O SA 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 (e.g., 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 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, joint 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 symptoms 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.16 Age-matched (±2 years) normal pediatric 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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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 Protect 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 Airway15,16 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

Respiratory event scoring was based on AASM criteria for SDB in adults.17

Apnoea, subdivided into obstructive, mixed, and central, was defined as complete absence of air exchange for at least 10 s, whereas hypopnoea was defined as a reduction in nasal pressure signals by ≥30% of baseline for at least 10 s accompanied by a ≥4% desaturation from pre-event 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 hypopnea18 and often was associated with flow limitation based on the nasal cannula flow wave contour form.19,20

Calculation 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 syndrome19 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
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). All presented with unrefreshing, fragmented sleep and daytime fatigue, and 33 (97.1%) reported snoring and mouth breathing, particularly during sleep (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 = 19) 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 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 (98)</td>
<td>8 (80)</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 (80)</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 \( F = .01 \)), and the presence of orthostatic evaluation, which was more prevalent in the sleep clinic group (\( \chi^2 \) statistics \( F = .001 \)). The internal medicine clinic patients with Ehlers-Danlos syndrome were also significantly older than the sleep clinic patients with Ehlers-Danlos syndrome.

**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/m(^2)</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>SaO(_2), %</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. (%). \( \text{AHI} = \text{apnea-hypopnea index}; \text{PSG} = \text{polysomnography}; \text{RDI} = \text{respiratory disturbance index}; \text{SaO}_2 = \text{arterial oxygen saturation}; \text{TST} = \text{total sleep time.} \)

\(^{a}\)Significantly different at \( P = .01 \) (Mann-Whitney \( U \) test).

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

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**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, internasal, nasal, and temporomaxillary cartilages are critical elements in facial growth.\(^{21,22}\) 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,\(^{21}\) 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.)

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of teeth crowding. The mean BMI was 22.95 kg/m² (range, 14-31.1 kg/m²).

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 ± 2.71 kg/m².

**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.
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 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$_2$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. If not systematically searched for, Ehlers-Danlos syndrome often is unrecognized, particularly when type 2 and 3 are present because they represent the syndrome in its most common and often mildest form. 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.

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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.\textsuperscript{25,26}

Flow limitation leads to EEG changes similar to those seen with apnea and hypopnea, likely causing the perceived daytime impairments.\textsuperscript{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.\textsuperscript{11,12} It may be inherited in an autosomal-dominant, autosomal-recessive, or X-linked fashion.\textsuperscript{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 non-obese patients has been associated with SDB,\textsuperscript{9} and familial occurrence of OSA in subjects presenting with similar facial traits has been well demonstrated.\textsuperscript{1-4} Maxillary growth during childhood is related to endochondral ossification in which hyaline cartilage is replaced by fibrocartilage and, later, bone.\textsuperscript{10} Certain craniofacial growth impairments have been related to the risk of developing SDB.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsuperscript{11, 21, 27, 28} can limit the development of OSA in these patients.

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Other contributions: This work was performed at the Stanford University Sleep Medicine Division and Ehlers-Danlos Clinic, Hôpital de L'Hôtel-Dieu, Paris (Stanford IRB #18494, Hôpital-Dieu Hôpital-Dieu-AFIP-Hôtel-Dieu-25-11-2010). The authors thank Oscar Carrillo, RS, for retrieving recordings and for analyses of respiratory muscle activity during flow limited breathing and Gerard Meskill, MD, and Brandon Peters, MD, for help in editing the manuscript.

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