UARS: an unrecognized syndrome

2009
Upper Airway Resistance Syndrome (UARS)

- Upper airway resistance syndrome (UARS) was first recognized in children in 1982
- The term UARS, however, was not used until adult cases were reported in 1993
- The description of UARS brought clinicians' attention to a group of patients that was left undiagnosed and untreated despite severe impairment.
UARS

• Since the first description of a polygraphic pattern called obstructive sleep apnea in the Pickwikian syndrome in 1965, sleep medicine has undergone an evolution.
• There was the description of Obstructive Sleep Apnea Syndrome
• UARS was born as part of the efforts to describe a generally unrecognized patient population that is non-obese and with clinical features not matching those reported with OSAHS.
Hypopnea

- Apnea is easy to recognize
- What is an hypopnea is more difficult to define:
- Atlases have defined it based since 2000 on investigation of
- nasal cannula pressure transducer (i.e., a decrease of the contour of the curve of the pressure measurement by at least 30% (sometimes 50)% compared to prior breathing)
- And presence of an oxygen Saturation drop of 3 to 4%
UARS

- However there are clearly identified subjects who present
- Complaints
- Clinical signs: a syndrome
- also
- Polygraphic findings
- Response to treatment aimed at improving airway
- BUT do not fit in the definitions for OSAS
Definition of UARS

• With the introduction of better monitoring techniques,
• With the occurrence of the obesity epidemic that involves abdominal obesity and a restrictive chest syndrome when supine
• With results of at least monitoring of 300 patients that we defined as UARS (compared to 60 age matched controls)
• We have defined UARS as followed:
UARS: definition:

- UARS is defined by presence of complaints and signs and polysomnographic (PSG) findings.
- At PSG:
  - Patients have no apnea and
  - hypopnea index < 5 and SaO2 drops not lower than 92%.
- Presence of flow limitation with different patterns such as “flattening” of curve to decrease in nasal flow above 30% compared to non obstructed breathing supine.
- Definitions are based on nasal flow, subject may be mouth breathing.
PSG findings

• With use of new techniques, such as the esophageal catheter for esophageal pressure (Pes) measurement and nasal cannula/pressure transducer, it has become more convenient to identify subtle changes in breathing patterns during sleep.

• And one must remember that 3 to 4 % of oxygen Saturation drop is important if oxygen tension is normal (Hemoglobin/oxyhemoglobin dissociation curve)
Polysomnography

- Per definition UARS is not associated with apnea
- Is not associated with SaO2 drops below 92%
- It is based on a good analysis of the curve of the nasal cannula-pressure transducer
- And/or a good analysis of the esophageal pressure curve
Flow limitation-1

- The subject may snore but there is no apnea and no hypopnea as defined by AASM
- Definition:
  - There is an abnormal contour of the nasal cannula pressure transducer curve:
  - Instead of having a round shape the abnormal breath are flat on the top of the curve: this indicates: flow limitation
  - Some of the changes of the curve may be different (6 different patterns were described)
  - This is abnormal breathing even if no oxygen drop.
  - BUT the patterns when repetitive leads to disturb sleep and change in autonomic nervous system activity
A normal breath
FLOW LIMITATION-2

• **Definition**: flattening of the peak of the nasal cannula pressure transducer wave contour
• Or change in the normal round presentation of the peak of the nasal cannula.
• It is very often but not always, associated with changes in esophageal pressure (Pes) recording (and a change in Pes may not be associated with a pattern of flow limitation)
• It is also often associated with snoring
• It may interest one or several breaths
• It is not associated with a 3 or 4 % SaO2 drop
Flow limitation

• Stanford Sleep Clinic scoring rule:
• At least 4 successive breaths must be associated with abnormal wave contour
• The duration of flow limitation is calculated from the time of the start of flattening to the time when the wave contour normalizes or returns to baseline.

• Report the total time of flow limitation from total sleep time, and the longest episode of flow limitation (in min and sec).
FLOW LIMITATION

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UARS

• Another pattern seen in UARS patients is noted when using esophageal monitoring and demonstration of increase in respiratory effort with each breath lasting again for more than 4 breaths:
• Continuous sustained increased inspiratory effort during sleep.
Continuous sustained effort

• Repetitive, abnormally negative peak end inspiratory pressures, ending at same negative inspiratory pressure without a crescendo pattern. Associated with discrete flow limitation on nasal cannula/pressure transducer signal, with “flattening” of the breath signal curve for at least 4 successive breaths.
Continuous sustained effort
Pes Crescendo

- Sometime there is presence of flow limitation and simultaneous increase in inspiratory effort with each breath: we defined this as a Pes crescendo:

- A sequence of 4 or more breathes that show increasingly negative peak end inspiratory pressure. May be seen with flow limitation on nasal cannula. (See Figure.)
Pes Crescendo
Prospective study of UARS patients

• Complaints: tiredness, fatigue, unrefreshing sleep, sleep maintenance insomnia, joint pain, decrease cognitive performances, or morning headache, present for over 6 months.

• Unexplained despite in-depth internal medicine work-up, and poorly responsive to previous symptomatic treatment trials
investigation

- Sleep Disorder Questionnaire
- Epworth Sleepiness Scale
- Fatigue Severity Scale (FSS) a validated fatigue scale with 9-item scored from 1 to 7, where 1 indicates no impairment and 7 indicates severe impairment, designed to assess functional outcomes related to fatigue.
- Beck Depression Inventory
- 10 days of sleep diaries indicating sleep habits and disturbances
investigation

• Sleep medicine evaluation, and calculation of body mass index and neck circumference

• Cranio-facial and upper-airway evaluation with usage of clinical scales: Mallampatti scale, Friedman et al tonsil size scale, and subjective scales for nasal septum deviation, inferior turbinate enlargement, and evaluation of external and internal nasal valves
subjects

- Prospectively accrued patients (n=30) reporting chronic fatigue n=30;
- non-refreshing sleep n=28,
- disrupted nocturnal = 26,
- morning headache n= 17
- daytime performance impairment n= 29.
- Controls: Age (± 1 and ½ year) and gender matched n= 30
- general good health, absence of sleep complaint
- regular nocturnal sleep habits
polysomnography

- Two nights: one with and one without Pes
- EEG (C3/A2, C4/A1, O1/A1, Fp1/A1, Fz/A1-A2),
- chin and leg EMG,
- ECG (V2 lead),
- right and left EOG,
- nasal cannula-pressure transducer system, mouth thermistors,
- thoracic and abdominal piezzo-electric bands, neck-microphone,
- finger pulse oximetry
- and position sensor.
Analyses

• Blind scoring
• Nocturnal sleep scoring (international criteria including ASDA short EEG arousals)
• Cyclic alternating pattern (CAP)
  Subdivision in phase A of the 2 components-A and B- of a CAP cycle
Results

• mean ESS score:
  patients = 8.5±2.0 controls = 4.0±1.5 (p=0.001)

• fatigue scale:
  Patients = 4.9±0.9 controls = 2.3±1.0 (p=0.001)
Results: anatomy

- **Patients**: BMI = 22.8± 1.6 kg/m2, abnormal nasal valve, n=21
- small maxilla or mandible  n=30
- narrow upper airway with elongated pharyngeal soft tissue n=30
- **Controls**: BMI = 22.6 ±1.8 kg/m2
- retro-position of the maxilla without soft tissue change n=1
### Results

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apnea index</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypopnea index</td>
<td>2.6±1.5 *</td>
<td>0.6±0.7</td>
</tr>
<tr>
<td>RDI</td>
<td>9.1±2.6 *</td>
<td>0.9±0.8</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>374.2±64.7</td>
<td>377.2±75.5</td>
</tr>
<tr>
<td>Sleep Efficiency (%)</td>
<td>85.0±9.6****</td>
<td>90.6±4.6</td>
</tr>
<tr>
<td>Stage 3/4 (%)</td>
<td>14.9±6.12 ***</td>
<td>25.4±6.7</td>
</tr>
<tr>
<td>REM sleep (%)</td>
<td>17.9±7.7</td>
<td>19.4±4.7</td>
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<tr>
<td>Arousal index/h</td>
<td>14.5±3.0 **</td>
<td>9.3±5.2</td>
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- * p=0.0001 (U-test); ** p=0.001 (U-test); ***p=0.00001 (Chi-square)
Instability

• A **new concept** has developed in the field of human sleep pathology - the concept of “instability”.
• This is a fundamental phenomenon in physics and biology that occurs from cells to higher organisms.
• Many systems oscillate from one state to another (for example from “+” to “-”). The time between + and −, even if infinitively brief, is a state of transition and instability.
• Abnormal breathing is associated with an “unstable sleep” well investigated with the “cyclic alternating pattern”-CAP- atlas
CAP

• CAPs are seen in everybody during NREM sleep with passage from wakefulness to Slow Wave Sleep.

• But when CAP increase in rate, this increase indicates that Slow Wave Sleep considered as a “stable state” cannot be reach easily due to disturbances.

• It is said that NREM sleep is “unstable” This is a system that is more sensitive than looking for short EEG arousal.
EG, male, 50 y, UARS patient.
GP, female, 35 y, UARS patient.
CAP results

• UARS (n=30) Controls (n=30)

• CAP rate %  57 ± 9 *  34 ± 6
  CAP time (s)  172 ± 41 *  77 ± 25
  CAP cycles  374 ± 101 *  148 ±76

Index of CAP subtypes %
  A1  59 ± 13 *  68 ± 16
  A2  25 ± 9 *  19 ± 12.5
  A3  16.1 ± 7 *  11 ± 7.4
summary

• UARS had:
  • Greater index of EEG arousal
  • Significant decrease in Phase A1 index—an indicator of normal development of slow wave sleep (SWS)
  • significant increase in phase A2 and phase A3
  • As phase A3 includes short EEG arousal, this increase was expected considering the arousal index difference, but the increase in phase A2 is never tabulated in standard sleep scoring and indicates a further disruption of NREM sleep.
Correlation

- Pearson correlation coefficient analysis:
  - positive correlation between CAP rate and ESS scoring ($r=0.38$, $p=0.01$)
  - positive correlation between CAP rate and FSS scoring ($r=0.51$, $p=0.0001$)
  - positive correlation was also found between Phase A2 index and FSS ($r=0.29$, $p=0.05$) as we requested $p=0.01$ considering the group size this was not significant
UARS and CAP scoring

- Scoring of CAP has shown that UARS is associated with a clear disturbance of NREM sleep
- But there is not a direct correlation with occurrence and termination of flow limitation:
  - Phase A1 of CAP overall decreases
  - Phases A2 and A3 (indicative of nocturnal sleep disturbances) increase
  - Phase A3 correlate with “short EEG arousal” (AASM)
Conclusion

• UARS patients have continuous disturbances and instability of NREM sleep

• This instability of NREM sleep correlates with daytime complaints of tiredness and fatigue
Using a definition based on PSG recording

- We have had clear association between patients presenting PSG of UARS and
- Sleepwalking/terror (Parasomnia)
- Bruxism
- Insomnia
- Depression
- Myalgia
- Fatigue
- Morning headache
- Difficulty to concentrate and perform professional activities
Other Associations

- 40% of the subjects recognized with UARS reports: mild symptoms of vagal activity:
  - Light-headness at abrupt movement from supine to standing up
  - Cold hands and feet
  - BP with mean systolic BP=101±8 and diastolic 63±5
- 9% report having fainted once usually in late teen-age
- Association with local anatomic problems in 69%
Autonomic Nervous System- ANS- investigation

• Study:
• Analysis of heart-rate-variability in patients with mild OSA and with patients with UARS
Heart rate variability

- **Method**: evaluation of heart rate variability of RR-Interval (RRI) using period amplitude analysis in different sleep stages, selection of stable sequences of RRI, application of FFT with spectrum of 0-1Hz of heart rate
- Identification of
- **low frequency band** (LF=0.1-0.15Hz) (cumulative variation of sympathetic and parasympathetic components)
- **high frequency band** (HF= 0.15-0.25 Hz) containing almost exclusively parasympathetic component of HR
- **Ratio LF/HF** considered as descriptive of sympathetic component
HRV

- Analysis of HRV at termination of:
  - hypopnea (OSA)
  - flow limitation (UARS)
- Selection 60 seconds before and after event indicated by change in esophageal pressure (Pes)
HRV

• During NREM sleep independent of sleep stage, consistent change:
• In OSAS patient termination of hypopnea always associated with an increase in the LF/HF ratio (sympathetic activity)
• In UARS subjects consistent decrease in HF component (vagal activity)
• (Sleep Med 2005, 6: 451-457)
UARS-ANS

• In summary: there is a different autonomic nervous system response between UARS and OSAS with abnormal breathing events:
  • In OSAS, an increase in sympathetic tone is seen,
  • in UARS subjects there is a decrease in sympathetic activity and modulation of HR and BP is prominently secondary to vagal activity
Association

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Based on the PSG criteria and request for complaints and signs

- We reviewed 500 cases that responded to our clinical criteria
- 83% of the subjects that we recognized as UARS have previously consulted but never treated for abnormal breathing during sleep
- In our clinical sample we have a larger prominence of women: 67% versus 33%
- We have a greater percentage of pre-menopausal women: 71% versus 29%
- We have a mean BMI of 23.9±2.8 kg/m2
- We have only 6% of subjects older than 65 years that consult.
Subjects presented clinical findings

- They had **abnormalities of upper airway**
- These abnormalities involved
  - The **nose** with abnormal nasal resistance
  - The **upper airway** with involvement of
    - the pharyngeal soft tissues
    - the hard palate or base of tongue due to change in maxillary or mandibular presentation
• Photos
What have the clinical studies indicated

- **UARS patients complain of:**
  - Insomnia
  - Fatigue (chronic fatigue syndrome)
  - Morning Headache
  - Difficulty to perform
  - Muscle pain (fibromyalgia)
  - Depression
  - Parasomnias

- They are considered often with “functional somatic syndromes”
- They are not considered as patients with abnormal breathing during sleep
Conclusion

• UARS subjects are patients
• Unrecognized, they go untreated
• Despite the fact that treatment can eliminate their complaints
Example: Studies in women

- 157 pre-menopausal were studied with a mean BMI of 21.6 kg/m² (all< 25kg/m²),
- 28 had no apnea and no hypopnea has currently defined and presented only flow limitation as defined above.
- They had the anatomic findings that explained their clinical complaint
- They responded the same way to treatment that included nasal CPAP and upper airway surgery*
- *Tantrakul et al (Lung, 2009)