARS it is important to note that the findings of this study, by Gold and associates, parallel the findings among IBS patients who complained of non-restorative sleep with
daytime sleepiness/fatigue, but whose inspiratory airflow dynamics during sleep, sleep architecture and fragmentation did not differ significantly from those of healthy controls. (2)

IBS patients were distinguished from healthy controls by qualitative difference in sleep, unrelated to sleep architecture or fragmentation by arousals. (2)

IBS patients demonstrated increased alpha frequency power in their EEG, a frequency associated with wakefulness. (2)

Guillimeninault et al. demonstrated similar phenomenon of increased alpha frequency power during sleep among UARS patients compared to healthy controls and sleep apnea patients. (2)

Gold and associates observed that alpha delta sleep (Intrusion of alpha frequency into slow wave sleep) is one of the signs of CSS observed among UARS patients. (2)

Patients with either syndrome also demonstrated poor sleep consolidation which has been quantified as increased sleep stage shifts. (2)

Increase in alpha frequency power and decreased sleep consolidation observed among UARS patients can account not only for their sleepiness/fatigue, but also for their CSS symptoms.

According to this neural sensitization paradigm, UARS present a state of limbic system sensitization to mild pharyngeal collapse during sleep.

The limbic system is linked to emotional life, long term memory, behavior, motivation, sensory processing, attention, instinct and olfaction. It influences the endocrine and autonomic nervous system. It is interconnected with the brain's pleasure center, which plays a role in sexual arousal. (Nucleus accumbens)

As a result, mild pharyngeal collapse is perceived as a stressor that chronically activates the hypothalamic-pituitary-adrenal (HPA) axis resulting in a state of chronic stress and a variety of symptoms such as sleepiness/fatigue, insomnia, body pain, affective symptoms of diarrhea, believed to be associated with chronic stress.

Increased alpha frequency power in EEG is thought to mark a predisposition toward limbic system sensitization and increased sleep stage shifts are postulated to be manifestations of increased stress.

In this context, an individual are healthy either because they do not experience pharyngeal collapse during sleep, or because their limbic system have not been sensitized to mild pharyngeal collapse as a stressor (primary snorers)

This then explain the presence of IFL among healthy controls seen in the study by Gold and associates, a similar study of females with IBS and among healthy controls in Gulf War Illness (GWI).

These findings are consistent with a paradigm of UARS as a state of chronic stress.

Large proportion of veterans from the first Persian Gulf War (1991) experienced a group of symptoms including fatigue, insomnia, body pain, mood and cognitive disturbances, chronic fatigue syndrome,
fibromyalgia and IBS, known as Gulf War Illness (GWI) grouped together as functional somatic syndromes (FSS).(3)

Adult chronic fatigue syndrome patients are distinguished from healthy controls by a history of childhood sexual abuse, emotional abuse and emotional neglect.

Fibromyalgia patients suffer a more frequently history of infection as well as emotional and physical trauma.

Among women reporting situations of domestic violence to the police, 47% reported current IBS.

Symptoms of FSS are more common among patients with UARS and mild to moderate sleep apnea.

Inspiratory airflow limitations is more common among young females with IBS than healthy controls.(3)

Sleep disordered breathing (SDB) is also common among females with fibromyalgia.

Treating fibromyalgia patients with nasal continues positive airway pressure (CPAP) relieves fibromyalgia symptoms.

The FSS are from unknown etiology and the symptoms of the FSS are associated with individuals who have undergone an episode of physical/emotional stress in their lives.(3)

Veterans who served during the first Persian Gulf War was exposed to a variety of stressors including heat, sleep deprivation, combat stress, smoke inhalation and air pollution from burning oil.

In a comparative study of airflow dynamics, between veterans with GWI and veterans from the same war with no symptoms, it was found that veterans with GWI had an increased frequency of arousal from sleep related to sleep-disordered breathing and they had a greater prevalence of flow-limited breaths during stage 2 NREM sleep, reflecting a more collapsible upper airway.(3)

Symptoms of GWI and FSS have been attributed to the activation of the HPA axis.

Studies have demonstrated that activation of the HPA axis by stress can sensitize the limbic system of the brain altering the response to internal and external stimuli (neural sensitization)

The findings of the study hypothesize that war-related stress sensitizes the limbic system of soldiers to perceive pharyngeal collapse during sleep as an internal stress.

In this way, after their service, veterans with pre-existing pharyngeal collapse during sleep experienced nightly exposure to an internal stress while those without pharyngeal collapse do not experience this same nightly stress.

Imagine the relationship of war-related stress and sleep-disordered breathing to GWI through a model of stress-related neural sensitization of the limbic system to pharyngeal collapse. (3)
Underdiagnoses of UARS

UARS is a multidisciplinary disease, by the time the patients is sent for a sleep study, in some cases as a last resort, they have been treated by many in the medical field, with persistence of their problems e.g. anxious, depressed, insomnia, bipolar, ADHD, CSS/FSS and other.

Patient send for Polysomnography (PSG) which is usually within the bounds of normal for OSA, with an AHI < 5, limited oxygen desaturation.

Patient told that they do not suffer from OSA and therefore have no SDB problem affecting them.

NO RERAs noted or not looked for, an automated analysis of PSG is done.

Polysomnography (PSG) has been promulgated as the “gold standard” for the diagnosis of SDB as it can quantify both the abnormal breathing events and neurophysiologic 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 omit 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 suggests that all PSG studies should be manually scored, do 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)

Missing the association between e.g. emotional/physical abuse, surgery, physical trauma, infection, other traumatic events and the allostatic challenge which exists simultaneously.(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

Patients with insomnia symptoms prior to CPAP treatment show a negative influence on CPAP compliance.(10)

Treating the patient while the allostatic challenge/challenges persist e.g. treating SDB while patient continuously suffer emotional/physical abuse.

Treating the patients current condition BUT missing the initial trigger, trauma/event in the diagnoses. Ask about history, look for initial trigger of which SDB became the chronic allostatic challenge.

Treatment of UARS, by utilizing CPAP or mandibular advancement device (MAD), must be seen as long term and multidisciplinary, see the treatment as long term deactivation of the chronically activated limbic system and HPA axis.

It is not an overnight quick fix treatment!

**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/ size zero dress
- Urinary frequency, regular trickle
- Gastro intestinal tract- Increase mobility
- Anxious, depressed, Bipolar, ADHD, etc.
- 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
- Adrenal, Fear and flight response
- Hypertensive/ increased heart rate
- High BMI/ overweight to obese
- Full Bladder
- Gastro intestinal tract-Decrease mobility
- Cardiovascular and metabolic symptoms
- Tolerate CPAP treatment
- Tolerate MAD treatment
PSG and Hypnogram reports for patient.

Go to bed 9-9.30pm.

Patient is very anxious and battle to fall asleep, take medication to help her fall asleep. If she wake up during the night she would take more medication to get back to sleep. She does not feel that the medication make her sleep. She sweat during her sleep at night.

She wake up at 5am, feeling tired and lousy. She thinks she slept +/- 6 hours.
Generally feel tired and fatigued all day, must force herself to do things during the day.

She just feel that “life is a drag”.

She does not think she snores, had never been told that she snore, suffers from dry mouth, and do not suffer from restless legs.

She goes to gym regularly and she does not smoke and seldom have an alcoholic drink.

She has a steady work and feel she does not cope as well as she should.

No time for a nap in the week, sometimes during weekends.

Her fatigue severity scale is 51 and Epworth sleepiness scale 8.

She had been suffering of anxiousness and depression for many years, and does not feel she is coping well in general. She had been on antidepressant medication for a few years but do not feel that it is effective.

It was felt that her sleep could have an influence and she was send for a sleep study.

When analyzing the **PSG report on the right** (correct study) the following is seen

AHI 1.6/ hour, RDI 63.0/ hour, Arousals 67.8/ hour, oxygen desaturation 91%, base of 97% and EEG show alpha intrusion.

On analyzing the hypnogram the RERAs can clearly be seen at the bottom of the graph.

The RERAs give an indication of the reason for the arousals seen in the report.

Taking all this and patient history into consideration, UARS would be part of a differential diagnoses as the PSG results indicated that she is suffering from a SDB problem.

Treatment considerations for SDB would include CPAP or MAD.

When analyzing **PSG report on the left** (this report was changed for purpose of explanation) the difference is clearly visible.

AHI 1.6/ hour, RDI 1.6/ hour, Arousals 67.8/ hour, oxygen desaturation 91 %, base of 97% and EEG show no alpha intrusion.

On analyzing the hypnogram no RERAs are noted as seen at the bottom of the graph.

There is not much in the report that give any indication for the arousals that is noted.

Taking all of this and patient history into consideration there is no obvious signs of any SDB problem, patient don’t have OSA.

No treatment consideration, patient do not have SDB problem.

This is a clear indication of how UARS is underdiagnosed in a patient with an obvious SDB problem.

This is a clear indication that PSG studies should be manually analyzed
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