REVIEW ARTICLE

The upper airway resistance syndrome: origins and evolution

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Introduction

The term 'UARS' describes a form of mild sleep-disordered breathing (SDB), which is increasingly recognised as a cause of daytime symptoms associated with disrupted sleep, but without many of the physiological and clinical features ascribed to obstructive sleep apnoea syndrome (OSAS) [1]. Much debate has ensued since its proposal as a syndrome, as to whether it constitutes a separate entity from or is merely a part of the spectrum of OSAS [2, 3]. The age-old cohorting of protagonists and doubters into 'lumpers or splitters' has not detracted from a general appreciation that certain patients with clinical symptoms of daytime sleepiness can be found to have respiratory effort-related arousals (RERAs) on testing. These patients often do not have the classic phenotype or concurrent physiological criteria for OSAS. Indeed, it is for that reason that these patients were and are often left undiagnosed and untreated despite their symptoms. That said, whether one considers upper airway resistance syndrome (UARS) as a distinct entity, as a variant of OSAS or as a part of a spectrum of SDB, alongside OSAS is not clear. The latest International Classification of Sleep Disorders classifies it as part of OSAS [4]. This narrative review reminds the reader of its definition, origins and distinctions from other forms of SDB and suggestive further reading.

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Background

UARS is characterised by abnormal respiratory effort, breath flow limitation, absence of diagnostic criteria for OSAS, minimal fluctuations in nocturnal oxygenation saturation and frequent nocturnal arousals or reflex brainstem activation [1].

Yet, recognition of this entity had developed only in the last decade through investigation of children presenting to the Stanford Sleep Disorders Clinic, with various symptoms of snoring, sleep disturbance and daytime symptoms (personal communication CG). Thus, in a group of twenty-five such children, ranging from 2-14 years, an increased respiratory resistive load was identified. On polysomnography (PSG), all were noted to have negative endo-oesophageal pressure swings, but in the absence of desaturation or other features of OSAS. Moreover, there was symptom benefit and physiological improvement following tonsillectomy or adenoidectomy in all cases – tested by the multiple sleep latency test or the Wilkinson Addition test [5]. It should be noted that the term 'UAR' was published in 1990 and that UARS was not used until the first adult cases were reported in 1993 [1, 6].

Epidemiology

The actual prevalence of upper airway resistance syndrome (UARS) is unclear, not least because of the debate surrounding accurate definitions, and the evolution of physiological measurements used to refine those criteria, with later studies using nasal pressure transducers in studied cohorts.

Estimates suggest that obstructive sleep apnoea syndrome (OSAS) affects 1-5% of adult men in Western countries [7]. Limited data are available on the prevalence

of UARS in the general population. In earlier descriptions, the estimated prevalence was 6% in men and 11% in women[8, 9]. Kristo found a prevalence of 8.4% in a 12-month review with polysomnography (PSG)[10]. More recently, in a study conducted as part of the São Paulo epidemiological study, in which a population-based cohort of 1042 patients aged 20-80 years were studied by questionnaire and PSG, the prevalence of UARS was 18.7%, being more common in women and in young people[11,12]. The inference from epidemiological studies to date, and the positioning of UARS along a spectrum of sleep-disordered breathing (SDB) is that it is likely to affect a significantly higher group of people, particularly females, than OSAS, with a broader range of associated symptoms, as is discussed below.

Pathophysiology

Both UARS and OSAS present as intermittent upper airway collapse physiologically [13]. In UARS, an increase in upper airway resistance is associated with a resistive load, which accompanies airflow limitation, cortical arousals, but little desaturation[14, 15].

Patients with OSAS, have histological evidence of atrophied oromucosal buccal cavity muscles, and the suggestion of a polyneuropathy or at least neurogenic alteration of these muscles, which determine pharyngeal patency during sleep[16, 17]. Functionally, delayed electrical reflex responses are demonstrated within the palate of patients with OSAS as compared with controls[18]. Furthermore, altered afferent and efferent receptor responses, attenuated brain responses in certain brain areas on functional magnetic resonance imaging and remodelling of the upper airway dilator muscles have all been shown in OSAS[19-21]. Thus, a hyporesponsiveness to upper airway stimuli and delayed response to pharyngeal closure may lead to the profound airway collapse in OSAS. Study of patients with UARS reveals inferred differences. Thus, it has been shown that palatal two-point discrimination is no different from controls[22]. Hence, a lack of hyporesponsiveness, and preservation of the dilator reflex or a fast reflex response, may prevent the extent of airway collapse apparent in OSAS. Indeed, there is a number of stimuli for airway collapsibility, such as nasal airflow, nasal valve changes, altered airflow dynamics, etc., yet, the possibility of a faster response to change in airway calibre may distinguish UARS from OSAS[23]. It is further suggested that this airway reflex causes subcortical activation, for which the EEG correlate is the A1 phase, seen more often in UARS during so-called cycling alternating patterns (CAPs) than in OSAS[24].

Clinical Features

The symptoms of UARS are most frequently those of mild OSAS. However, as is illustrated from a large study below, differences are also apparent, either with or instead of classical sleep-related breathing symptoms. In particular, symptoms of sleep disturbance characterised by sleep onset and maintenance insomnia, nocturnal wakenings as well as fatigue are more prevalent[25].

It appears that the prevalence rates of symptoms of sleep disturbance (sleep-onset insomnia, and wakefulness after sleep) are higher in UARS, than might be expected by modelling for likelihood, based on a spectrum of patients with severe-to-mild OSA, who underwent questionnaires and multiple sleep latency testing (MSLT) [26].

Perhaps the largest retrospective analysis of clinical features of UARS, as compared with primary snorers (PSs), sleep apnoea without daytime symptoms (OSAH) and classical OSAS, was conducted between 1996 and 2006 at two German sleep centres. There was a clinical history review and PSG of 157 patients with PS, 424 with UARS, 562 with OSAH and 1610 with OSAS [27]. Those categorised as UARS tended more often to be female (3:1 cf. OSAS), less overweight, with lower weight gain over 5 years. UARS sufferers had more arousals than did simple snorers, and a higher Epworth sleepiness scale, although less than OSAS. Patients with UARS had the highest prevalence of sleep-onset insomnia, although differences in sleep disturbance between groups were not explained by PSG findings. UARS had the highest number of reported somatic symptoms, such as headaches, and unrefreshed waking and as much oesophageal reflux as well as rhinitis. Reflux and rhinitis have been proposed as evidences of increased autonomic dysfunction, particularly parasympathetic activation in UARS as compared with the more sympathetic drive in OSAS [28]. A quality-of-life (QOL) score (incorporating questions on mood, daily activities, joy for life, concentrating ability and sleep satisfaction), adjusted for gender, age, feeling refreshed on awakening, presence of sleep-onset insomnia, daily self-reported sleep deficit, RDI and daytime sleepiness being present, demonstrated odds ratios for impaired QOL against PS of 2.91 for UARS and 2.13 for OSAS[28].

Age differences between this older cohort of German

patients with UARS as compared with a group from Stanford, California, have not been explained clearly [29]. That said, there was consistency of higher reported somatic, and psychosomatic symptoms, non-obese individuals, with a female predominance from both cohorts.

Other workers have reported associations with chronic fatigue syndrome, fibromyalgia and attention-deficit disorder[30-32]. Dizziness associated with lower blood pressure (in contrast to the generally higher blood pressures seen in OSAS) has been suggested to be more common in UARS[33].

It is suggested that craniofacial abnormalities, such as mild retrognathia, as well as nasal blockage, reduced mouth opening and narrow oropharyngeal passage should be picked up as possible indicators[34].

Diagnostic criteria

Clinical features of UARS include symptoms of but often with symptoms atypical for OSAS, such as the functional somatic disorders alluded to above. Thus, patients may complain of tiredness, rather than sleepiness. A corroborative partner history remains important, particularly when enquiring regarding sleep-related breathing features.

Conclusive diagnostic criteria for UARS have not been established. PSG reveals AHI <5/h, oxygen saturation >92% and the presence of respiratory effort-related arousals (RERAs) [35]. Perhaps the key finding on PSG is the presence of RERA in the absence of apnoeas and hyponoeas[36]. The gold-standard measure for non-apnoea/hypopnoea respiratory events is oesophageal pressure monitoring (Pes), using paediatric feeding or purpose-made catheters. That said, measurement of respiratory effort is challenging and non-invasive surrogates have been proposed. Thus, the most commonly used measure of respiratory events is the nasal flow/pressure cannulae. These are more sensitive at detecting respiratory events than are nasal thermistors[37,38]. Nasal flow cannulae and inductance plethysmography have been accepted by the American Academy of Sleep Medicine as reliable tools for measuring upper airway resistance.

Respiratory Parameters

The key recognisable features when using oesophageal catheters to measure changes in pleural pressure are a

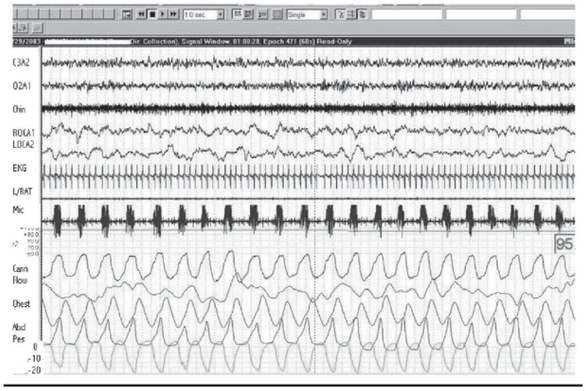

Figure 1: PSG recording revealing sustained effort

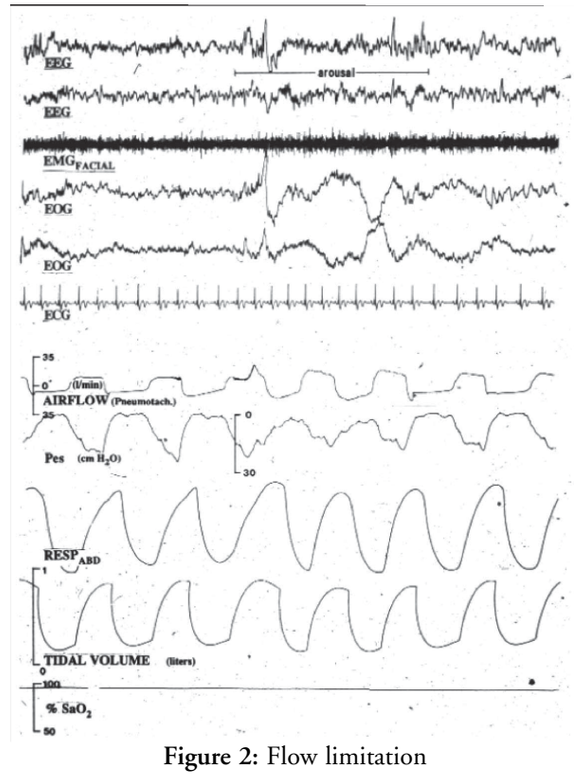

Figure 2: Flow limitation

progressively negative peak inspiratory pressure Pes, terminated by an EEG arousal (Pes crescendo). A second pattern is the sustained negative inspiratory Pes followed by an arousal, and finally so-called Pes reversal, where progressive negative inspiratory pressure is followed by a sudden reduction in peak inspiratory pressure (ie, respiratory effort), independent of the EEG. All of these patterns are seen with <3% drop in oxygen saturation (Figure 1).

Similar correlates of Pes may be seen in the

inspiratory breath profiles of the nasal cannulae. A number of polygraphic monitoring devices provide information on so-called breath flow limitation (BFL). Changes in pleural pressure upon termination of the 'resistive load' are more negative, more numerous and associated with more cortical arousals than similar features in matched control subjects[39]. However, caution has been advised by these and other authors. BFL allows a surrogate for Pes, in the context of RERAs and desaturation criteria, when oesophageal catheters are not used. The visualisation of intermittent flow limitation is difficult to reliably quantify. Some have used the length of airflow limitation episodes or the percentage of BFL with respect to total sleep time. The termination of inspiratory flow limitation has been linked to EEG arousal or Pes reversal without alpha EEG arousal. However, BFL can be present without negative Pes swings, and coincidental EEG arousals are seen. Thus, the relevance of the association of RERA with BFL, but absent Pes events in diagnosing UARS remains uncertain. Additional information provided by autonomic cardiovascular parameters, such as tachycardia, is suggested to facilitate diagnosis of UARS[40].

The potential value of inspiratory flow profiles as surrogates for upper airway resistance, and for inferring RERA without need for PSG, would be desirable. Portable home-testing devices that allow such basic data have been utilised[12]. A number of definitions of BFL has been published[37, 38, 41]. However, their further validation against the gold standard of Pes and cortical EEG changes will be required.

EEG parameters

UARS patients are said to have unstable sleep; ie, a lower arousal threshold for given inspiratory resistive loads. This is characterised by a cyclic alternating pattern (CAP) in NREM sleep [38], which predisposes to the occurrence of arousals. These findings correlate with symptoms such as tiredness and fatigue. CAPs are periodic electrocortical events distinct from background EEG activity. The CAP has been described in other situations [42], such as fibromyalgia, chronic fatigue syndrome and also in OSAS, but less frequently than in UARS [43, 44]. The correlation of CAP with such somatic symptoms carries the implication that normalisation of breathing events in patients with UARS/SDB may not be sufficient to fully treat their daytime symptoms (Figure 3).

Other than CAP, there is an increase in alpha rhythm,

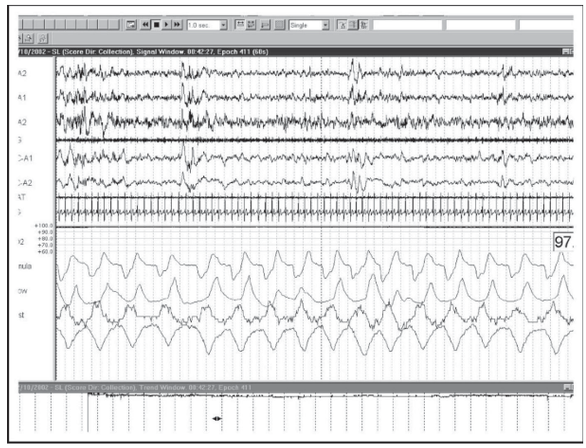

Figure 3: Cycling alternating pattern

and a relative increase in delta sleep, which persists in the later cycles of sleep. Thus, patients with UARS have more alpha time, more high alpha and low theta powers during NREM (ie, 7-9 Hz bandwidth), so-called alpha intrusions, more delta in REM and a higher frequency of RERAs than in OSAS and normals while asleep [44, 45].

Management

Treatment options for UARS are naturally based on overcoming the component of SDB, and managing associated or additional non-respiratory components. In the original description of UARS, adult patients were successfully treated with continuous positive airway pressure (CPAP) [1]. Moreover, even children with daytime symptoms and UAR had improvements of these symptoms after surgical relief of the upper airway obstruction (ie, adenoidectomy and tonsillectomy) [5].

Although lifestyle changes, CPAP, oral appliance therapy and surgery have all been utilised, it is clear that no single intervention has been universal as an effective therapy. Perhaps, it is unrealistic to expect this, given the frequent somatic associations.

Nevertheless, a multidisciplinary approach that involves scrupulous attention to details such as sleep confounder assessment, sleep hygiene and managing psychosomatic associations, is necessary. The use of cognitive behavioural therapy (CBT) with CPAP was suggested to be beneficial in patients with UARS and insomnia.

CPAP was believed to be the gold standard for UARS. Initial studies have described a good response to CPAP

treatment, which was originally considered to be diagnostic criteria for the syndrome. However, as in mild-to-moderate OSAS, compliance and adherence are low. Protocols for CPAP titration have emerged, which unsurprisingly reflect practice for OSAS. Thus, after reaching the optimal CPAP, the oesophageal 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 H_2O [48]. Some reports exist of worsening after CPAP treatment. No published studies on the use of autotitrating devices, with and without forced oscillatory time (FOT) technology exist. Neither is there any current research into the use of transnasal insufflation (TNI). The use of nasal cannulae with humidified air at flow rates of up to 20l/min has been demonstrated to overcome physiological OSA (AHI <15/h) and reduce BFL. It is suggested to be more tolerable than conventional CPAP nasal interfaces[49, 50].

With poor adherence to CPAP treatment in mild OSAS, oral devices may be a good alternative for UARS. However, predictable efficacy of such appliances is lacking to date (Loube 1998; Guerrero 2001; Yoshida 2002; Rose 2000). There is also a scarcity of data on the usefulness of positional treatment or electrical stimulation of the muscles of the upper airway in patients with UARS, or regarding pharmacological treatment.

Surgical options that include laser-assisted uvulopalatoplasty, uvulectomy, snoreplasty injection, radiofrequency submucosal needle therapy and somnoplasty have all been tried, but without sufficient data to make any firm conclusions[50].

Follow-up and Outcomes

With respect to the evolution of UARS patients, it has been suggested that if UARS is merely a milder form of OSAS, then it should progress into the latter given the appropriate factors[3]. RERA may be an intermediate event between snoring and hypopnoea. In a 5-year follow-up study of untreated UARS patients, Guilleminault report that only 10% developed OSAS and then only following weight gain [51]. Jonzak, in a retrospective 6-year follow-up study, also reported obesity as an aggravating factor for UARS symptoms [52].

Summary

Twenty years on from the first reports of UARS, and thirty years since the introduction of the concept of UAR in children, it is clearly established as a condition within the spectrum of SDB. There are many similarities to OSAS pathophysiologically, and yet the phenotype of clinical expression differs. In particular, characteristics in sleep architecture, the presence of frequent RERAs, BFL and EEG features often seen in functional somatic syndromes such as chronic insomnia, fibromyalgia and chronic fatigue syndrome, confer a distinctness to UARS from OSAS clinically. However, it remains somewhat of a Cinderella diagnosis, cohorted at one end of the spectrum of OSAS, for which standard measures to overcome the UAR (ie, CPAP) may not serve the same effect as in OSAS. This condition provides ongoing intrigue that necessitates more of research into its features, diagnostics and epidemiology that its proposers Guilleminault and colleagues have produced over three decades.

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