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Sleep-disordered-breathing in Ehlers-Danlos Syndrome (a genetic model of obstructive sleep apnea)

Christian Guilleminault DM, MD, DBiol, 1 Michelle Primeau MD, 1 Hsiao-yean Chiu RN, MS, 1 Kin Min Yuen MD, 2 Damien Leger DM, DBiol, 2 Arnaut Metlaine DM

1 Stanford University Sleep Medicine Division, Stanford Outpatient Medical Center, Redwood City California
2 Centre de la vigilance, Hopital de L’Hotel-Dieu, Universite Paris-Descartes, Paris France

e-mails: cguil@stanford.edu, mprimeau@stanford.edu, happyone680315@hotmail.com, kyuen@stanford.edu, damien.leger@htd.aphp.fr, arnaud.metlaine@htd.aphp.fr

Running Head: Ehlers Danlos and Obstructive-Sleep-apnea

Corresponding Author:
Christian Guilleminault DM, MD, DBiol.
Stanford University Sleep Medicine Division,
Stanford Outpatient Medical Center
450 Broadway, Redwood City CA 94063

cguil@stanford.edu

Institutions at which the work was performed: Stanford University Sleep Medicine Division and Ehlers Danlos Clinic Hopital de L’Hotel Dieu, Paris. (Stanford IRB #15494, Hotel Dieu IRB:: CCPRPB-Hotel Dieu- APHP - Hotel Dieu-25-11-2010)

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Abstract

Aims: Investigation of the presence of sleep-disordered-breathing (SDB) in patients with Ehlers-Danlos (ED) Syndrome. ED is a genetic disorder characterized by cartilaginous defects, including nasal-maxillary cartilages.

Method: A retrospective series of 34 ED patients presenting to clinic with complaints of fatigue and poor sleep were evaluated via clinical history, physical examination, polysomnography (PSG) and in some cases with anterior rhinomanometry. Additionally, a prospective clinical investigation of 9 ED patients was performed in a specialized medical ED clinic.

Results: All ED patients evaluated had SDB on PSG. In addition to apneas and hypopneas, SDB included flow limitation. With increasing age, flow limitation decreased in favor of apnea and hypopnea events, but clinical complaints were similar independent of the type of PSG finding. In the subgroup of patients who underwent nasal rhinometry, increased nasal resistance was increased relative to normative values. Nasal CPAP improved patient symptoms. ED patients in medical clinic presented with symptoms and clinical signs of SDB, but they never were referred for evaluation of SDB.

Conclusion: In ED patients, abnormal breathing during sleep is commonly unrecognized and is responsible for daytime fatigue and poor sleep. ED patients are at particular risk for SDB due to genetically related cartilage defects that lead to the development of facial structures known to cause SDB. ED may be a genetic model for obstructive sleep apnea because of abnormalities of oral-facial growth. Early recognition of SDB may allow treatment with orthodontics and myofacial reeducation.

Key-words: Ehlers Danlos, Sleep-Disordered Breathing, Genetics, Flow limitation, nasal CPAP

Abbreviation List

AAR = Anterior Active Rhinomanometry
AASM = American Association of Sleep Medicine;
AHl=apnea-hypopnea index
APHP=Assistance Publique-Hopitaux de Paris
BMI= Body Mass Index;
CPAP = Continuous Positive Airway Pressure
Cwp= centimeter water pressure
ED= Ehlers Danlos
ESS= Epworth Sleepiness Scale
HRR= High Resolution Rhinometry
OSAS = Obstructive Sleep Apnea Syndrome
Pa/cm3/s=Pascal/centimeter 3/ second
POTS= postural orthostatic tachycardia syndrome
PSG = Polysomnography
RDI= respiratory disturbance index
RERA= Respiratory event related arousal
Reff =effective resistance
SDB= Sleep-Disordered Breathing
SDQ= Sleep Disorders Questionnaire
Reff-T= effective nasal resistance of the entire breath
Rr= effective nasal resistance of entire breath (Reff-T) on the right
Rl= effective nasal resistance of entire breath (Reff-T) on the left
TNR= total nasal resistance
UARS= Upper Airway Resistance Syndrome- VAS= Visual analogue scale
VR= Vertex Resistance
Introduction

Obstructive sleep apnea syndrome (OSAS) has been shown to aggregate in families, and epidemiologic studies on familial associations have indicated that genetic factors might constitute a risk factor for OSAS and sleep-disordered breathing (SDB) (1-4). However, simple genetic models do not explain the occurrence of OSAS (5). Risk of OSAS varies depending on ethnicity (6-8). In non-obese individuals, genetic factors controlling cranial-facial development have been proposed to be involved in the development of the anatomical features leading to familial aggregation of OSAS (9).

The craniofacial complex involves the maxilla and the mandible. The size of these components likely is the element that is most influenced by genetics, which is important because size influences shape (10). For example, a change in the length of the mandibular body alters the shape of the face. Changing only one dimension can alter how the other parts fit together. The direction in which growth occurs is influenced by the surrounding hard and soft tissues. Genes involved in the development of one tissue (for example cartilage) will have a secondary epigenetic effect on another tissue (10).

We report here on the presence OSAS in Ehlers-Danlos (ED) Syndrome. ED is a well-known genetic disorder characterized by cartilaginous defects (11, 12), including nasal-maxillary cartilages. Over time, we have observed more ED patients presenting to our sleep clinic than would be expected based on population prevalence alone. The primary aim of this report is to describe the appearance of sleep-disordered breathing in ED patients; we utilized both a four-year retrospective investigation of our sleep clinic population as well as a separate cohort of ED patients followed in a clinic devoted only to ED.

The retrospective investigation was approved by the Stanford Internal Review Board and the prospective investigation was approved by Hotel Dieu Hospital (Paris, France) IRB

Sleep Clinic Patients
Observed Population
We identified thirty four consecutive patients diagnosed with ED, who were referred to the sleep clinic for daytime fatigue/ poor sleep (n= 34), and daytime sleepiness (n=8). Most had ED type II, characterized by skin hyperextensibility, joint hypermobility, skin fragility, and easy bruising, although one patient had type III (joint hypermobility, commonly with subluxation, dislocation and degenerative joint disease), and two had type IV (minimal skin hyperextensibility, digit hypermobility, marked bruising, and association with arterial rupture) (11).

Clinical Evaluation

A detailed sleep-specific clinical interview and physical was completed for each patient. Subjects filled in questionnaires including the Stanford Sleep Disorder Questionnaire (SDQ) (13) that uses a Likert-type scale (1 to 5) and the Epworth Sleepiness Scale (ESS) (14). Physicians performed structured interviews concerning symptom description, past medical history, family history and medication use. Physicians completed a standardized, sleep-focused physical examination form including anthropomorphic measurements (e.g. BMI or neck circumference) as well as nasal and upper airway examination.

Rhinomanometry

A subgroup of 7 subjects underwent high-resolution rhinomanometry (HRR) (15,16) to determine nasal resistance. This technique can be used to quantify nasal resistance. Tests were performed using a four-phase rhinomanometer (RhinoLab GmbH, Rendsburg, Germany) following the technical and practical methodology and normative data published in the literature (15). The data of the normal controls used here were from age matched (± 2 years) normal subjects used for calibration of the four phase rhinomanometer. Subjects were first given a five-minute rest period in a quiet procedure room at constant temperature, they were positioned at a 30-degree incline and measurements were taken. All measurements were completed within a 15-minute mid-morning interval to ensure nasal state continuity (see reference 15 for details on calculation).
Polysomnography

All patients underwent overnight systematic in-laboratory polysomnography (PSG). The recording consisted of four-channel electroencephalography, two-channel electrooculography, chin and leg electromyography, one-lead electrocardiography, body position, and video monitoring. Respiration was monitored with a nasal cannula pressure transducer system (Protec Inc., Pittsburgh, PA, USA), oral thermistor, thoracic and abdominal respiratory inductance plethysmography (RIP), and pulse oximetry. All variables were calibrated and monitored using a computerized acquisition system (Sandman™, Ontario, Canada).

ED Internal Medicine Clinic Patients

In order to recruit comparable ED patients not presenting with a primary sleep complaint, we approached patients in a specialized ED clinic at the time that they presented for a general medical appointment. Nine patients consented to participate in the study, and none had ever been investigated for a sleep-related problem. Six were considered ED type II, one type III, and two type IV. The evaluation was performed by two physicians (one from local hospital and one from the research team involved in retrospective study) who used the same standardized clinical interview and physical evaluation as was implemented in the sleep clinic. Patients additionally completed a visual analogue scale (VAS), concerning the four weeks prior to the visit, with respect to fatigue, nocturnal sleep, and daytime sleepiness. A photo of the palate and nasal cavities was obtained on each subject.

Following the research evaluation, clinical sleep medicine follow up was recommended and left to the discretion of the treating physicians. Four patients had in-laboratory PSG similar to the recording performed on the sleep clinic patients, one subject had a four-channel recording (nasal cannula, thoraco-abdominal bands, ECG, finger oximetry), and one had auto-CPAP testing. The last three subjects were scheduled to have clinical testing based on availability of clinical services in their geographic location.
Data Analysis

Rhinomanometry

We used the “Standardization Committee on Objective Measurement of The Upper Airway” (15,16) for classification of nasal resistance in 7 patients.

Polysomnography

Sleep staging was completed in accordance with the American Academy of Sleep Medicine (AASM) 2007 recommendations (17). Arousals were scored using the American Sleep Disorders Association’s three-second arousal criteria (18). Respiratory event scoring was based on the AASM’s criteria for SDB in adults (17). Apnea, subdivided into obstructive, mixed and central, was defined as complete absence of air exchange for at least 10 seconds, while hypopnea was defined as a reduction in nasal pressure signals by ≥30% of baseline for at least 10 seconds duration accompanied by ≥ 4% desaturation from pre-event baseline (17). Respiratory event-related arousal (RERA) was defined as a sequence of breaths characterized by increasing respiratory effort leading to an arousal but not meeting the criteria for apnea or hypopnea (17) and often associated with flow limitation based on the nasal cannula flow wave contour form (19,20). Tabulation of the PSG included apnea hypopnea index (AHI) (the number of apneas and hypopneas per hour of sleep), and the respiratory disturbance index (RDI) (the total number of apneas, hypopneas, and RERAs). Upper Airway Resistance Syndrome (UARS) (19) was diagnosed if participants had symptoms of excessive daytime sleepiness and/or chronic daytime fatigue not meeting the criteria for OSAS but had an apnea index of 0, a hypopnea index of 5 or less, and an RDI of less than 5 events per hour.

Ambulatory Four-Channel Recorder

Sleep onset and awakening time were determined by a sleep log filled by the patient. Apnea and hypopnea scoring utilized the AASM criteria (17). RDI could not be assessed due to the absence of electroencephalogram leads to detect arousals.
Statistical Analysis

Statistical analyses were performed with SPSS17.0 for Windows (SPSS Statistics, IBM, Armonk, NY, USA) with statistical significance defined at $p < 0.05$. Descriptive analyses and frequency distributions described the distributions of the demographic characteristics, disease characteristics and sleep parameters. Data were presented as mean and standard deviations (SD), or percentages accordingly. Comparisons of variables of nasal rhinomanometry were performed with the Mann-Whitney U test. Pearson product-moment correlation coefficient was applied to access the relation between age and flow limitation and age and AHI.

Results

Clinical Symptoms

Of the sleep clinic ED patients ($n=34$), 19 (55.8%) were women. The mean age at presentation was 26.55 years (range 7-48) (Table 1). All (Table 2) presented with unrefreshing, fragmented sleep and daytime fatigue, and 33 (97.1%) reported snoring and mouth breathing while sleeping. Many patients ($n=19$, 55.9%) reported orthostatic hypotension to be a major problem.

Of the ED internal-medicine clinic patients ($n=9$), 5 (55.5%) were women. The mean age at presentation was 37.6 yrs (range 27-52) (Table 1). All (Table 2) presented with unrefreshing, fragmented sleep and fatigue, and daytime sleepiness was present in 5/9. Snoring (8; 89%) and initiation insomnia (8; 89%) were also frequent complaints.

Physical Exam

All patients, both at the sleep clinic and at the internal-medicine clinic, demonstrated characteristics suggesting the presence of sleep-disordered breathing (SDB):

All sleep clinic patients had clinically significant nasal septum deviation, with internal valve collapse, but no evidence of enlarged inferior nasal turbinates. They also demonstrated a high, arched
palatal vault, with some (n=6, 17.6%) having cross bite. Micrognathia was present in 24 patients (70.6%) with evidence of tongue scalloping, overlapping teeth, or a history of having wisdom teeth or canines pulled in early teenage years due to teeth crowding. The mean body mass index (BMI) was 22.95 kg/m² (range 14-31.1).

All ED internal-medicine clinic patients demonstrated a high, arched palatal vault, and three patients had a cross bite (33%). Seven patients had crowded teeth and a history of wisdom tooth extraction early in life (77%) (figure1). A deviated nasal septum was present in 8/9. The mean BMI was 24.67±2.7 kg/m².

Rhinomanometry

The mean nasal resistance in seven of our subjects was significantly higher (0.68± 0.197 Pa/cm³/s; p=0.01) than an age- and gender-matched control group (0.38± 0.20 Pascal (Pa)/cm³/s) (see Figure 2 and Table 3).

Polysomnography

All sleep clinic patients were evaluated with in-laboratory overnight PSG. Table 1 presents the respiration findings during sleep. All patients were found to meet criteria for OSA (AHI>5). The mean AHI was 14.21 (range 5.1-38) and the mean RDI was 21.53 (range 5.1- 32). The average oxygen nadir was 90.1% (range 87-93%) (see Table 1). Patients also had flow limitation for more than 65% of the night (see Figures 3 and 4).

ED internal-medicine clinic patients (n=5) were evaluated with objective sleep monitoring as per their local recommendations, as presented in Table 1. The mean in-lab AHI was 19.38 (+/- 9.2) and the mean in lab RDI was 25.81(+/-10.24). Ambulatory monitoring was performed on one patient, who had an AHI of 15.14. Nadir oxygen was 87.2% (+/- 2.77). Flow limitation was present for 62.75% of the night.

With increasing age, flow limitation decreased and AHI increased (Figure 5). However, there were no differences in clinical complaints and relative severity of SDB.
Nasal CPAP treatment

All sleep clinic patients were treated with nasal CPAP. CPAP pressure ranged from 10-14 cm H2O (mean 11.44 ± 1 cm H2O). There was no relationship between the severity of the SDB and the nasal CPAP pressure needed. At 3-month follow up, all patients reported subjective clinical improvement in morning headache and difficulty concentrating with elimination of “poor sleep” and “daytime sleepiness” and very limited mention of “fatigue” (5/34). Information downloaded from the CPAP equipment showed that patients were compliant (defined as use >6 hours/night, 90% of the time). ED internal medicine clinic patients on CPAP (n=5) had a mean pressure of 12.2 cwp (± 0.84).

Discussion

Our report describes the frequent presence of SDB in patients with ED syndrome. SDB was frequently diagnosed in a sleep clinic population, but similar findings were also observed in a sample of ED patients presenting for routine medical care in an internal-medicine ED clinic. Clinical history and physical evaluation were the same in both groups, and ED internal-medicine clinic patients who underwent PSG showed results similar to findings noted in the age-matched sleep clinic ED subjects.

If not systematically searched for, Ehlers-Danlos syndrome is often unrecognized (21), particularly when type II and III are present, as they represent the syndrome in its most common and often, mildest form (12). Similarly, the association between ED and abnormal breathing during sleep also may be overlooked. None of the ED internal-medicine clinic patients had been referred for evaluation of SDB despite symptoms and clinical presentation strongly supporting the diagnosis.

Our study suggests that the presence of SDB in ED patients is not related to a referral bias. Fatigue is a common symptom of ED patients, often assumed to be associated with cartilaginous disease and considered by some as an overlap with chronic fatigue syndrome (22, 23, 24). Fatigue is frequently associated with poor sleep, and patients with ED who report more severe fatigue also report greater psychological distress and sleep disruption (22). ED patients present not only with typical apnea and hypopnea but also with flow limitation. As has been demonstrated previously (25,26), younger subjects
have a greater amount of flow limitation and fewer apneas or hypopneas while older subjects have less flow limitation with a greater number of apneas and hypopneas. It appears that SDB exists as a continuum of progressively increasing severity. Interestingly, subjective complaints are similar regardless of age and AHI severity, which has also been seen in other groups (25, 26). Flow limitation leads to EEG changes similar to those seen with apnea and hypopnea, likely causing the perceived daytime impairments (25,26). In our cohort, nasal CPAP treatment led to improvement in the complaints of poor sleep and daytime sleepiness even if “fatigue” related to other causes is not eliminated.

Finally, our observation is also of theoretical interest related to the development of SDB. Ehlers-Danlos syndrome (ED) is a hereditary collagen-vascular disease seen in at least 0.2% of the population in the United States. There are many types described (11,12). It may be inherited in an autosomal dominant, autosomal recessive or X-linked fashion (11,12). It involves variable genetic mutations located on proteins (COL1A1, 1A2, 3A1, 5A1, 5A2, TNXB) or enzymes (ADAMTS2, PLOD1, BUGALT7), with the most common types I and II involving COL 1A1, COL 5A1, and COL 5A2.

Our patients had abnormalities of nasal and maxillary cartilage and evidence of a narrow jaw. Presence of specific facial features in non-obese patients has been associated with SDB (9) and familial occurrence of OSA in subjects presenting with similar facial traits has also been well demonstrated (1-4). Maxillary growth during childhood is related to endochondral ossification in which hyaline cartilage becomes replaced by fibrocartilage and later, bone (10). Certain craniofacial growth impairments have been related to the risk of developing SDB (27,28,29). Recently we reviewed evidence (primarily from the orthodontic literature) synthesizing the continuous interaction between function and oral-facial growth in children (29). In sum, abnormal development of the maxillary complex occurs with the continuous interaction between nasal breathing impairment during sleep, mouth breathing, and changes occurring in the naso-maxillary complex and mandible growth and positioning (30-33). In a monkey model, an increase in nasal resistance at birth leads to abnormal oral-facial muscle EMG discharges, mouth breathing, and abnormal maxilla-mandibular growth (34). In children, abnormal nasal resistance associated with enlargement of adenotonsils leads to mouth breathing, which is associated with the
development of a high, arched palate, long face, airway narrowing, and SDB (35-37). Similar oral-facial anatomical changes are regularly observed in ED patients. ED patients have abnormal growth of the naso-maxillary complex that leads to both increased nasal resistance and altered maxillary development. ED syndrome can be used as a genetic model for the development of SDB due to the heritable predisposition to disordered cartilaginous growth, and study of ED patients will allow investigation of the interaction between abnormal facial growth and regional muscle tone and activity.

**Conclusion:**

ED is an important and often unrecognized cause of SDB and further investigation can lead to a better understanding of development of the OSA in non-obese individuals. Future research should focus on better characterizing SDB in this population and also exploring if orthodontics and myofunctional therapy (29-33) can limit development of OSA in these patients.

**Acknowledgement**

We thank Oscar Carrillo for retrieving recordings and for analyses of expiratory muscle activity during flow limited breathing. We also thank Drs. Gerard Meskill and Brandon Peters for their help in editing the manuscript.

Role of authors: Christian Guilleminault, Michel Primeau, Kin Yuen Hsiao-yean Chiu reviewed the retrospective data from the sleep clinic, performed the data-analysis including the statistical analyses, participated in the writing of the manuscript and reviewed the final manuscript. Damien Leger and Arnaut Metlaine and Christian Guilleminault investigated the patients from the Ehlers Danlos medical clinic, collected the data and reviewed the manuscript.
References


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40 Seo WH Guilleminault C Periodic leg movements, nasal CPAP and expiratory muscles *Chest* 2012 ;142:111-118.

Table 1 Demographic and PSG sleep-respiratory findings in Sleep Clinic and ED Clinic Patients

Table 2: Comparison of reported clinical symptoms

Table 3 Results of nasal rhinometry in seven ED subjects.

Figure Legends

Figure 1: Abnormal oral-facial anatomy in internal medicine clinic ED: Presence of an “open-bite” with maxillary-mandibular growth problem. During childhood, intermaxillary, nasal and temporo-maxillary cartilages are critical elements in facial growth (29-31). The collagen-vascular mutations seen in ED will lead to abnormal facial growth. These changes lead to narrow nasal passages, forcing mouth breathing, particularly during sleep (30), which leads to the development of a narrow hard palate and other orthodontic impairments including, overcrowding of the upper frontal teeth with overlap (see above) and secondary “tongue thrust” which leads to an “open-bite” as seen in this patient.

Figure 2: Comparison of the measurement of the nasal resistance of a (A) normal subject and (B) an age-matched ED sleep clinic patient. Legend: Graph of the nasal resistance measurement in a normal subject (A-left graph), obtained from pool of subjects without ED or sleep complaints used to calibrate equipment, and of an age (±2 years) and of a gender matched ED patient (B-right graph): The figure presents the graphical representations of flow versus pressure (cm³/second and Pascal units) for right and left nostrils during inspiration and expiration for each individual. The left nostril inspiration is in the lower right quadrant and left nostril expiration is in the upper left quadrant; right nostril inspiration is in the upper right quadrant and right nostril expiration is in the lower left quadrant (ie both inspiratory measurements are on the right and expiratory measurement on the left) for each of the 2 studied subjects 2000 data points over 5 breaths are computed to present this visual graph (15). Normal flow is characterized by a more vertical presentation, as seen in the control subject, versus the more flattened presentation of the ED subject.

Figure 3: Example of flow limitation and mouth breathing in a 22 years old patient during 120 seconds during NREM sleep

Legend: From top: 3 EEGs, chin muscle, right and left electro-oculogram,pulse (ECG), right and left leg muscles, finger plethysmography pulse oximetry, neck microphone (snore) nasal cannula (#13 from top) oral thermistor (#14) thoracic and abdominal inductive plethysmography, intercostal-diaphragmatic EMG note the abnormal presence of continuous mouth breathing indicated by the tracing monitored with the oral thermistor (channel #.14 from top)
Note the presence of continuous “flow limitation” and mouth breathing. The inspiratory flow curve measured by the nasal cannula/transducer system varies with the level of upper airway resistance, and flow shapes consistent with partial airway collapse occur and have been defined as “flow limitation” (38). Flow limitation has been defined as any series of two or more breaths (lasting > 10 seconds) that had a flattened or nonsinusoidal appearance on the inspiratory nasal cannula flow signal and ends abruptly with a return to breaths with sinusoidal shape (17,20). Such pattern has been associated with clinical symptoms similar to those seen with sleep apnea and hypopnea and symptoms and is eliminated with nasal CPAP (25,26). Flow limitation has been seen with and without snoring and has been monitored with indication of disturbance of the sleep EEG. This segment of the recording shows the pattern of flow limitation on channel #13 (from top) with the inspiratory nasal flow curve presenting a pattern of two peaks. Also, channel #14 (oral thermistor) demonstrates continuous mouth breathing. Normally human are nose breathers because mouth breathing requires more respiratory effort, and leads to abnormal tongue position and a progressive decrease in upper airway muscle tone (30-33).

Figure 4

Example of flow limitation and “active” expiration in a 23 years old patient during 90 seconds of NREM sleep

Legend: From top : 4 EEGs, chin muscle, right and left electro-oculogram, pulse (ECG), left anterior tibialis muscle, right anterior tibialis EMG, pulse oximetry, finger plethysmography, neck microphone (snore), nasal cannula (#14 from top), oral thermistor, thoracic and abdominal inductive plethysmography bands, intercostal-diaphragmatic EMB and abdominal expiratory muscle EMG

As in figure 3, this figure demonstrates flow limitation; channel #14 again shows two peaks, but with a down-slope toward the lower 2nd peak. But the segment also monitor the abdominal expiratory muscles (lateral oblique muscles) (bottom channel). The right side of the abdominal muscle recording, obtained from surface recording of the lateral oblique muscles (bottom channel), indicates that abdominal expiratory muscles become active mid-tracing. This represents progressive development of inspiratory as well as expiratory flow limitation and the need to recruit expiratory muscles to exhale because of the presence of an obstructive expiratory component. Such involvement of expiratory muscles has been demonstrated previously during sleep obstructive hypopnea and apnea and flow limitation (39,40). Note that oxygen saturation (channel #11) changes by only 1% during the total recording of the segment and drops to 93% with activation of the expiratory muscles.

Figure 5. Distribution and correlation between (A) age and flow limitation and (B) age and Apnea-hypopnea Index in sleep clinic ED subjects (n=34).

Legend

The downward evolution of flow limitation with increasing age is showed in Figure 6A: a significant negative correlation was found ($R^2= 0.171, p=0.015$); while the progressive increase in AHI with age is shown in Figure 3-B. This progressive increase in AHI with age is also significantly and positively associated with AHI ($R^2= 0.214, p=0.006$).
A similar finding was noted by Palombini et al in the investigation of flow-limitation in the Sao-Paulo epidemiological study performed on a representative sample of the general population of Sao-Paulo (41)
Table 1. Demographic and PSG sleep-respiratory findings in Sleep Clinic and ED Clinic Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Sleep Clinic (n=34)</th>
<th>Mean (SD)</th>
<th>ED Clinic (n=9)</th>
<th>Mean (SD)</th>
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<tr>
<td>Age, years</td>
<td>26.55 (9.63)</td>
<td></td>
<td>37.6 (12.25)*</td>
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</tr>
<tr>
<td>Male (n, %)</td>
<td>15 (44%)</td>
<td></td>
<td>4 (44%)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>22.95 (1.97)</td>
<td></td>
<td>24.7 (2.67)</td>
<td></td>
</tr>
</tbody>
</table>

Sleep Parameters
- AHI (in lab) 14.21 (7.32) 19.38 (9.2) n=4,*
- RDI (in lab) 21.53 (7.17) 25.8 (10.2) n=4,
- AHI (ambulatory) -------- 15.41 n=1
- SaO2 (%) 90.06 (1.8) 87.2 (2.77) n=5,
- Flow limitation (% of TST) 80.03 (13.53) 62.8 (17.3) n=4**

Abbreviation: SD= standard deviation, AHI= apnea-hypopnea index, RDI= respiratory disturbance index, SaO2= oxygen saturation. % of TST: percentage of total-sleep-time * significantly different (p=0.01 MannWhitney U) ** significantly different (Chi-square statistics, p=0.01)
Table 2: comparison of reported clinical symptoms

<table>
<thead>
<tr>
<th></th>
<th>Sleep Clinic ED n=34</th>
<th>ED internal medicine clinic N=9</th>
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</thead>
<tbody>
<tr>
<td>Poor sleep</td>
<td>34 (100%)</td>
<td>9 (100%)</td>
</tr>
<tr>
<td>Fragmented sleep with nocturnal awakenings</td>
<td>34 (100%)</td>
<td>9 (100%)</td>
</tr>
<tr>
<td>Daytime Fatigue</td>
<td>34 (100%)</td>
<td>9 (100%)</td>
</tr>
<tr>
<td>Snoring</td>
<td>33 (88%)</td>
<td>8 (89%)</td>
</tr>
<tr>
<td>Difficulty Concentrating</td>
<td>21 (62%)</td>
<td>5 (55.5%)</td>
</tr>
<tr>
<td>Sleep onset insomnia</td>
<td>10 (24.4%)</td>
<td>8 (89%)</td>
</tr>
<tr>
<td>Morning headache</td>
<td>10 (24.4%)</td>
<td>5 (14.7%)</td>
</tr>
<tr>
<td>Daytime sleepiness</td>
<td>8 (23.5%)</td>
<td>5 (14.7%)</td>
</tr>
<tr>
<td>Somnambulism</td>
<td>6 (17.6)</td>
<td>1 (11.1%)</td>
</tr>
<tr>
<td>Orthostatic Hypotension</td>
<td>19 (55.9%)</td>
<td>2 (22.2%)</td>
</tr>
</tbody>
</table>

Legend: The only major differences between the 2 groups are the report of sleep onset insomnia that was more prevalent in the ED clinic group (Chi-Square statistics p=0.01) and the presence at time of evaluation of orthostatic evaluation more prevalent in sleep clinic ED (Chi-square statistics: p=0.001). The ED clinic patients were also significantly older than the ED sleep clinic patients.
Table 3. Results of nasal rhinometry in seven ED subjects.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean(SD)</th>
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<tbody>
<tr>
<td>LogVRIn</td>
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<td>LogVREx</td>
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<td>LogReffIn</td>
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<td>LogReffEx</td>
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<tr>
<td>LogReffT</td>
<td>1.11(0.28)</td>
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</tbody>
</table>

Abbreviation: SD= standard deviation. AHI= Apnea-hypopnea index. RDI= respiratory disturbance index. BMI= body mass index.

**Vertex Resistance** (VR) is the resistance (differential pressure divided by flow) of the nasal airstream at the point of maximum flow during inspiration (VR-in) or expiration (VR-ex) in a breath. (14) **Effective Resistance** (Reff) described the computerized measurement and calculation of 2000 effective flow and differential pressure measurements (effective differential pressure divided by effective flow) recorded for each averaged breath in inspiration (Reff-in), expiration (Reff-ex), and for the entire breathe (Reff-T) (14). *Normative data: <0.75: Very low resistance, high conductance; 0.75-1.00: Low resistance/high conductance; 1.00-1.25: Moderate resistance/moderate conductance; 1.25-1.50: High resistance/low conductance; >1.50: Very high resistance/very low conductance.*) Overall the group showed “moderate resistance and conductance” ie an abnormal nasal resistance (14)
Figure 2. Comparison of nasal resistance measurements in a normal subject (A) and an ED patient (B).
Figure 5 Correlation between (A) age and flow limitation and (D) age and Apnea-hypopnea Index in ED subjects (n=54).

A

B

282x365mm (72 x 72 DPI)