Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder that ultimately progresses to death. Upper airway dysfunction due to bulbar muscle involvement is common and may lead to swallowing problems, abnormal speech, and recurrent aspiration. Respiratory muscle weakness is usually progressive and death is usually due to respiratory failure. Studies in other neuromuscular diseases have found significant sleep-disordered breathing.1-3 If this occurs in ALS, then these patients may benefit from nocturnal ventilation as is used in other neuromuscular disorders.4-8 We and others have previously published uncontrolled observations of sleep and breathing in ALS,9-11 but there is a lack of controlled studies addressing these issues.

ALS patients with bulbar involvement have abnormal upper airway muscles. With sleep onset, further muscle hypotonia may contribute to the development of obstructive sleep apnea (OSA). This in turn could lead to sleep fragmentation, and the complaints of excessive daytime sleepiness and difficulty initiating and maintaining sleep reported by some ALS patients. There are reports of OSA occurring in other neurologic disorders affecting the bulbar musculature.12

Because of the complaints of poor sleep and our suspicions that sleep-disordered breathing might be a cause of sleep disruption, we undertook a study of sleep and breathing in ALS patients. We had two main objectives: first, to determine if the subjective sleep complaints were consistent with the objective measurement of sleep by polysomnography and second, to determine if ALS patients with bulbar muscle weakness have OSA and nocturnal hypoventilation.
Materials and Methods

Patients

Eighteen ALS patients were recruited from the Motor Neuron Disease Clinic, University Hospital, London, Canada. Ten asymptomatic age-matched control subjects were recruited through advertisements in the general community. The ALS patients had definite ALS with a bulbar predominance and/or respiratory muscle weakness. Definite ALS requires the presence of progressive upper and lower motor neuron signs in at least three different regions (bulbar and at least two of cervical, thoracic, or lumbar sacral spinal segments). Multisegmental lower motor neuron involvement was confirmed by electromyography (EMG). This study was approved by the Review Board for Health Sciences Research Involving Human Subjects at the University of Western Ontario. All ALS patients and control subjects underwent a full history with completion of a sleep questionnaire, the Stanford Sleepiness Scale, the Borg Dyspnea Scale, and a detailed physical examination. ALS patients were assigned a disability score based on parameters of upper and lower extremity function, nutritional status (swallowing), speech, and pulmonary function testing (modified from Hillel et al.16-19). ALS patients underwent pulmonary function testing, including spirometry with a dry rolling seal spirometer (PK Morgan; Chatham; Kent, England) and blood gases. Maximal inspiratory pressures and maximal expiratory pressures were measured according to the method of Black and Hyatt.17

Polysomnography

Overnight polysomnography was performed on one or two nights in the ALS patients and on one night in control subjects. An additional night was reserved for nasal continuous positive airway pressure or nasal bilevel positive airway pressure (BiPAP [ventilatory support system]; Respironics Inc; Murrysville, Pa) if OSA or sleep-disordered breathing was present. The sleep study montage included EEG (C3/A2, C4/A1, O2/A1), electro-oculogram, submental EMG, left and right anterior tibialis EMG, ECG, thoracoabdominal motion (Respirac; Ambulatory Monitoring Equipment; Ardsley, NY), oronasal airflow (expired CO2), and arterial oxygen saturation with pulse oximetry using an ear probe sensor (Ohmeda Biox 3700; Ohmeda; Louisville, Colo). This was recorded on a recorder (Grass Polysomnograph model 78; Grass Instrument Company; Quincy, Mass). Sleep was staged manually in 30-s epochs from the EEG, electro-oculogram, and EMG by the criteria of Rechtschaffen and Kales.18 Total sleep time (TST), sleep efficiency (TST per total time in bed), percentage of time in each stage of sleep (stages 1, 2, 3, 4, and rapid eye movement [REM]), arousals per hour, awakenings, limb movements, apneas, and hypopneas were determined for each study. Limb movements were scored according to published guidelines.19 The total apnea and hypopnea index (AHI, number per hour TST) was calculated for the night and was subdivided into the AHI during non-REM (NREM) and REM sleep. Obstructive apneas were defined as the cessation of airflow for at least 10 s accompanied by ongoing respiratory effort. Central apneas were defined as the cessation of airflow and respiratory effort for at least 10 s. Mixed apneas were defined as a combination of an obstructive and central apnea lasting for at least 10 s. Hypopneas were defined as a reduction in airflow of at least 50% for at least 10 s accompanied by a reduction in respiratory effort and accompanied by an arousal or an arterial oxygen desaturation of at least 3%. Arousals were defined as an abrupt shift in EEG frequency from the baseline lasting at least 3 s.20 Awakenings were scored when wakefulness was sustained for more than 1 min.

Statistical Analysis

The data from the patients with ALS and control subjects were compared using an unpaired t test. The data from the first- and second-night studies were compared with a paired t test. The frequencies of symptoms were compared by χ2 analysis. Because the AHI values were not normally distributed, these data were log-transformed prior to t tests being performed.

Results

Patients

Eighteen ALS patients with mild to severe bulbar muscle involvement and ten age-matched control subjects were studied. One patient with ALS did not have significant bulbar muscle involvement but had significant respiratory muscle weakness. One patient had a TST less than 10 min; therefore, none of his clinical, respiratory, or sleep data is presented. (His clinical and pulmonary function data did not differ from those of the other ALS patients.) Therefore, there were eight men and nine women in the ALS group and ten men in the control group. There were no significant differences between the men and the women with ALS with respect to clinical variables, sleep, or pulmonary function data. The men and women were compared separately with the control subjects, and because the differences between the control subjects and the ALS patients were the same regardless of sex, the data were pooled.

Patient characteristics are presented in Table 1. Most patients complained of difficulty initiating and maintaining sleep. By history, only seven ALS patients were snorers and four had witnessed apneas during sleep. Most of the control subjects had a history of mild intermittent snoring but none had a history of witnessed nocturnal apneas. Twelve of the 17 ALS patients (71%) had complaints of dyspnea and the Borg Dyspnea Scale averaged 1.5±1.5 (mean±SD) (slight dyspnea). Fourteen ALS patients (82%) complained of orthopnea. None of the control subjects had any pul-

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### Table 1—Patient Characteristics*

<table>
<thead>
<tr>
<th></th>
<th>ALS Patients (n=17)</th>
<th>Control Patients (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>63.7±7.1 (49-75)</td>
<td>56.4±12.0 (42-71)</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>8/9</td>
<td>10/0</td>
</tr>
<tr>
<td>Body mass index, kg/m2</td>
<td>22.8±3.5 (13.5-27.7)</td>
<td>27.9±2.8 (22.5-33.1)</td>
</tr>
<tr>
<td>Stanford Sleepiness Scale</td>
<td>2.7±1.4 (1-6)</td>
<td>0.7±1.7 (1-3)</td>
</tr>
<tr>
<td>Excessive daytime sleepiness</td>
<td>7 (41)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Snoring†</td>
<td>7 (41)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Nocturnal choking†</td>
<td>8 (47)</td>
<td>0</td>
</tr>
<tr>
<td>Witnessed apneas</td>
<td>4 (24)</td>
<td>0</td>
</tr>
<tr>
<td>Difficulty initiating sleep†</td>
<td>12 (71)</td>
<td>0</td>
</tr>
<tr>
<td>Difficulty maintaining sleep†</td>
<td>17 (100)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Values are expressed as mean±SD (range) or number (percent).†p≤0.005, ‡p≤0.05.
Pulmonary polysomnography in ALS patients. There was a significant difference between the sleep structure of the 17 ALS patients and the 10 age-matched control subjects (Table 3). The percentage stage 1 sleep, arousals per hour, and stage changes per hour were greater in the ALS patients and TST was less (p<0.05).

Twelve ALS patients had two consecutive nights of polysomnography (Table 4). There were significant differences between the first and second nights. The TST was longer on the second night (p=0.003) and sleep efficiency improved (p=0.02). There was less stage 1 (p=0.04) and more REM sleep (p=0.009) on the second night. Arousals per hour (p=0.027) and stage changes per hour (p=0.013) from the second-night study in the ALS patients were greater than in the control subjects (who had one night of polysomnography).

Sleep Parameters

Eighteen ALS patients had at least one night of polysomnography but the patient with a TST less than 10 min was excluded from the analysis. There were significant differences between the sleep structure of the 17 ALS patients and the 10 age-matched control subjects (Table 3). The percentage stage 1 sleep, arousals per hour, and stage changes per hour were greater in the ALS patients and TST was less (p<0.05).

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Respiratory Parameters

The ALS patients had a greater AHI than the control subjects (Table 3). Eight ALS patients had sleep-disordered breathing that was concentrated predominantly in REM sleep. This consisted of periods of hypoventilation (nonobstructive hypopneas) with an AHI REM of 10 or more per hour (range, 10 to 120), that were accompanied by a significant fall in arterial oxygen saturation (Fig 1). The mean arterial oxygen saturation during REM sleep was 89.4±4.7 (range, 76 to 94). However, in the patients with an AHI REM of 10 or more per hour, it was 87.2±6.4 (range, 76 to 91.7). The average arterial oxygen saturation was greater than 90% during wakefulness and NREM sleep for the ALS patients and during wakefulness and sleep in the control subjects. Only 3 ALS patients had an AHI of 10 or more per hour TST and only 1 patient had severe sleep-disordered breathing with hypoventilation in both REM (AHI REM 120) and NREM sleep (AHI NREM 95). No OSA was seen in any of the ALS patients. Two control subjects had an AHI during REM sleep of 10 or more per hour (10 and 13, respectively), but these events were obstructive in nature.
Four patients with REM-related hypoventilation went on to have overnight studies performed with nasal continuous positive airway pressure and/or bilevel positive airway pressure. Only one patient was able to tolerate the ventilatory support system (BiPAP; Respironics Inc; Murrysville, Pa) and he continued to receive nocturnal support for 14 months until death. This provided an improvement in his nocturnal hypoventilation and normalized his nocturnal arterial oxygen saturation. The other patients complained of difficulty breathing out against even low pressures.

**Periodic Limb Movements**

Two patients with ALS complained of restless legs. The periodic limb movement index for the 17 ALS patients was $28.1 \pm 38.5$ and was 10 or more per hour in 8 patients (mean index, $56 \pm 37$). Two of the control subjects had a periodic limb movement index greater than 10 per hour ($28$ and $49$, respectively). There was no difference in the mean periodic limb movement index between the ALS patients and the control subjects (Table 3) or between night 1 and 2 (Table 4) in the ALS patients.

**Discussion**

To our knowledge, this study represents the first controlled study of sleep and breathing in patients with definite ALS. The polysomnographic findings confirmed the patients' complaints of poor sleep. The TST was reduced, stage 1 sleep was increased, and there were more frequent arousals and stage changes per hour when compared with healthy, age-matched control subjects. The patients in this study demonstrated a reduction in respiratory muscle strength despite the near-normal vital capacity. Overall, oxygenation and ventilation were preserved with fairly normal daytime blood gas values. Sleep-disordered breathing was similar to patients without ALS with respiratory muscle weakness and consisted of REM-related nonobstructive hypopneas and central apneas. This is also compatible with previous reports in ALS.

No significant OSA was seen despite the degree of bulbar muscle weakness. This may relate to an inability of weakened respiratory muscles to generate an inspiratory pressure sufficient to suck the upper airway closed. Although measurements of esophageal pressure would have addressed this issue, we were concerned that placement of a catheter in patients with bulbar dysfunction would disrupt sleep and increase the risk of aspiration.

Degenerative neurologic disorders are a heterogeneous group of conditions with varying involvement of the motor system (eg, respiratory and bulbar muscles), CNS, and brain stem. Reported sleep disturbances
have included insomnia, hypersomnia, circadian rhythm disturbances, parasomnias, and sleep-disordered breathing. In ALS, motor neurons of the ventral spinal cord and the lower brainstem degenerate. There is also a loss of Betz cells in the motor cortex. ALS has not been shown to affect the sleep-regulating areas of the brain and it is likely that indirect effects of the disease cause the sleep disruption. Periodic limb movements associated with arousals and sleep-disordered breathing contributed to the sleep disruption in some patients with ALS. However, some patients without any respiratory disturbance or periodic limb movements still had sleep fragmentation. Although the ALS patients were middle-aged or older and sleep disruption increases with increasing age, they had more disturbed sleep than age-matched control subjects. This suggests that factors other than aging contribute to poor sleep in patients with ALS. These factors may include anxiety, depression, pain, choking, excessive secretions, fasciculations and cramps, and the inability to get comfortable or turn oneself freely in bed. Orthopnea was a complaint in 83% of the ALS patients and this may also contribute to sleep disruption.

Our study has certain limitations. First, our sample size is small and the patients were not randomly selected. Second, these patients were compared with normal, healthy age-matched control subjects. It would be preferable to compare them to patients with mild ALS who are without respiratory involvement and bulbar dysfunction. However, most patients have diffuse motor impairment by the time of presentation. Third, it would have been ideal to perform two-night studies in all the ALS patients and control subjects. The improvement in sleep quality on the second night of study is what one would anticipate. This may be attributed to the “first night effect” that has been described in other groups. The second night did not differ in these patients with respect to the presence of sleep-disordered breathing or periodic limb movement disorder and in general, a single-night study is adequate for the diagnosis of OSA.

In summary, ALS patients with bulbar and peripheral respiratory muscle weakness have disrupted nocturnal sleep. Upper airway obstruction (OSA) does not occur despite the presence of flaccid bulbar muscles. Similar to other neuromuscular and restrictive pulmonary diseases, nocturnal hypventilation can produce significant desaturations during sleep, but this occurs predominantly in REM sleep. Neither the degree of sleep-disordered breathing nor of the periodic limb movements explained the sleep fragmentation in all of the patients and other factors such as orthopnea, choking, and excessive secretions may be important. Overnight polysomnography is useful to evaluate the sleep complaints of patients with ALS and reveals the presence of sleep-disordered breathing in some individuals. The ALS patients in this study with respiratory muscle weakness and sleep-disordered breathing were mostly intolerant of nasal positive pressure (either continuous or intermittent) during sleep. Further studies are needed to understand the sleep abnormalities in ALS and to assess their impact (if any) on daytime sleepiness, performance, and the progression of respiratory failure and to evaluate the impact of sleep disorders on quality of life and patient outcome.

REFERENCES