

# CON: Upper Airway Resistance Syndrome Does Not Exist as a Distinct Disease

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Upper airway resistance syndrome (UARS) does not exist as a discrete disease state, but as a milder form of the obstructive sleep apnea syndrome (OSAS). The elevation of UARS to a distinct medical “syndrome” in 1993 by Guilleminault and colleagues, attempting to set it apart from OSAS has no biological underpinnings. Since its creation, the concept of UARS has been subjected to endless debates between sleep clinicians and researchers, contesting its existence, its nature, its etiology, and its treatment.

UARS fails each of the defining areas needed to set itself apart from OSAS: (1) unique diagnostic criteria; (2) distinct clinical presentation; (3) discrete polysomnographic findings; (4) characteristic pathophysiology; (5) distinctive associated comorbidities, and (6) particular treatment(s). I will proceed to highlight shortcomings in each of these critical areas.

## 1) UARS as an Extension of OSAS Diagnostic Criteria

UARS was first described by Guilleminault and colleagues in 1993.<sup>1</sup> It was born from the systematic observation of patients with complaints of excessive daytime sleepiness (EDS) with otherwise non-diagnostic OSA polysomnography by formal apnea and/or hypopnea criteria. By implementing an esophageal balloon catheter (Pes) and airflow pneumotachography during the polysomnography (PSG), the author was able to identify more subtle inspiratory airflow limitation (IFL) coupled with brief cortical arousals as the etiology of EDS. In these patients, the use of continuous positive airway pressure (CPAP) reversed the upper airway resistance physiology, decreasing the number of cortical arousals, and improving the associated excessive daytime sleepiness. So, are these observations enough to set UARS apart from OSAS?: (1) there is no significant difference in maximal esophageal pressure measured by a balloon catheter between hypopneas (OSAS) and upper airway resistance episodes (UARS); (2) the increase in inspiratory flow limitation (IFL) parallels the increase in airway collapsibility found across the full spectrum of obstructive respiratory events in OSAS; (3) the fact that respiratory arousals can occur without concomitant oxygen desaturation reflects upon an individual variability in oxygen reserve in OSAS patients rather than an unique characteristic of UARS patients; (4) transient, respiratory-related cortical arousals are well known to produce sleep fragmentation and subsequent EDS in OSAS; and finally, (5) reversal of upper airway resistance with use of CPAP improves neurocognitive symptoms along the full spectrum of OSAS.<sup>2-5</sup>

So, more than two decades ago, the definition of UARS as a “new” syndrome was founded on nonspecific observations,

overlapping with OSAS. It was created simply to fill the gap left by the rigid diagnostic criteria of OSAS, where the definition of apneas and hypopneas overlooked the spectrum of milder forms of airway resistance associated with cortical arousals and related symptoms.

## (2) Clinical Presentation: UARS and OSAS are Indistinguishable

Both OSA and UARS often present with signs/symptoms of snoring, fragmented sleep, daytime sleepiness, and fatigue. However, in comparison to OSA patients, UARS patients are described by early studies as younger, predominantly female, and associated with greater prevalence of insomnia, fatigue, body pain, and irritable bowel (known as functional somatic syndrome).<sup>6</sup> In 2008, Gold and colleagues showed no difference in hypersomnolence symptoms between mild OSAS and UARS. In this study, the hypersomnolence symptoms increased in parallel to increase in OSAS severity. Contrary to hypersomnolence, the prevalence of insomnia increased with decrease in severity of upper airway collapsibility, being prominent in patients with mild OSAS. Therefore, the milder is the form of OSAS, the less severe is the hypersomnolence and, therefore, the higher is the incidence of sleep-onset insomnia, explaining the finding of sleep onset insomnia in UARS, as a mild form of OSAS.<sup>7</sup>

Finally, it has been shown that when compared UARS and OSAS patients, not even sleep disorders specialists are able to dissociate the two syndromes based upon clinical evaluation. Clinical presentation such as daytime sleepiness complaints and ESS scores are not different between patients with OSAS and those with UARS. Both syndromes also share similar report rates of unrefreshing sleep upon awakening in the morning as well as the need of taking naps during the daytime.<sup>8,9</sup>

## 3) Overlapping Polysomnographic Findings between UARS and OSAS

UARS is defined by the presence of EDS associated with more than 50% of respiratory related arousals (RERAS), otherwise “not better explained by another sleep disorder.” This operational definition already recognizes that “RERAS” present in the mixed of other respiratory events, such as apneas and hypopneas, along the continuum of OSAS.

Unfortunately, the diagnosis of UARS based on PSG findings is overwhelmed by lack of standardization in measurement techniques and homogenous diagnostic criteria, challenging any attempt to compare study results; however, the following issues in PSG are worth highlighting:

#### **a) The shortcoming of defining RERAs upon the absence of hypopneas**

It is challenging to define a disease (UARS) by the absence of another (OSAS), when the definition of both diseases and scoring of respiratory events (e.g., hypopneas, RERAs) have been in continuous flux in the last two decades. The scoring of apneas and hypopneas is the result of a consensual designation of what a respiratory event is and the measurement techniques used. For example, hypopnea has been initially measured by using a thermistor, a method replaced by a nasal cannula pressure transducer. This method is more sensitive in detecting semiquantitative changes in flow amplitude, affecting hypopneas and RERA scoring, with subsequent changes in disease identification, severity grading, and comparability of results between different laboratories and research studies.<sup>10</sup>

#### **b) Hypopneas and RERAs, two sides of the same coin**

UARS is defined by RERAs. These are respiratory events of  $\geq 10$  seconds, characterized by increasing respiratory efforts (esophageal balloon) or by flattening of the nasal pressure waveform (or PAP device flow), leading to arousals when it does not meet criteria for apnea or hypopnea. Does RERAs scoring depend on hypopnea's definition? RERAs' score varies fundamentally based upon the hypopnea definition selected for scoring. The AASM Manual for Scoring, Rules and Terminology (version 2.0), states that a hypopnea is defined by a " $\geq 30\%$  drop of nasal pressure for more or equal to 10 seconds, associated with a desaturation or arousal." If arousals instead of desaturation are chosen to define hypopneas, then the scoring of RERAs is relegated to subjective measures of pressure signal drop of  $< 30\%$ .<sup>11</sup> Other serious limitations in the standard scoring of RERAs are: (1) RERA scoring requires a consistent good flow signal quality throughout the study; (2) inspiratory flow limitation is an indirect consequence of respiratory effort, which may be less accurate in REM; and finally, (3) RERAs are delineated by cortical arousals, which cannot be determined by current out-of-center sleep testing (OCST) technology, limiting UARS to an in-laboratory diagnosis.

#### **c) Arousals as normal variance in the definition of UARS**

The frequency of arousals in defining UARS has been traditionally defined by an arousal index (AI) of more than 10 arousals per hour of sleep. Unfortunately, this disease-defining criterion is already overlapping with well-established EEG arousal norms based on age, identifying normal AI of  $16.8 \pm 6.2$  at age 31–40, increasing up to  $21.9 \pm 8.9$  at age 51–60.<sup>12</sup> In fact, when compared with normal subjects, UARS patients have no difference in frequency of arousals ( $12.7 \pm 5.8$  in UARS patients vs.  $10.1 \pm 4.3$ , p-value 0.22).<sup>13</sup>

#### **d) Common PSG findings between UARS and OSAS**

In comparison to OSAS, UARS patients have no difference in polysomnographic sleep architecture parameters such as sleep efficiency, sleep latency, slow wave sleep latency, and REM sleep latency.<sup>8</sup>

Regarding electrocortical activity, alpha-delta sleep is defined by the intrusion of waking alpha rhythm into deep, slow wave sleep (delta). If present in a cyclical alternating

pattern (CAP), it correlates with increased sleep instability and fatigue in UARS patients. However, CAP is a nonspecific electroencephalographic pattern present in a wide variety of other disorders, including OSAS.<sup>14</sup>

#### **4) A Common Pathway and Risk Factors Shared by UARS and OSAS**

If considered a distinct clinical entity from OSAS, UARS should present a different pathophysiology and natural history. However, when studied from the perspective of upper airway physiology, patients with UARS and patients with OSA are similar, although the severity of the upper airway collapsibility during the sleep is different. Recent data have suggested that patients with UARS present with upper airway closing pressures intermediate between OSAS and normal controls.<sup>15</sup> Notably, other studies have also found inspiratory flow limitation (IFL) during sleep associated with arousals even in healthy individuals. In comparison to healthy individuals, UARS patients have only slightly increased of IFL during supine, stage 2 sleep, and no difference in inspiratory effort. As they age, healthy individuals demonstrate increase of IFL, hypopneas, and even apneas during sleep.<sup>16</sup> These findings support the progression in the continuum of increasing upper airway collapsibility, where individuals may transition from "normal" (asymptomatic) all the way up to OSAS as they age.

The natural history of UARS further supports the idea that UARS belongs to the clinical spectrum of OSAS. During a 6-year follow-up study, a significant number of patients originally diagnosed with UARS developed signs of OSAS. In this study, the progression from UARS to OSAS was related to increase in BMI, a well-known risk factor for OSAS.<sup>17</sup>

#### **5) Nosological Classification: UARS is Subsumed into OSAS**

Since its original description in 1993, the American Academy of Sleep Medicine (AASM) has not recognized UARS as a separate disease from OSAS. Although, considered a preclinical stage of OSAS by the AASM Task Force in 1999, the UARS was only included into the group of OSAS in 2005.

The diagnosis of UARS is not recognized as a discrete nosological entity by the International Classification of Sleep Disorders (ICSD-3) published in 2014. This task force, composed of members of American Academy of Sleep Medicine (AASM), the World Sleep Federation (WSF), and Diagnostic and Statistical Manual of Mental Disorders (DSM-5), has agreed to subsume the so-called UARS into obstructive sleep apnea (ICD-9-CM code 327.23), as the "pathophysiology has not shown to differ from that of the obstructive sleep apnea."<sup>18</sup>

#### **6) No Distinctive Cardiovascular Outcomes in UARS**

Currently, there is lack of evidence to support an association or a cause-effect relationship between UARS and a cardiovascular disease or metabolic derangement. Conflicting data exist regarding blood pressure in patient with UARS. In a 4-year follow-up study, Guilleminault and colleagues have shown that untreated patients with UARS had no significant change in blood pressure or cardiovascular or neurological status.<sup>19</sup> Like mild OSAS, UARS have the lowest systolic and diastolic blood

pressure values, as well as type 2 diabetes when compared to moderate-severe OSA.<sup>8</sup> Until large epidemiological and/or interventional studies are available, the impact of UARS on cardiovascular outcomes remains unknown.

## 7) Treatment: No Difference in Treatment Recommendations for AURS and OSAS

Therapeutic data about UARS treatment are few and plagued by inadequate methodology and small patient samples, without precise sample estimation. Only small case series and observational studies support the beneficial impact of CPAP and/or mandibular advancement devices in UARS.<sup>1,20</sup> These therapeutic interventions are not different from those recommended for mild OSAS, also sharing barriers such as poor compliance and insurance refusal to cover treatment.

## CONCLUSION

Does upper airway resistance syndrome exist as a discrete disease state?

The short answer is no. The independent existence of UARS from OSAS cannot be supported based on current literature. Therefore, the academic sleep community has not accepted UARS as a discrete nosological entity, separate from OSAS. Instead, it is considered a mild expression of OSAS in the continuum of increasing upper airway resistance associated with neurocognitive changes. The use of a new term (UARS) to describe what is already known (OSAS) will only introduce confusion of both patients and nonspecialists alike. I am confident that after reviewing the failure of UARS to reach the status of a distinct medical condition from OSAS, those who still call it UARS, not OSAS, should remember the old adage: “if it looks like a duck and swims like a duck, and quacks like a duck, then it probably is a duck.”

## CITATION

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## DISCLOSURE STATEMENT

The author has indicated no financial conflicts of interest.