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Original Research Article

Upper airway resistance syndrome: evaluation of patients with excessive day time sleepiness non-invasively

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ABSTRACT

Background: Upper airway resistance syndrome (UARS) is a recent concept introduced among sleep disordered breathing (chronic snoring and Obstructive sleep apnea) disorders. UARS also presents with excessive daytime sleepiness (EDS), which is associated with impaired social functioning, work performance and driving ability. However, UARS is not merely a continuum between chronic snoring and obstructive sleep apnea (OSA). Not only UARS patients have equal gender distribution and thin body habitus but they also do not fulfil Polysomnographic criteria of OSA. UARS diagnosis requires oesophageal manometry for diagnosing increased respiratory efforts against increased upper airway resistance (without complete cessation of airflow or hypoxia) and correlating it with EEG arousals to mark an event. Oesophageal manometry is invasive and uncomfortable, therefore, non-invasive means are desirable for evaluation of UARS. The aim of the study is to evaluate the patients with EDS for UARS non-invasively.
Methods: 25 consecutive patients with EDS (Epworth Sleepiness Score >9) visiting sleep clinic at a tertiary level hospital in North India were enrolled after informed consent. It was a non-blinded, interventional trial. All enrolled patients underwent nocturnal polysomnography using VIASYS healthcare sleep screen apnea screen cardio polysomnography machine. After PSG, those patients satisfying criteria for OSA were not analysed further. In remaining patients, greater than 10 alpha EEG arousals/h (Spontaneous Arousals) along with flattening or plateau of inspiratory flow contour (by nasal cannula) was employed to diagnose UARS non-invasively. Epi-info software was used in statistical analysis.
Results: Out of 25 patients with EDS, 60% (15) were diagnosed as OSA based on Apnea-Hypopnea Index (AHI) > 10/hr. Among 15 OSA patients,10 patients had severe (AHI >30); 2 had moderate (AHI 15-30) and 3 had mild OSAS (AHI 10-15). Only one patient was provisionally diagnosed as UARS based on nasal air flow graph and spontaneous arousals/hr >10.
Conclusions: Upper airway resistance syndrome (UARS) is a distinct sleep disorder from obstructive sleep apnea syndrome (OSAS) with unique pathophysiology and it need be evaluated in all patients with unexplained arousals.

Keywords: Excessive day time sleepiness, Obstructive sleep apnea, Oesophageal manometry, Snoring, UARS

INTRODUCTION

Excessive daytime sleepiness (EDS) is a frequent sleep disorder in clinical practice. Recognizing it is important as the sleepiness impairs social functioning, work performance and driving ability and accounts for a major socio-economic burden on the community.[1] After ruling out disruption of normal sleep cycle / use of sedatives/

hypothyroidism etc. traditional approach has been to subject these patients to Polysomnography(PSG), as justifiably Obstructive Sleep Apnea (OSA) is the most common organic cause of EDS. Also OSA as a distinct clinical entity has been firmly established after decades of clinical and experimental research after it was first recognized in 1965.[2] However, studies by Guilliminalt and others have shown that some EDS patients with apneas/hypopneas below threshold for OSA diagnosis , have sleep disruption on EEG closely associated with increased Upper airway resistance(measured with oesophageal manometry).[3] This clinical condition was termed Upper Airway Resistance Syndrome (UARS).UARS should not be considered a continuum between loud snoring and OAS, since patients with OSA and UARS have different clinical profiles.

As there is no complete obstruction of airflow (cf OSA), demonstration of an event using increased airway resistance using increasingly negative intrathoracic pressures (by esophageal manometry) and associated EEG awakenings is used for diagnosing UARS. Obviously, use of esophageal manometry is invasive and uncomfortable.

The term "upper airway resistance syndrome" was first used by Guilleminault and colleagues in 1993 to describe a subgroup of patients with conditions that were formerly diagnosed as idiopathic hypersomnia or CNS hypersomnia.[3] Approximately 5 to 10 percent of patients evaluated for EDS are classified in this category.[4]

These terms were used to describe excessive daytime sleepiness (EDS) without a cause that was clearly defined by a nocturnal polysomnogram (PSG) or the multiple sleep latency test (MSLT).[5] The patients with UARS displayed repetitive increased upper airway resistance (IUAR) that was defined by increasingly negative inspiratory esophageal pressure (Pes) that occurred concomitant with decreased oronasal airflow in the absence of frank apnea or oxygen desaturation (in contrast to Obstructive sleep apnea syndrome). These periods of IUAR were brief, typically lasting one to three breaths, and resulted in brief EEG arousals (from 2 to 14 s), followed immediately by decreased upper airway resistance.

Since Upper airway resistance syndrome is treatable by Continuous positive airway pressure (CPAP), recognition of this syndrome is important to prevent unnecessary medical therapy (e.g. CNS stimulants) which obviously fails to reverse this sleep disordered breathing.

The existence of upper airway resistance syndrome is still a matter of controversy with no clear diagnostic criteria. Standardized criteria for the diagnosis of UARS are still lacking, hampering the epidemiologic investigation. In this study, we have attempted to employ non-invasive criteria for diagnosing UARS in patients with EDS.[6]

METHODS

The study was conducted on patients visiting sleep clinic at a Tertiary Level Hospital in North India with complaints of excessive day time sleepiness.

Patients aged more than 12 years with complaints of excessive sleepiness as evidenced by either prolonged sleep episodes or day time sleep episodes that interferes with their normal functioning were screened. Only patients with Epworth sleepiness score(ESS) >9 were included in the study.

Patients with diagnosed sleep disorders (narcolepsy, circadian rhythm sleep disorder or a para-somnia), symptoms occurring during the course of another mental disorder or symptom attributable to any drug or a general medical condition were excluded from the study.

A group of 25 patients satisfying above criteria were enrolled for study after written informed consent. Each patient's symptoms were scored using Epworth sleepiness score questionnaire. A complete medical evaluation was performed, including a clinical interview investigating medical, psychiatric and sleep-wake history. All patients were analyzed for excessive daytime sleepiness, snoring, restless sleep, frequent arousals, morning headaches, memory loss, witnessed apneic episodes, decreased attention span, personality changes, depression, frequent nocturia, sexual dysfunction and lethargy

Drug intake was reviewed and all subjects withdrawn from therapy with any psychoactive or recreational drugs (including alcohol) that might affect sleep, for a minimum of 15 days. Each subject underwent a nocturnal polysomnographic monitoring for 6-8 hours of sleep. Sleep monitoring was performed using VIASYS Healthcare Sleep Screen Apnea Screen Cardio polysomnography machine. Following parameters were recorded: -

- Central and/or occipital EEG (C3/A2, C4/A1, O2/A1, and O1/A2 of the international 10–20 electrode placement system)
- Electrooculogram
- Submental electromyogram.
- Anterior tibialis electromyogram for monitoring leg movements.
- ECG (modified lead V2) for cardiac monitoring.
- Continuous pulse oximetry using a finger probe.
- Thoracic and abdominal piezoelectric strain gauges for detecting abdominal and thoracic movements.
- Oro-nasal thermistor to measure airflow at the nose and mouth.
- A nasal cannula consisting of a ± 2 cm H2O pressure transducer to measure airflow at the nose.

Arousals were defined as appearance of waking α rhythm into deep slow sleep for >3 sec. Apnea was defined as a decrease of inspiratory airflow to <20% of waking levels, and hypopnea was defined as a decrease in inspiratory airflow to <50% of waking levels. The clinical diagnosis of OSAS was established by an apnea/hypopnea index (AHI) of at least 10 events per hour of sleep.

The diagnosis of UARS was evaluated with a nasal inspiratory flow contour analysis which has been shown to accurately identify changes in upper airway resistance. A flattening or plateau of inspiratory flow contour implies flow limitation (the shape of a normal inspiratory flow versus time signal is rounded or sinusoidal). Patients presenting with symptoms of sleep-disordered breathing, but a flattening or plateau of inspiratory flow contour associated with EEG arousals, received a presumptive diagnosis of UARS.

Statistical analysis

The data generated from the study was analyzed by appropriate statistical methods.

RESULTS

There were 21 males (84%) and 4 females (16%) and most patients (10) were in 45-54-year age group (40%).

Analysis of patients'symptoms

Snoring, restless sleep, frequent nocturnal arousals and nocturia were the most frequent symptoms with prevalence of 100%,80%, 56% & 52% respectively (Figure 1), with mean duration of 51, 11.5 ,11.8 and 20.5 months respectively (Figure 2). Other symptoms viz. morning headaches, lethargy, memory loss and personality changes were seen in less than 50% of patients with EDS.

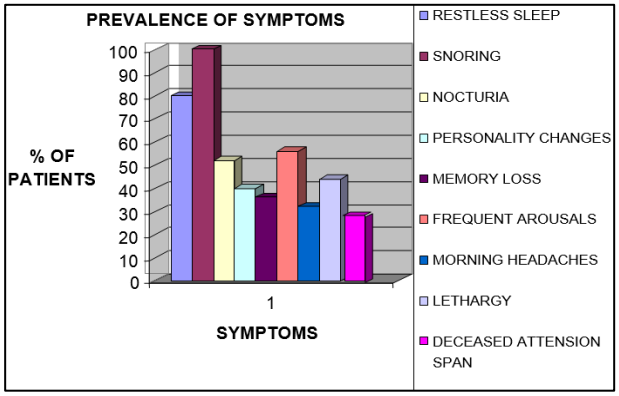

Figure 1: Prevalence of symptoms.

There were 11 hypertensives (44%), 2 diabetics and 1 patient with hyperthyroidism. With respect to Body Mass Index 80 % were obese: 20% were overweight and none had normal BMI (Figure 3).

Analysis of polysomnographic parameters

Relevant parameters obtained in Polysomnography were Obstructive Apnea/hr, Central Apneas/hr, Mixed Apneas/hr, Hypopneas/hr, Apnea-Hypopneas Index, Spontaneous Arousals/hr, Total Arousals/hr, PLMs/hr (sleep), Desaturation Index, Basal and Minimum Oxygen Saturation, Sleep Efficiency (%), Sleep onset and Sleep REM Latency and Brady/Tachy Index.

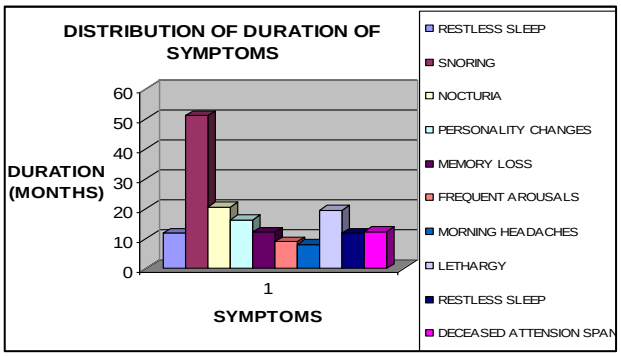

Figure 2: Distribution of duration of symptoms.

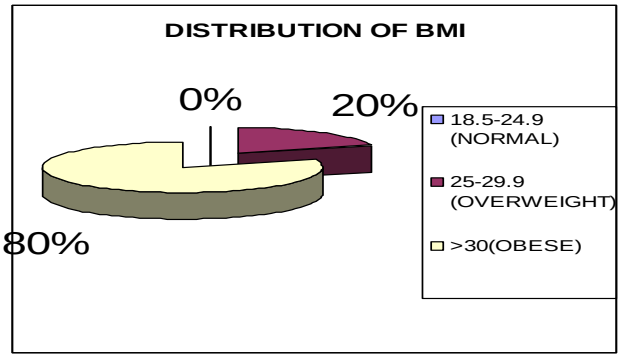

Figure 3: Distribution of body-mass index.

As would be expected in this population of predominantly obese patients with EDS, the mean Apnea-Hypopneas Index was 29.9/hr and number of desaturation events per hr (Desaturation Index) was 31.8/hr. Severity of desaturation (basal and minimal O2) were determined, with mean lowest nocturnal O2% was 75.9 (Minimum 45 -maximum 94% Range 49).

Arousals are sequelae of respiratory events (apneas/hypopneas) and play important role in pathophysiology of Excessive Day time Sleepiness (EDS). Spontaneous arousals are arousals not associated with respiratory or desaturation events and limb movements. They are important in non-invasive determination of UARS. Mean number of Total Arousals /hr was 7 and mean number of Spontaneous Arousals/hr was 4.5.

Apneas result in repeated autonomic arousals associated with cyclic variations in heart rate which is reflected in the Brady/Tachy Index. Mean Brady/Tachy Index was

8.1. Sleep Efficiency is the most commonly used objective measure of sleep quality. It is defined as the percentage of time in bed spent asleep. Sleep onset latency is a measure of propensity to fall asleep. Sleep REM latency is decreased in narcolepsy without cataplexy, which is a cause of EDS. Therefore, its importance lies in EDS not explained by sleep breathing disorders. In this study, mean of Sleep Efficiency (%) was 77; Sleep onset latency was 7.38 min and Sleep REM latency was 42.2 min.

More than 10 alpha EEG arousals/h (without identifiable cause) along with flattening or plateau of inspiratory flow contour (by nasal cannula) and Respiratory Disturbance Index <10 was employed to diagnose UARS non-invasively. Diagnosis of UARS was also supported by Spontaneous Arousal Index >10/hr.

Out of 25 patients, 10 patients (40%) had AHI score <10/hr. These patients had their nasal air flow graphs evaluated and only one patient had flattening of air flow graph. This patient also had Spontaneous Arousal Index of 18.4/hr, which supported the diagnosis of UARS. However, because of small sample size (1 UARS patient versus 15 OSAS patients) no correlation could be performed.

Body Mass Index and Apnea-Hypopnea Index were correlated using non- parametric Spearson's coefficient as data was not normally distributed. Correlation was found to be statistically significant ($p < 0.05$). This agrees with increased prevalence of OSAS in obese subjects.

Frequent arousals leading to sleep fragmentation is important in pathophysiology of EDS. Epworth Sleepiness Score and Total Arousal Index were correlated using non-parametric Spearson's coefficient as data was not normally distributed. Both indices were found to be significantly correlated ($p < 0.05$).

Hypoxia secondary to apneic events have been associated with development of hypertension. Hypertension and desaturation index were not found to have significant statistical correlation by using Mann-Whitney test. Similarly, patients with and without hypertension were compared for correlation with Apnea- Hypopnea index employing non-parametric Mann-Whitney test. These variables were not found to be significantly correlated ($p > 0.05$).

DISCUSSION

Sleep related breathing disorder viz. OSA has been classically associated with obese and heavy snorers, therefore clinical suspicion has also been largely focused on these individuals.

Pioneering work of Guilleminault and others in past three decades has given sufficient evidence for existence of another sleep related breathing disorder termed "Upper Airway Resistance Syndrome".[7-9] This syndrome has EDS and similar symptoms as compared to OSAS, however clinical profile of patients differs and diagnosis also requires invasive procedure (esophageal manometry) for confirmation of diagnosis.

The prevalence of UARS in the general adult population is unknown, yet it has been estimated to be 6% to 11% in study by Vettori et al and about 8.4% in study by Kristo et al.[10,11]

Patients with UARS are typically non-obese, with mean BMI <25 kg/m2.They also have lower mean age compared to OSAS patients. The distribution in both genders is equal in contrast to male: female ratio of 2-3:1 in OSAS patients.[12]

In a series of 400 cases by Guilleminault et al, the mean respiratory disturbance index was 1.5 and the oxygen saturation was >95%.[13] Their craniofacial anatomy revealed a predominantly high and narrow hard palate, an abnormally small intermolar distance and a thin soft palatal mucosa with a short uvula. In 88% of the subjects, there was a history of early extraction or absence of wisdom teeth. Their psychological profile showed a high anxiety score. Other clinical features were cold extremities, postural hypotension, history of fainting, and low blood pressure. In a subgroup of 15 subjects, between 20 and 30 year of age, orthostasis was present by tilt testing, and was associated with a low mean systemic arterial blood pressure.

In UARS, the arousal threshold is lower. The recognition of the internal respiratory load is exquisitely sensitive, therefore allowing the patient to wake up in response to small increases in inspiratory effort. The sleep EEG in UARS shows an increase in alpha rhythm.[14] There is a relative increase in delta sleep, which persists in the later cycles of sleep. These patients may present with hypotension. In contrast, sleep in OSAS shows a predominance of stage 1 and 2 NREM sleep with a decrease in delta sleep. In addition, there is over activation of the autonomic nervous system with demonstrable increases in muscle sympathetic nerve activity and increased blood pressure both during sleep and waking hours. Clearly, UARS and OSAS markedly differ from each other in terms of their clinical presentation, sleep EEG, and autonomic nervous system responses.

Repetitive arousals have been described to be linked to excessive day time sleepiness in both OSAS and UARS patients.[15] Philip et al have demonstrated decreased Mean Sleep Latency Test (MSLT) employing repetitive auditory stimuli to cause sleep fragmentation.[16]

Study by Pelin et al suggested the role of average maximum inspiratory effort in excessive daytime sleepiness in patients with obstructive sleep apnea syndrome (OSAS) and upper airway resistance syndrome

(UARS).[17] ESS was significantly correlated with the average maximum Pes (oesophageal pressure) in both Obstructive sleep apnea syndrome and Upper airway resistance syndrome patients. However, no significant correlation was found between the MSLT score and average Pes in both Obstructive sleep apnea syndrome and Upper airway resistance syndrome patients. Thus, ESS though being subjective has been found to be correlated with severity of IUAR while MSLT, even though objective for determining EDS has not been found to be correlated with IUAR.

In UARS sleep disruption from multiple brief arousals occurs as a result of increasingly negative intrathoracic and airway pressure, with the response most likely mediated by mechanoreceptors in the upper airway. Guilleminault et al have noted that one fourth of patients diagnosed as UARS did not report snoring. Relying only on symptom of snoring will obviously miss diagnosis in many patients. A high index of suspicion for UARS is thus required in appropriate clinical setting i.e. patients with EDS and normal or inconclusive polysomnography studies and those diagnosed as "idiopathic hypersomnia"

UARS has been defined with following criteria employing esophageal manometry:

- Transient Arousals associated with
- Increased upper airway resistance (IUAR) defined by 'crescendo Pes` (progressively more negative peak end-inspiratory Pes, esophageal pressure)
- Terminated by `Pes reversal` (normalization of Pes) following arousal.

Respiratory related arousals >5 per hour of sleep not corresponding to definitions of `apnea` or `hypopnea`, defines upper airway resistance syndrome (UARS).[18]

Arousals were defined as appearance of waking α rhythm into deep slow sleep for >3 sec. Apnea was defined as a decrease of inspiratory airflow to <20% of waking levels, and hypopnea was defined as a decrease in inspiratory airflow to <50% of waking levels.

Establishing diagnosis of UARS is difficult because the only confirmatory test is esophageal manometry. It is an invasive procedure with low patient acceptance and availability. Until recently, the standard tool used for monitoring respiratory airflow in poly-somnography has been the thermistor. This device is effective at identifying complete cessation of airflow (apnea). However, detection of intermittent reduction of flow (hypopnea) is much more subjective and many respiratory events are missed by thermistor.

The published American Association of Sleep Medicine guidelines approve use of a nasal cannula/pressure transducer to detect apneas/hypopneas, but require esophageal manometry for Respiratory Effort-Related Arousals (RERAs). However, esophageal manometry may be poorly tolerated by many subjects.

Ayappa et al in a study compared detection of respiratory effort-related arousals (RERAs) by a nasal cannula/pressure transducer system and esophageal manometry and found good agreement between the number of events detected by the two techniques.[30] They concluded that nasal cannula/pressure transducer provides a non-invasive reproducible detector of all events in sleep disordered breathing and it detects the same events as esophageal manometry (RERAs). The diagnosis of UARS therefore, can be evaluated with a nasal inspiratory flow contour analysis. A flattening or plateau of inspiratory flow contour implies flow limitation (the shape of a normal inspiratory flow versus time signal is rounded or sinusoidal).[19]

A noninvasive test for diagnosis of UARS is desirable for obvious reasons. Surrogate EEG markers along with study of nasal air flow contour by nasal cannula have been used to diagnose this syndrome in this study. Spontaneous arousals i.e. arousals not associated with oxygen desaturation, periodic limb movements or heart rate variations was temporally associated with respiratory events detected by nasal cannula. Woodson also reported a pattern of crescendo snoring followed by transient EEG arousals in the absence of oxyhemoglobin desaturation as highly suggestive of UARS.[20] Lofaso and colleagues proposed beat-to-beat BP evaluation by infrared plethysmography as a more sensitive marker of IUAR than brief arousals.[21]

This study aims to determine non-invasively presence of this syndrome in group of patients with Excessive Daytime Sleepiness (ESS >9). The study group was male predominant (84%) and all the patients were obese/overweight. Snoring and excessive day time sleepiness were present in all patients while other symptoms in order of decreasing prevalence were: Restless sleep (80%), Frequent arousals (56%), Frequent nocturia (52%), Lethargy (44%), Personality changes (40%), Memory loss (36%), Morning headaches (32%) and Decreased attention span (28%).

These symptoms are explained by poor sleep quality associated with frequent arousals and nocturnal hypoxia. However, these symptoms are not specific for sleep disordered breathing nor are they helpful in distinguishing Obstructive Sleep Apnea Syndrome (OSAS) and Upper Airway Resistance Syndrome.

Poor sleep quality in this study group is corroborated with mean sleep efficiency of 78%; mean desaturation events per hr of 32 and mean minimal O2 saturation of 76%. 21 patients had ESS score between 9-18 ('sleepy') and 4 had ESS score >18 ('very sleepy').16 patients (15 OSAS and 1 UARS) had their excessive sleepiness explained by sleep related breathing disorders.

Three patients had REM latency <5 min. They were planned for Mean Sleep Latency Test (MSLT) to assess objectively for increased sleepiness and to reproduce short REM latency. Out of 25 patients, 60% patients had OSAS (AHI >10/hr). Out of 15, 10 patients had severe (AHI >30); 2 had moderate (AHI 15-30) and 3 had mild OSAS (AHI 10-15). Out of 15 patients diagnosed as OSAS, 2 were females and 13 were males. The sex ratio is 6.5:1 (M: F) which was higher when compared to predicted 2-3:1 ratio in general population. The mean BMI of patients with OSAS was 34.3 Kg/m2 while in the rest of patients it was 31.0 Kg/m2.

Thus, patients with OSAS had higher mean BMI. This is expected as obesity has been proved as risk factor for sleep apnea syndrome. Out of 25 patients, one patient was diagnosed as UARS based on nasal air flow graph and spontaneous arousals/hr >10. This patient had age 39 yrs, which was less than mean age of the study group (45.5 yrs). This patient's BMI was 33 kg/m2, which was approximating the mean BMI of the study group.

In comparison to the study by Guilleminault et al where majority of UARS patients had BMI <25 Kg/m2, BMI of patient diagnosed UARS is high.[13] This patient had ESS score of 18, while the mean score of the whole group was 12.8. This patient's Apnea-hypopnoea index was 5.2/hr and spontaneous arousals/hr was 18.4. This patient didn't show severe desaturation as was observed in other studies. Patient's basal O2 saturation was 94% and desaturation index was 5 per hr. Thus, this UARS patient conformed to features of younger age and mild oxygen desaturation during sleep as in study by Guilleminault et al.[13] Because of small sample size, parameters of UARS patient cannot be statistically compared to those of OSAS patients. Also, oesophegeal manometry should be done for definitive diagnosis of UARS, which was not done in this study.

Mean sleep efficiency in the study group of 25 patients was 77%. No comparative data for sleep efficiency was available from other studies. Body Mass Index and Apnea-Hypopnea Index were correlated to be statistically significant ($p < 0.05$). This agrees with increased prevalence of OSAS in obese subjects. Epworth Sleepiness Score and Total Arousal Index were found to be significantly correlated ($p<0.05$). This shows role of frequent arousals in pathophysiology of EDS scored using ESS. No significant correlation could be derived between HTN and AHI, desaturation index and total arousal index. The shortcomings of the study are the small number of candidates analysed and lack of Oesophageal manometry for confirmation of diagnosis of UARS.

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