CHEST

Original Research

SLEEP DISORDERS

Sleep-Disordered Breathing in Ehlers-Danlos Syndrome

A Genetic Model of OSA

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Objectives: **The objective of this study was to investigate the presence of sleep-disordered breathing (SDB) in patients with Ehlers-Danlos syndrome. Ehlers-Danlos syndrome is a genetic disorder characterized by cartilaginous defects, including nasal-maxillary cartilages.**

Methods: **A retrospective series of 34 patients with Ehlers-Danlos syndrome and complaints of fatigue and poor sleep were evaluated by clinical history, physical examination, polysomnography (PSG), and, in some cases, anterior rhinomanometry. Additionally, a prospective clinical investigation of nine patients with Ehlers-Danlos syndrome was performed in a specialized Ehlers-Danlos syndrome clinic.**

Results: **All patients with Ehlers-Danlos syndrome 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 rhinomanometry, increased nasal resistance was increased relative to normative values. Nasal CPAP improved symptoms. Patients with Ehlers-Danlos syndrome presenting to the medical clinic had symptoms and clinical signs of SDB, but they were never referred for evaluation of SDB.**

Conclusions: **In patients with Ehlers-Danlos syndrome, abnormal breathing during sleep is commonly unrecognized and is responsible for daytime fatigue and poor sleep. These patients are at particular risk for SDB because of genetically related cartilage defects that lead to the development of facial structures known to cause SDB. Ehlers-Danlos syndrome may be a genetic model for OSA because of abnormalities in oral-facial growth. Early recognition of SDB may allow treatment with orthodontics and myofacial reeducation.** ***CHEST 2013; 144(5):1503–1511***

Abbreviations: AASM = American Association of Sleep Medicine; AHI = apnea-hypopnea index; IRB = institutional review board; PSG = polysomnography; RDI = respiratory disturbance index; SDB = sleep-disordered breathing

OSA has been shown to aggregate in families, and epidemiologic studies on familial associations have indicated that genetic factors might comprise a risk factor for OSA and sleep-disordered breathing (SDB).[1-4] However, simple genetic models do not explain the occurrence of OSA.[5] Risk of OSA varies depending on ethnicity.[6-8] In nonobese individuals, genetic factors that control craniofacial development have been proposed to be involved in the development of the anatomic features that lead to familial aggregation of OSA.[9]

The craniofacial complex involves the maxilla and 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 (eg, cartilage) will have a secondary epigenetic effect on another tissue.[10]

We report on the presence OSA in Ehlers-Danlos syndrome, a well-known genetic disorder characterized by cartilaginous defects,[11,12] including the nasal-maxillary cartilages. Over time, we have observed more patients with Ehlers-Danlos syndrome presenting to our sleep clinic than would be expected on the basis

of population prevalence alone. The primary aim of this study was to describe the appearance of SDB in patients with Ehlers-Danlos syndrome. We used both a 4-year retrospective investigation of our sleep clinic population and a separate cohort of patients with EDS followed in a clinic devoted only to Ehlers-Danlos syndrome. The retrospective investigation was approved by the Stanford institutional review board (IRB), and the prospective investigation was approved by Hôtel-Dieu Hospital (Paris, France) IRB.

Materials and Methods

Sleep Clinic Patients

Observed Population: We identified 34 consecutive patients with Ehlers-Danlos syndrome who were referred to the sleep clinic for daytime fatigue and poor sleep (n = 34) and daytime sleepiness (n = 8). Most had Ehlers-Danlos syndrome type 2 (skin hyperextensibility, joint hypermobility, skin fragility, and easy bruising), although one patient had type 3 (joint hypermobility commonly with subluxation, dislocation, and degenerative joint disease) and two had type 4 (minimal skin hyperextensibility, digit hypermobility, marked bruising, and association with arterial rupture).[11]

Clinical Evaluation: A detailed sleep-specific clinical interview and physical were completed for each patient. Patients completed the Stanford Sleep Disorder Questionnaire,[13] which uses a Likert scale of 1 to 5, and the Epworth Sleepiness Scale.[14] Physicians performed structured interviews that included symptom description, medical history, family history, and medication use. Physicians completed a standardized, sleep-focused physical examination, including anthropomorphic measurements (eg, BMI, neck circumference) and a nasal and upper airway examination.

Rhinomanometry: A subgroup of seven patients underwent high-resolution rhinomanometry[15,16] to quantify nasal resistance. Tests were performed with a four-phase rhinomanometer (RhinoLab GmbH) while following the technical and practical methodology and normative data published in the literature.[15] Age-matched (± 2 years) normal control subject data were used for calibration of the rhinomanometer. Subjects were given a 5-min rest period in a quiet procedure room at constant temperature and then positioned at a 30° incline for measurements. All measurements were completed within a 15-min midmorning interval to ensure nasal state continuity. Details on the calculations have been previously published.[15]

Polysomnography: All patients underwent overnight, systematic, in-laboratory PSG. The recording comprised four-channel EEG, two-channel electrooculography, chin and leg electromyography, one-lead ECG, body position, and video monitoring. Respiration was monitored with a nasal cannula pressure transducer system (U Protec Inc), oral thermistor, thoracic and abdominal respiratory inductance plethysmography, and pulse oximetry. All variables were calibrated and monitored with a computerized acquisition system (Sandman; Embla Systems).

Internal Medicine Clinic Patients With Ehlers-Danlos Syndrome

To recruit comparable patients with Ehlers-Danlos syndrome not presenting with a primary sleep complaint, we approached those seen in a specialized Ehlers-Danlos syndrome clinic at the time of their general medical appointment. Nine patients consented to participate in the study, and none had ever been examined for a sleep-related problem. Six had Ehlers-Danlos syndrome type 2, one type 3, and two type 4. Two physicians performed the evaluation (one from a local hospital and one from the research team involved in the retrospective study) who used the same standardized clinical interview and physical evaluation as implemented in the sleep clinic. Patients also completed a visual analog scale about the 4 weeks before the visit with respect to fatigue, nocturnal sleep, and daytime sleepiness. A photo of each patient's palate and nasal cavity was taken.

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 for the sleep clinic patients, one patient had a four-channel recording (nasal cannula, thoracoabdominal bands, ECG, finger oximetry), and one had auto-CPAP testing. The remaining three patients were scheduled to have clinical testing on the basis of the 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] classification for nasal resistance in seven patients.

Polysomnography: Sleep staging was completed in accordance with the American Academy of Sleep Medicine (AASM) 2007 recommendations.[17] Arousals were scored on the basis of American Sleep Disorders Association 3-s arousal criteria.[18] Respiratory event scoring was based on AASM 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 s, whereas hypopnea was defined as a reduction in nasal pressure signals by ≥ 30% of baseline for at least 10 s accompanied by a ≥ 4% desaturation from preevent baseline.[17] Respiratory event-related arousal was defined as a sequence of breaths characterized by increasing respiratory effort that led to an arousal but did not meet the criteria for apnea or hypopnea[17] and often was associated with flow limitation based on the nasal cannula flow wave contour form.[19,20] Tabulation of the PSG included the 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 respiratory event-related arousals). Upper airway resistance syndrome[19] was diagnosed if patients had symptoms of excessive daytime sleepiness, chronic daytime fatigue, or both that did not meet the criteria for OSA but had an apnea index of 0, a hypopnea index of ≤ 5, and an RDI < 5 events/h.

Ambulatory Four-Channel Recorder: Sleep onset and awakening time were determined by a sleep log completed by the patient. Apnea and hypopnea scoring used the AASM criteria.[17]

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RDI could not be assessed because of the absence of EEG leads to detect arousals.

Statistical Analysis

Statistical analyses were performed with SPSS version 17.0 for Windows (IBM), with statistical significance defined at $P < .05$. Descriptive analyses and frequency distributions were used to describe demographic characteristics, disease characteristics, and sleep parameters. Data were presented as mean ± SD or percentages. Comparisons of variables of nasal rhinomanometry were performed with the Mann-Whitney *U* test. Pearson product-moment correlation coefficient was applied to assess the relationship between age and flow limitation and age and AHI.

Results

Clinical Symptoms

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

Of the nine patients with Ehlers-Danlos syndrome at the internal medicine clinic, five (55.5%) were women. The mean age at presentation was 37.6 years (range, 27-52 years) (Table 1). All presented with unrefreshing, fragmented sleep and fatigue, and five (55.5%) had daytime sleepiness (Table 2). Snoring and initiation insomnia were also frequent complaints (eight patients [89%] each).

Physical Examination

All patients, both at the sleep clinic and at the internal medicine clinic, demonstrated characteristics suggesting the presence of SDB. All patients at the sleep clinic 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 a crossbite. Micrognathia was present in 24 patients (70.6%) with evidence of tongue scalloping or overlapping teeth or a history of having wisdom teeth or canines pulled in their early teenage years because

Table 1—*Demographic and PSG Sleep-Respiratory Findings in Sleep Clinic and Internal Medicine Clinic Patients With Ehlers-Danlos Syndrome*

Characteristic	Sleep Clinic (n = 34)	Internal Medicine Clinic (n = 9)
Age, y	26.55 ± 9.63	37.6 ± 12.25[a]
Male sex	15 (44)	4 (44)
BMI, kg/m^2	22.95 ± 1.97	24.7 ± 2.67
Sleep parameters		
AHI (in laboratory)	14.21 ± 7.32	19.38 ± 9.2 (n = 4)[a]
RDI (in laboratory)	21.53 ± 7.17	25.8 ± 10.2 (n = 4)
AHI (ambulatory)	…	15.41 (n = 1)
Sao_2, %	90.06 ± 1.8	87.2 ± 2.77 (n = 5)
Flow limitation, % TST	80.03 ± 13.53	62.8 ± 17.3 (n = 4)[b]

Data are presented as mean ± SD or No. (%). AHI = apnea-hypopnea index; PSG = polysomnography; RDI = respiratory disturbance index, Sao_2 = arterial oxygen saturation; TST = total sleep time.
[a]Significantly different at $P = .01$ (Mann-Whitney *U* test).
[b]Significantly different at $P = .01$ (χ^2 statistics).

Table 2—*Comparison of Reported Clinical Symptoms in Patients With Ehlers-Danlos Syndrome*

Symptom	Sleep Clinic (n = 34)	Internal Medicine Clinic (n = 9)
Poor sleep	34 (100)	9 (100)
Fragmented sleep with nocturnal awakenings	34 (100)	9 (100)
Daytime fatigue	34 (100)	9 (100)
Snoring	33 (88)	8 (89)
Difficulty concentrating	21 (62)	5 (55.55)
Sleep onset insomnia	10 (24.4)	8 (89)
Morning headache	10 (24.4)	5 (14.7)
Daytime sleepiness	8 (23.5)	5 (14.7)
Somnambulism	6 (17.6)	1 (11.1)
Orthostatic hypotension	19 (55.9)	2 (22.2)

Data are presented as No. (%). The only major differences between the two groups are sleep onset insomnia, which was more prevalent in the internal medicine clinic group (χ^2 statistics $P = .01$), and the presence of orthostatic evaluation, which was more prevalent in the sleep clinic group (χ^2 statistics $P = .001$). The internal medicine clinic patients with Ehlers-Danlos syndrome were also significantly older than the sleep clinic patients with Ehlers-Danlos syndrome.

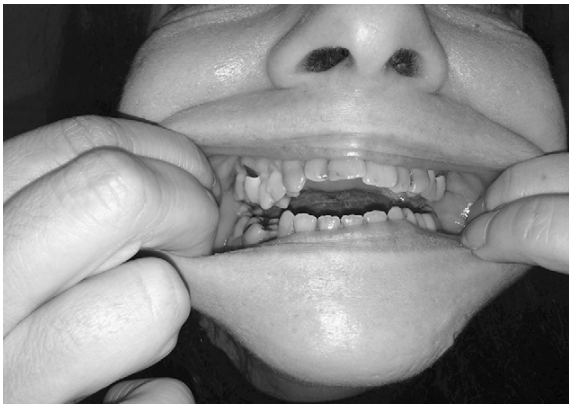

Figure 1. Abnormal oral-facial anatomy in a patient with Ehlers-Danlos syndrome at an internal medicine clinic showing the presence of an open bite with a maxillary-mandibular growth problem. During childhood, intermaxillary, nasal, and temporomaxillary cartilages are critical elements in facial growth.[21-23] The collagen-vascular mutations seen in Ehlers-Danlos syndrome lead to abnormal facial growth. These changes lead to narrow nasal passages, forcing mouth breathing, particularly during sleep,[22] which leads to the development of a narrow hard palate and other orthodontic impairments, including overcrowding of the upper frontal teeth with overlap and secondary tongue thrust, which leads to an open bite as seen here. (The patient provided written consent for the use of this photograph.)

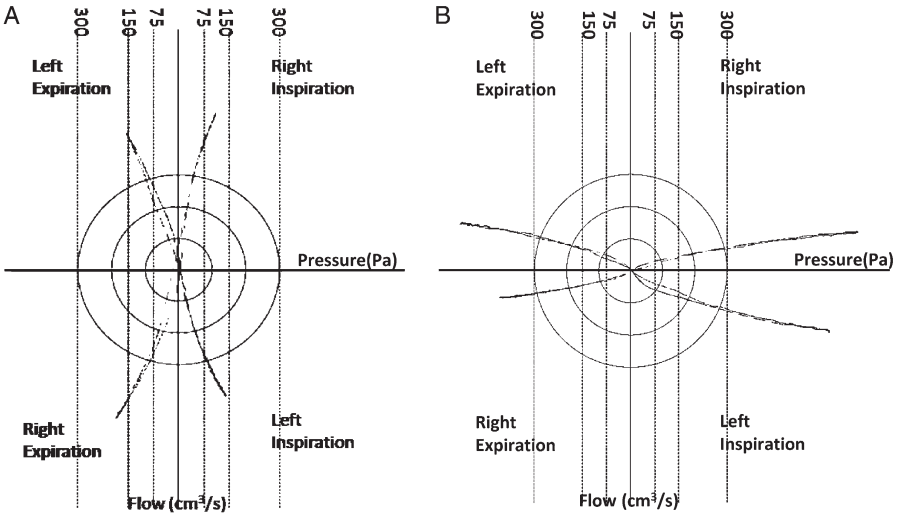

FIGURE 2. Comparison of the measurement of the nasal resistance between a normal subject and an age-matched sleep clinic patient with Ehlers-Danlos syndrome. A, Graph of the nasal resistance measurement in a normal subject from a pool of subjects without Ehlers-Danlos syndrome or sleep complaints used to calibrate equipment. B, An age- (± 2 years) and sex-matched patient with Ehlers-Danlos syndrome. The graphic representations of flow (cm^3/s) vs pressure (Pa) for the right- and left-side nostrils during inspiration and expiration for each individual. Inspiratory measurements are shown in the right quadrants and expiratory measurements in the left quadrants. For each subject, 2,000 data points over five breaths were computed to present this graph.[15] Normal flow is characterized by a more vertical presentation as seen in the control subject vs the more flattened presentation of the patient with Ehlers-Danlos syndrome.

of teeth crowding. The mean BMI was 22.95 kg/m^2 (range, 14-31.1 kg/m^2).

All patients with Ehlers-Danlos syndrome at the internal medicine clinic demonstrated a high, arched palatal vault, and three (33%) had a crossbite. Seven patients (77%) had crowded teeth and a history of wisdom tooth extraction early in life (Fig 1). A deviated nasal septum was present in eight of the nine patients in this group. The mean BMI was 24.67 ± 2.7.1 kg/m^2.

Rhinomanometry

The mean nasal resistance in seven patients with Ehlers-Danlos syndrome was significantly higher (0.68 ± 0.197 $Pa/cm^3/s$, $P = .01$) than that in the age- and sex-matched control group (0.38 ± 0.20 $Pa/cm^3/s$) (Fig 2, Table 3).

Polysomnography

All patients at the sleep clinic were evaluated with in-laboratory overnight PSG. Table 1 presents the respiration findings during sleep. All 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%) (Table 1). Patients also had flow limitation for > 65% of the night (Figs 3, 4).

Five patients with Ehlers-Danlos syndrome at the internal medicine clinic were evaluated with objective sleep monitoring as per local recommendations (Table 1). The mean in-laboratory AHI was 19.38 ± 9.2, and the mean in-laboratory RDI was 25.81 ± 10.24. Ambulatory monitoring was performed in one patient

Table 3—*Results of Nasal Rhinomanometry in Seven Patients With Ehlers-Danlos Syndrome*

Variable[a]	Mean ± SD
LogVR-in	1.09 ± 0.25
LogVR-ex	1.10 ± 0.26
LogReff-in	1.11 ± 0.26
LogReff-ex	1.12 ± 0.26
LogReff-T	1.11 ± 0.28

ex = expiration; in = inspiration; Reff = effective resistance; T = entire breath; VR = vertex resistance.

[a]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.[15] Reff described the computerized measurement and calculation of 2,000 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 the entire breath (Reff-T)[15] (normative data: very low resistance/high conductance, < 0.75; low resistance/high conductance, 0.75-1.00; moderate resistance/moderate conductance, 1.00-1.25; high resistance/low conductance, 1.25-1.50; very high resistance/very low conductance, > 1.50). Overall, the group showed moderate resistance and conductance, ie, an abnormal nasal resistance.[15]

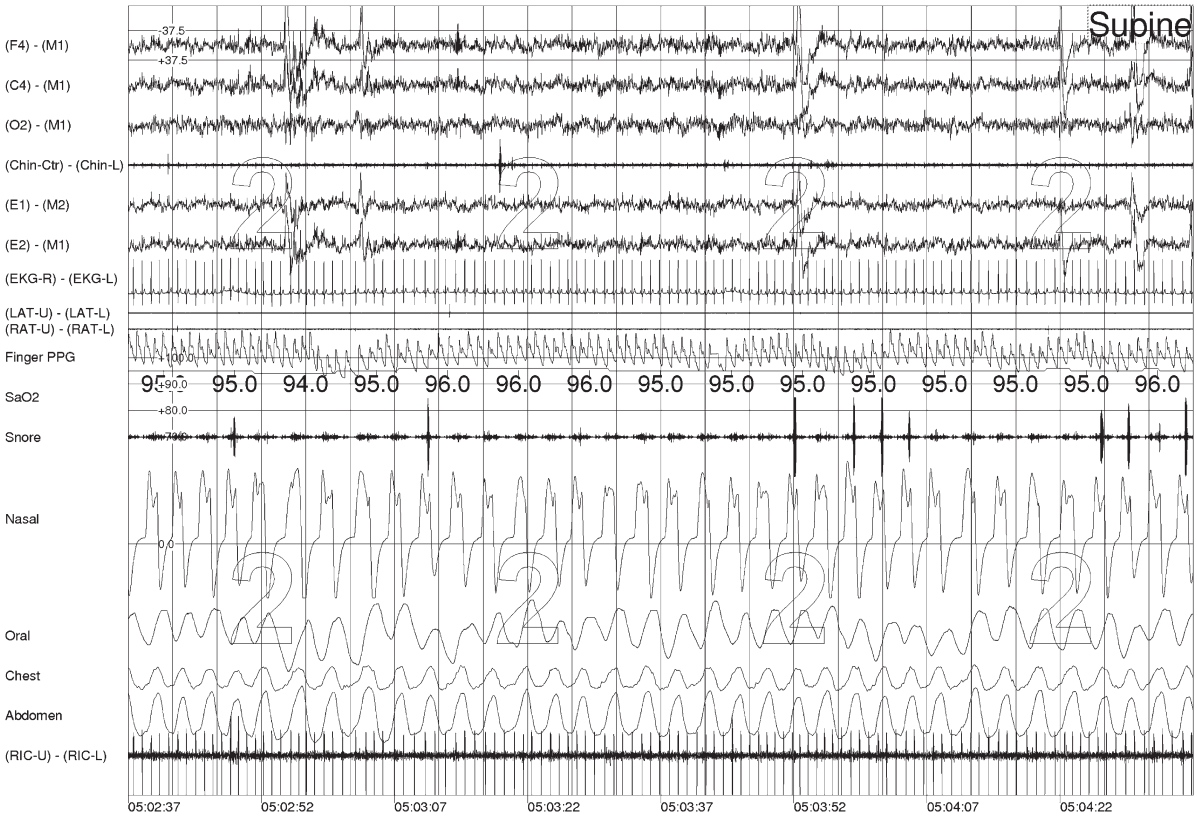

FIGURE 3. Example of flow limitation and mouth breathing in a 22-year-old patient during 120 s of non-rapid eye movement sleep. Starting from the top, three EEGs, chin muscle, right- and left-side electrooculogram, pulse (ECG), right and left leg muscle electromyogram (EMG), finger PPG, SaO_2, neck microphone (snore), nasal cannula, oral thermistor, thoracic and abdominal inductive plethysmography, and intercostal-diaphragmatic electromyography note the abnormal presence of continuous mouth breathing indicated by the oral thermistor tracing. Note the presence of continuous flow limitation and mouth breathing. The inspiratory flow curve measured by the nasal cannula and 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.[24] Flow limitation has been defined as any series of two or more breaths (lasting > 10 s) that have a flattened or nonsinusoidal appearance on the inspiratory nasal cannula flow signal and end abruptly with a return to breaths with sinusoidal shape.[17,20] Such a pattern has been associated with clinical symptoms similar to those seen with sleep apnea and hypopnea 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 nasal cannula (channel 13 from top), with the inspiratory nasal flow curve presenting a pattern of two peaks. Additionally, the oral thermistor (channel 14 from top) demonstrates continuous mouth breathing. Normally, humans 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.[22,23,27,28] LAT-L = lower-left anterior tibialis; LAT-U = upper-left anterior tibialis; PPG = plethysmography pulse oximetry; RAT-L = lower-right anterior tibialis; RAT-U = upper-right anterior tibialis; RIC-L = lower-right intercostal; RIC-U = upper-right intercostal; SaO_2 = arterial oxygen saturation.

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 (Fig 5). However, there were no differences in clinical complaints and relative severity of SDB.

Nasal CPAP Treatment

All patients at the sleep clinic were treated with nasal CPAP. CPAP pressure ranged from 10 to 14 cm H_2O (mean, 11.44 ± 1 cm H_2O). There was no relationship between the severity of the SDB and the amount of nasal CPAP 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 (five of 34 patients). Information downloaded from the CPAP equipment showed that patients were compliant (defined as use > 6 h/night [90% of the time]). Five patients with Ehlers-Danlos syndrome at the internal medicine clinic receiving CPAP had a mean pressure of 12.2 ± 0.84 cm H_2O.

DISCUSSION

This report describes the frequent presence of SDB in patients with Ehlers-Danlos syndrome. SDB was

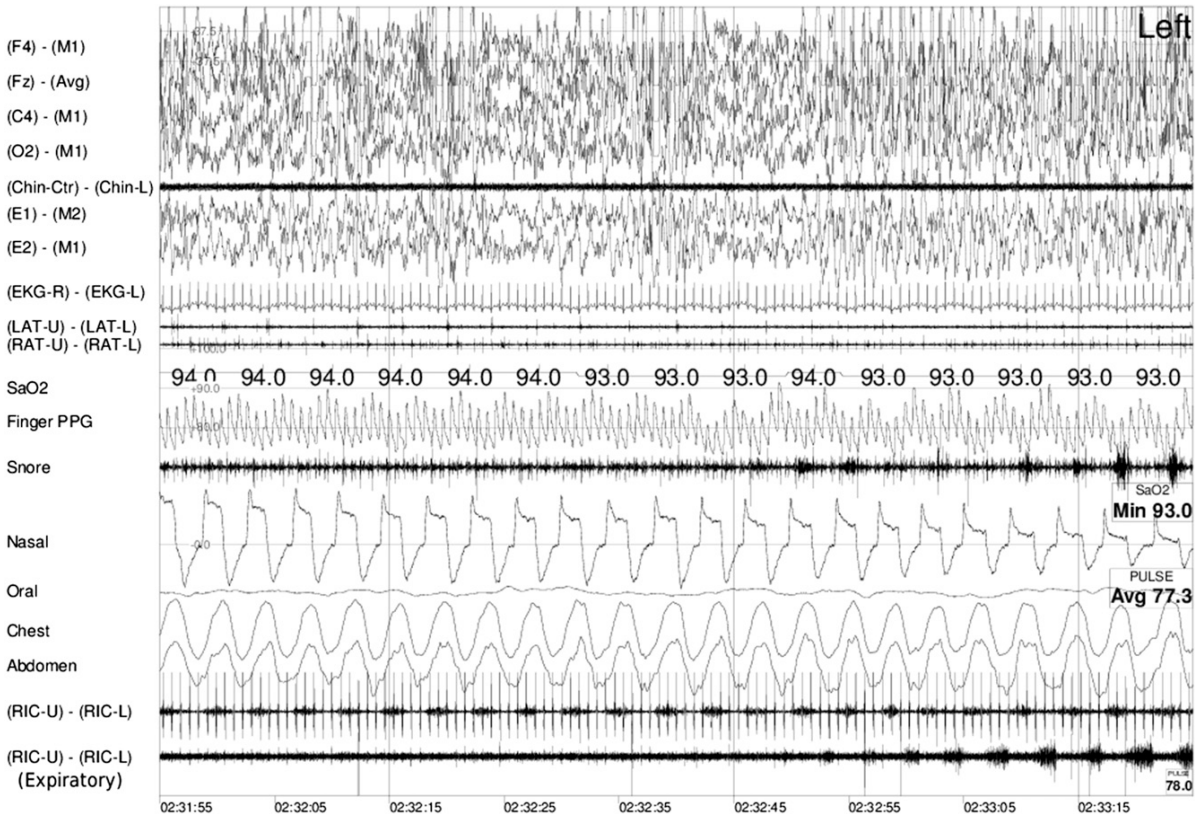

FIGURE 4. Example of flow limitation and active expiration in a 23-year-old patient during 90 s of non-rapid eye movement sleep. Starting from the top, four EEGs, chin muscle, right- and left-side electrooculogram, pulse (ECG), left and right leg muscle EMG, SaO_2, finger PPG, neck microphone (snore), nasal cannula, oral thermistor, thoracic and abdominal inductive plethysmography bands, intercostal-diaphragmatic EMG, and abdominal expiratory muscle EMG. As shown in Figure 3, flow limitation is demonstrated, with the nasal pressure cannula (channel 14 from top) again showing two peaks but with a downslope toward the lower second peak. But the segment also monitors 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, indicates that abdominal expiratory muscles become active midtracing. 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.[29,30] Note that oxygen saturation (channel 11 from top) changes by only 1% during the total recording of the segment and drops to 93% with activation of the expiratory muscles. See Figure 3 legend for expansion of abbreviations.

frequently diagnosed in a sleep clinic population, but similar findings were also observed in a sample of patients with Ehlers-Danlos syndrome presenting for routine medical care in an internal medicine Ehlers-Danlos syndrome clinic. Clinical history and physical evaluation were the same in both groups, and internal medicine clinic patients with Ehlers-Danlos syndrome who underwent PSG had similar findings to those noted in age-matched sleep clinic patients with Ehlers-Danlos syndrome.

If not systematically searched for, Ehlers-Danlos syndrome often is unrecognized,[32] particularly when type 2 and 3 are present because they represent the syndrome in its most common and often mildest form.[12] Similarly, the association between Ehlers-Danlos syndrome and abnormal breathing during sleep also may be overlooked. None of the patients with Ehlers-Danlos syndrome at the internal medicine clinic had been referred for evaluation of SDB despite symptoms and clinical presentation strongly supporting the diagnosis.

The study suggests that the presence of SDB in patients with Ehlers-Danlos syndrome is not related to a referral bias. Fatigue is a common symptom of patients with Ehlers-Danlos syndrome, which often is assumed to be associated with cartilaginous disease and considered by some as an overlap with chronic fatigue syndrome.[33-35] Fatigue frequently is associated with poor sleep, and patients with Ehlers-Danlos syndrome who report more severe fatigue also report greater psychologic distress and sleep disruption.[33] Patients with Ehlers-Danlos syndrome present not only with typical apnea and hypopnea but also with flow limitation. As has been demonstrated previously,[25,26] younger patients have a greater amount of flow limitation and fewer apneas or hypopneas, whereas older

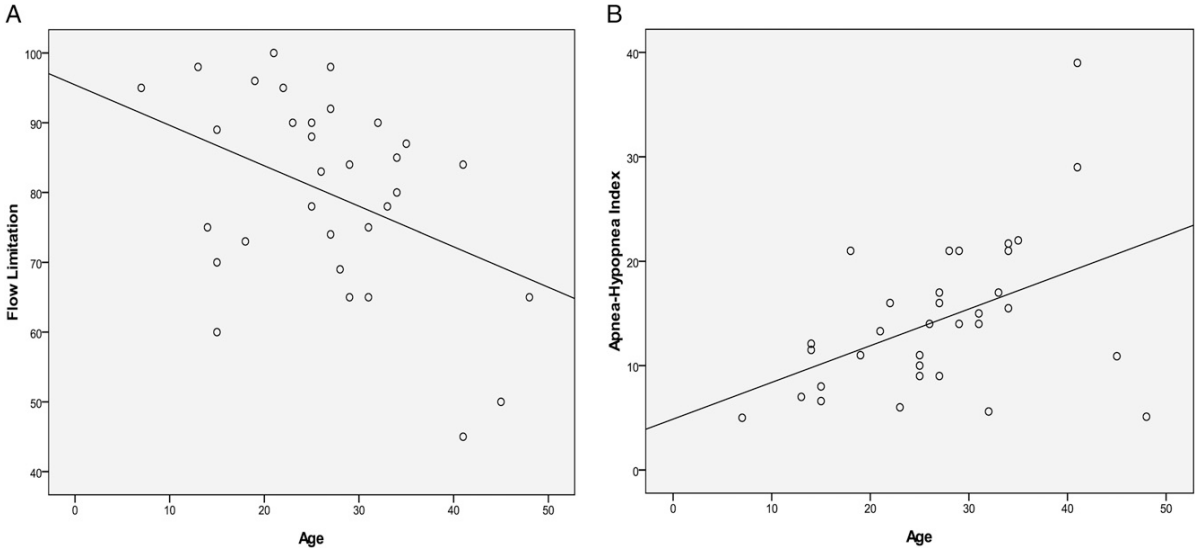

FIGURE 5. Distribution and correlation between age and flow limitation and between age and apnea-hypopnea index in sleep clinic patients with Ehlers-Danlos syndrome (n = 34). A, The downward evolution of flow limitation with increasing age is shown, with a significant negative correlation ($r^2 = 0.171$, $P = .015$). B, The progressive increase in apnea-hypopnea index with age is shown, with a significant positive correlation ($r^2 = 0.214$, $P = .006$). A similar finding was noted in an epidemiologic study investigating flow limitation in a representative sample of the general population of São Paulo, Brazil.[31]

patients have less flow limitation with a greater number of apneas and hypopneas. It appears that SDB exists as a continuum of progressively increasing severity. Of interest, 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 the present 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 of theoretical interest related to the development of SDB. Ehlers-Danlos syndrome is a hereditary collagen-vascular disease seen in at least 0.2% of the US population, and many types are described.[11,12] It may be inherited in an autosomal-dominant, autosomal-recessive, or X-linked fashion.[11,12] Ehlers-Danlos syndrome involves variable genetic mutations located on proteins (COL1A1, 1A2, 3A1, 5A1, 5A2, TNXB) or enzymes (ADAMTS2, PLOD1, BUGALT7), with the most common types 1 and 2 involving COL1A1, COL5A1, and COL5A2.

The patients in the present study had abnormalities of nasal and maxillary cartilage and evidence of a narrow jaw. Presence of specific facial features in nonobese patients has been associated with SDB,[9] and familial occurrence of OSA in subjects presenting with similar facial traits has been well demonstrated.[1-4] Maxillary growth during childhood is related to endochondral ossification in which hyaline cartilage is replaced by fibrocartilage and, later, bone.[10] Certain craniofacial growth impairments have been related to the risk of developing SDB.[21,36,37] Recently, we reviewed evidence (primarily from the orthodontic literature) that synthesizes the continuous interaction between function and oral-facial growth in children.[21] To summarize, abnormal development of the maxillary complex occurs with the continuous interaction between nasal breathing impairment during sleep, mouth breathing, and changes occurring in the nasomaxillary complex and mandible growth and positioning.[22,27,28] In a monkey model, an increase in nasal resistance at birth leads to abnormal discharges on oral-facial muscle electromyography, mouth breathing, and abnormal maxilla-mandibular growth.[38] 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.[39-41] Similar oral-facial anatomic changes are regularly observed in patients with Ehlers-Danlos syndrome. Patients with Ehlers-Danlos syndrome have abnormal growth of the nasomaxillary complex that leads to both increased nasal resistance and altered maxillary development. Ehlers-Danlos syndrome can be used as a genetic model for the development of SDB due to the heritable predisposition to disordered cartilaginous growth, and the study of patients with Ehlers-Danlos syndrome will allow investigation of the interaction between abnormal facial growth and regional muscle tone and activity.

Conclusions

Ehlers-Danlos syndrome is an important and often unrecognized cause of SDB, and further investigation can lead to a better understanding of the development of the OSA in nonobese individuals. Future research should focus on better characterizing SDB in this population and exploring whether orthodontics and myofunctional therapy[21, 27, 28] can limit the development of OSA in these patients.

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Dr Guilleminault: contributed to the investigation of patients from the EDS medical clinic, data collection, review of the retrospective data from the sleep clinic, data analysis, statistical analysis, writing of the manuscript, and review of the final manuscript.
Dr Primeau: contributed to the review of the retrospective data from the sleep clinic, data analysis, statistical analysis, writing of the manuscript, and review of the final manuscript.
Ms Chiu: contributed to the review of the retrospective data from the sleep clinic, data analysis, statistical analysis, writing of the manuscript, and review of the final manuscript.
Dr Yuen: contributed to the review of the retrospective data from the sleep clinic, data analysis, statistical analysis, writing of the manuscript, and review of the final manuscript.
Dr Leger: contributed to the investigation of patients from the EDS medical clinic, data collection, and review of the final manuscript.
Dr Metlaine: contributed to the investigation of patients from the EDS medical clinic, data collection, and review of the final manuscript.
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