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.

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.

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). However, simple genetic models do not explain the occurrence of OSA. Risk of OSA varies depending on ethnicity. 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.

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. 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.

We report on the presence OSA in Ehlers-Danlos syndrome, a well-known genetic disorder characterized by cartilaginous defects, 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. 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 rhinomanometry15,16 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

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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 suggestive of 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**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sleep Clinic (( n = 34 ))</th>
<th>Internal Medicine Clinic (( n = 9 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>26.55 ± 9.63</td>
<td>37.6 ± 12.25</td>
</tr>
<tr>
<td>Male sex</td>
<td>15 (44)</td>
<td>4 (44)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.95 ± 1.97</td>
<td>24.7 ± 2.67</td>
</tr>
<tr>
<td>Sleep parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHI (in laboratory)</td>
<td>14.21 ± 7.32</td>
<td>19.38 ± 9.2 (( n = 4 ))</td>
</tr>
<tr>
<td>RDI (in laboratory)</td>
<td>21.53 ± 7.17</td>
<td>25.8 ± 10.2 (( n = 4 ))</td>
</tr>
<tr>
<td>AHI (ambulatory)</td>
<td></td>
<td>15.41 (( n = 1 ))</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>90.06 ± 1.8</td>
<td>87.2 ± 2.77 (( n = 5 ))</td>
</tr>
<tr>
<td>Flow limitation, % TST</td>
<td>80.03 ± 13.53</td>
<td>62.8 ± 17.3 (( n = 4 ))</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or No. (%). AHI = apnea-hypopnea index; PSG = polysomnography; RDI = respiratory disturbance index; SaO₂ = arterial oxygen saturation; TST = total sleep time.

\*Significantly different at \( P = .01 \) (Mann-Whitney U test).

\{Significantly different at \( P = .01 \) (\( \chi^2 \) statistics).

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

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Sleep Clinic (( n = 34 ))</th>
<th>Internal Medicine Clinic (( n = 9 ))</th>
</tr>
</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 (55.55)</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>

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 (\( \chi^2 \) statistics \( P = .01 \)), and the presence of orthostatic evaluation, which was more prevalent in the sleep clinic group (\( \chi^2 \) statistics \( P = .01 \)). 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 car-tilages are critical elements in facial growth. 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, 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.)
Five patients with Ehlers-Danlos syndrome were evaluated with objective sleep monitoring as per local recommendations (Table 1). The mean in-laboratory AHI was 19.38 (range, 9.2-38), and the mean in-laboratory RDI was 25.81 (range, 10.24-32). 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).

### Rhinomanometry

The mean nasal resistance in seven patients with Ehlers-Danlos syndrome was significantly higher (0.68 ± 0.197 Pa/cm³/s, \( P = .01 \)) than that in the age- and sex-matched control group (0.38 ± 0.20 Pa/cm³/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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>LogVR-in</td>
<td>1.09 ± 0.25</td>
</tr>
<tr>
<td>LogVR-ex</td>
<td>1.10 ± 0.26</td>
</tr>
<tr>
<td>LogReff-in</td>
<td>1.11 ± 0.26</td>
</tr>
<tr>
<td>LogReff-ex</td>
<td>1.12 ± 0.26</td>
</tr>
<tr>
<td>LogReff-T</td>
<td>1.11 ± 0.28</td>
</tr>
</tbody>
</table>

ex = expiration; in = inspiration; Reff = effective resistance; T = entire breath; VR = 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. 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) (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.
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$_2$O (mean, 11.44 ± 1 cm H$_2$O). 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). Five patients with Ehlers-Danlos syndrome at the internal medicine clinic receiving CPAP had a mean pressure of 12.2 ± 0.84 cm H$_2$O.

DISCUSSION

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

Patients with Ehlers-Danlos syndrome present not only with typical apnea and hypopnea but also with flow limitation. As has been demonstrated previously, younger patients have a greater amount of flow limitation and fewer apneas or hypopneas, whereas older

![Figure 4](http://journal.publications.chestnet.org/)

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, &O2, 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. 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.
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. Flow limitation leads to EEG changes similar to those seen with apnea and hypopnea, likely causing the perceived daytime impairments. 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. It may be inherited in an autosomal-dominant, autosomal-recessive, or X-linked fashion. 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 non-obese patients has been associated with SDB, and familial occurrence of OSA in subjects presenting with similar facial traits has been well demonstrated. Maxillary growth during childhood is related to endochondral ossification in which hyaline cartilage is replaced by fibrocartilage and, later, bone. Certain craniofacial growth impairments have been related to the risk of developing SDB. Recently, we reviewed evidence (primarily from the orthodontic literature) that synthesizes the continuous interaction between function and oral-facial growth in children. 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. In a monkey model, an increase in nasal resistance at birth leads to abnormal discharges on oral-facial muscle electromyography, mouth breathing, and abnormal maxillomandibular growth. 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. 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 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 Leger: contributed to the investigation of patients from the EDS medical clinic, data collection, review of the final manuscript.

Ms Guilleminault: contributed to the investigation of patients from the EDS medical clinic, data collection, 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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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.

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