Sleep disordered breathing in patients with cluster headache

R.D. Chervin, MD, MS; S. Nath Zallek, MD; X. Lin, PhD; J.M. Hall, MA, MS; N. Sharma, BS; and K.M. Hedger, RN, BSN

Article abstract—Objective: To study subjects with active or inactive cluster headache (CH) for occult sleep disordered breathing (SDB). Background: CH frequently occurs during sleep. The authors previously found that symptoms of SDB predicted reported occurrence of CH in the first half of the night, which suggested that CH could be triggered in some cases by unrecognized SDB. Methods: The authors performed polysomnography in 25 adults (22 men) with CH. Subjects were not selected for any sleep-related complaint. In addition to standard measures, studies included monitoring of end-tidal carbon dioxide (n = 22), and esophageal pressure (n = 20). Results: The rate of apneas and hypopneas per hour of sleep was >5 in 20 subjects (80%; 95% CI, 64% to 96%), minimum oxygen saturation was <90% in 10 subjects, maximum negative esophageal pressure ranged from −13 to −65 cm H2O, and maximum end-tidal carbon dioxide was ≥50 mm Hg in eight subjects. The eight subjects with active (versus inactive) CH at the time of study had higher maximum end-tidal carbon dioxide levels (50 ± 3 versus 44 ± 5 mm Hg; p = 0.0007). More severe oxygen desaturation was associated with reports that CH typically occurred in the first half of the nocturnal sleep period (p = 0.008). Conclusions: SDB occurred in the majority of patients with CH. Evaluation of a patient with CH should include consideration that SDB may be present. Key words: Cluster headache—Obstructive sleep apnea—Polysomnography—Hypercapnia—Hypoxemia.

Cluster headache (CH) is particularly likely to occur during sleep,1-3 often during or at the end of an REM sleep period.4,5 Some patients may be able to prevent a regular nocturnal attack by avoiding sleep.1-3 Although abnormalities in hypothalamic and brain stem nuclei have been implicated as possible causes of CH susceptibility, no pathogenetic mechanism has been shown responsible for the tendency of CH to occur during sleep.

One potential nocturnal trigger is sleep disordered breathing (SDB), in the form of obstructive sleep apnea6 (OSA) or upper airway resistance syndrome.7 Although little is known about the epidemiology of upper airway resistance syndrome, OSA occurs at a level of severity thought to have potentially important impact on health8,9 in about 20% of adults.10 Even when excessive sleepiness is present, most persons with OSA remain undiagnosed.11 The condition is associated with recurrent nocturnal hypoxemia, hypercapnia, excessively negative intrathoracic pressures, increased intracranial pressures, and other physiologic changes, any of which could serve as a trigger for CH. Hypoxemia has been proposed previously as a trigger for CH,12-14 although counter arguments have also been raised.15 Obstructive sleep apnea tends to be worse during REM sleep than during non-REM sleep16; this observation could explain why CH appears to be linked to REM sleep.

Evidence that SDB does sometimes trigger CH includes case reports that treatment of SDB in patients with CH can lead to resolution or marked improvement in headaches.17,18 We recently found that among 36 subjects with CH, headaches that typically occurred in the first half of the night’s sleep period were associated with SDB symptoms, and especially with more frequent snoring.19 These findings suggested that SDB and associated physiologic changes may trigger CH early in the night in susceptible individuals. A refractory period may then prevent CH during the remainder of the night.1
fication of the upper airway resistance syndrome,\(^7\) in which increased respiratory effort creates large negative intrathoracic pressures during inspiration, compensates for a partially obstructed upper airway, maintains nearly normal airflow, but still leads to sleep disruption and other physiologic consequences.\(^2\)\(^1\)

In the current study, which involved many of the 36 subjects we previously identified for our survey on CH and SDB symptoms,\(^9\) we used polysomnography to assess for SDB. We also compared results from subjects with active and inactive CH to identify what sleep and breathing-related variables might distinguish the two states.

**Methods. Subjects.** We used a health system search of diagnostic codes for “migraine variant,” local newspaper and radio advertisements, and television news coverage to identify potential subjects. The advertisements did not mention sleep, snoring, breathing, or involvement of a sleep center, but television coverage did explain that sleep studies were involved with this research. We reviewed hospital charts of patients with “migraine variant” to determine whether CH was likely to be present. By telephone and then personal interviews, we identified adults who satisfied the CH criteria of the International Headache Society\(^2\)\(^2\) but had never been diagnosed with SDB and invited them to participate in an Institutional Review Board–approved study to assess symptoms, signs, and polysomnographic findings. A total of 40 subjects signed informed consent, enrolled, and provided historical data. To increase the number of subjects studied during active CH, those without active CH or near the end of their typical CH period were advised to delay polysomnographic testing until the beginning of their next cluster. However, the majority of such subjects had no cluster period, or had neglected to call long after their typical intercluster interval had elapsed; these subjects were then invited to undergo polysomnography even while CH was inactive. A number of subjects declined; a total of 25 underwent polysomnography, and these 25 are the focus of the current study. The studied subjects showed no significant differences compared with those who did not undergo polysomnography (n = 15) in age, gender, or reports of snoring frequency, loud snoring, observed apneas, or subjective sleepiness (Epworth Sleepiness Scale scores\(^2\)\(^3\)).

**Protocol.** Nocturnal polysomnography included four EEG leads (C\(_3\)-A\(_2\), C\(_4\)-A\(_1\), O\(_1\)-A\(_2\), and O\(_2\)-A\(_1\) of the 10-20 international electrode placement system), two electrooculographic leads (right and left outer canthi), chin and bilateral anterior tibialis surface electromyograms, two EKG leads, nasal and oral airflow (thermistors), thoracic and abdominal excursion (piezoelectric strain gauges), and finger oximetry. Most subjects (n = 22) also had end-tidal carbon dioxide monitoring, and most (n = 20) had esophageal pressure monitoring performed with a water-filled catheter\(^2\)\(^4\) that had little or no effect on sleep architecture.\(^2\)\(^5\) Sleep stages were scored according to standard methods\(^2\)\(^6\) by well-trained technicians who had correctly scored at least 90% of epochs in a set of reliability records. An apnea was defined as 10 or more seconds of complete airflow cessation during sleep. A hypopnea was defined as a 10-second or longer reduction in airflow, chest excursion, or abdominal excursion that led to a 4% or greater oxyhemoglobin desaturation, an arousal, or an awakening. The apnea-hypopnea index (AHI) was calculated as the number of recorded apneas and hypopneas divided by the total hours of sleep. Minimum oxygen saturation, maximal end-tidal carbon dioxide, and most negative esophageal pressure for each study were measured during sleep.

**Analyses.** Logistic regressions were used to model active (versus inactive) CH as the outcome variable and each polysomnographic measure as an explanatory variable. Logistic regression p values were calculated from the likelihood ratio \(\chi^2\) (for overall model results) and the Wald \(\chi^2\) (for explanatory variables in multiple logistic regressions). OR 95% CIs were calculated with the profile likelihood method. The significance level was set at 0.05. Analyses were performed with SAS® version 6.12 (SAS Institute Inc., Cary, NC).

**Results. Demographics.** The subjects’ mean age was 43 ± 14 (SD) years and 22 (88%) were men. The episodic form of CH was present in 23 (92%) of the subjects; the other two (8%) had the chronic form. Eight (32%) of the subjects (mean age 44 ± 18 years; seven men) were studied during an active cluster period.

**Polysomnographic measures.** Means for several measures of SDB—for all subjects, for those with active CH, and for those with inactive CH—are shown in table 1. If OSA is defined by an AHI of 5 or more,\(^3\) then 20 subjects (80%; 95% CI, 64% to 96%) qualified for the diagnosis. If

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**Table 1 Measures of sleep disordered breathing*\(^\)**

<table>
<thead>
<tr>
<th>Measure</th>
<th>All subjects</th>
<th>Active CH (n = 8)</th>
<th>Inactive CH (n = 17)</th>
<th>p Value†</th>
<th>OR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI, events/hour</td>
<td>15 ± 20</td>
<td>10 ± 9</td>
<td>17 ± 23</td>
<td>0.29</td>
<td>0.96 (0.85–1.02)</td>
</tr>
<tr>
<td>AHI in REM sleep, events/hour</td>
<td>22 ± 25</td>
<td>21 ± 29</td>
<td>23 ± 24</td>
<td>0.81</td>
<td>0.81 (0.95–1.03)</td>
</tr>
<tr>
<td>Minimum oxygen saturation, %</td>
<td>89 ± 5</td>
<td>88 ± 9</td>
<td>90 ± 2</td>
<td>0.23</td>
<td>0.91 (0.71–1.07)</td>
</tr>
<tr>
<td>Most negative esophageal pressure, cm H(_2)O</td>
<td>−29 ± 11</td>
<td>−31 ± 16</td>
<td>−28 ± 7</td>
<td>0.45</td>
<td>0.97 (0.88–1.05)</td>
</tr>
<tr>
<td>Maximum end-tidal carbon dioxide, mm Hg</td>
<td>46 ± 5</td>
<td>50 ± 3</td>
<td>44 ± 5</td>
<td>0.0007</td>
<td>1.61 (1.17–2.85)</td>
</tr>
</tbody>
</table>

* Summary data are expressed as mean ± SD.
† Results of a logistic regression of active CH on a one-unit increase in each measure.

AHI = apnea-hypopnea index; CH = cluster headache.
OSA is defined more conservatively by an AHI of 10 or more, then 11 subjects (44%; 95% CI, 25% to 64%) qualified. Minimum oxygen saturation was <90% in 10 subjects (40%; 95% CI, 21% to 59%). The maximum end-tidal carbon dioxide level was ≥50 mm Hg in eight subjects (36%; 95% CI, 16% to 56%). Esophageal pressures reached values more negative than −10 cm H₂O in every subject and exceeded −20 cm H₂O in 16 (80%; 95% CI cannot be calculated by normal approximation to binomial).

Active versus inactive cluster headache. The AHI, AHI during REM sleep, minimum oxygen saturation, and most negative esophageal pressure showed no significant difference between subjects with active CH and inactive CH (see table 1). However, subjects with active CH had higher maximum end-tidal carbon dioxide levels (figure); the OR for active CH and 1 mm Hg increase in maximum carbon dioxide levels was 1.6 (p = 0.0007). The association still showed a trend toward significance (p = 0.08) after adjustment for other covariates (AHI, minimum oxygen saturation, and most negative esophageal pressure).

**Headache timing and measures of sleep disordered breathing.** Proclivity to CH in the first half of the night, reported by 13 (52%) of the 25 subjects, showed a significant association with more severe SDB as measured by minimum oxygen saturation and most negative esophageal pressure (table 2). No significant association was detected with AHI, AHI during REM sleep, or maximum end-tidal carbon dioxide. A multivariable model showed that after accounting for esophageal pressure, minimum oxygen saturation still showed a marginally significant association with the timing of CH in the first half of the night (see table 2).

**Table 2 Sleep disordered breathing measures and headache timing**

<table>
<thead>
<tr>
<th>Measure</th>
<th>CH in first half of night (n = 13)</th>
<th>No CH in first half of night (n = 12)</th>
<th>Simple logistic regressions†</th>
<th>Multivariable logistic regression‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI, events/hour</td>
<td>14 ± 9</td>
<td>16 ± 28</td>
<td>0.8297 1.00 (0.95, 1.04)</td>
<td>0.0631 0.56 (0.25–0.92)</td>
</tr>
<tr>
<td>AHI in REM sleep, events/hour</td>
<td>24 ± 26</td>
<td>21 ± 25</td>
<td>0.7321 1.01 (0.97, 1.04)</td>
<td>0.4306 0.93 (0.74–1.09)</td>
</tr>
<tr>
<td>Minimum oxygen saturation, %</td>
<td>87 ± 6</td>
<td>92 ± 2</td>
<td>0.0081 0.68 (0.43, 0.93)</td>
<td>0.0631 0.56 (0.25–0.92)</td>
</tr>
<tr>
<td>Most negative esophageal pressure, cm H₂O</td>
<td>−34 ± 12</td>
<td>−24 ± 8</td>
<td>0.0151 0.86 (0.71–0.98)</td>
<td>0.4306 0.93 (0.74–1.09)</td>
</tr>
<tr>
<td>Maximum end-tidal carbon dioxide, mm Hg</td>
<td>46 ± 6</td>
<td>46 ± 5</td>
<td>0.9263 1.01 (0.85–1.20)</td>
<td>0.4306 0.93 (0.74–1.09)</td>
</tr>
</tbody>
</table>

* Data are expressed as mean ± SD.
† Results of simple logistic regressions of early-night CH on a one-unit increase in each measure.
‡ Results of a multiple logistic regression of early-night CH on one-unit increases in the two associated independent variables.

AHI = apnea-hypopnea index; CH = cluster headache.

**Discussion.** The principal finding of this study is that SDB was frequently present among individuals with CH who were studied with polysomnography. In addition, subjects with active CH showed higher maximum end-tidal carbon dioxide levels than did subjects with inactive CH. Two polysomnographic measures of SDB severity—minimum oxygen saturation and esophageal pressure—showed associations with reports that headaches occurred early in the nocturnal sleep period, but only oxygen saturation showed a marginally significant independent association.

The high frequency of OSA among our subjects with CH (80%) suggests a substantial elevation from the reported prevalence of 24% among 30- to 60-year-old men in the population-based Wisconsin Sleep Cohort. Debate exists over what types of polysomnographic equipment and scoring criteria are optimal to define OSA. Methods vary between studies and were not precisely identical in the current study and the Wisconsin cohort. Although such differences can affect estimates of OSA frequency, the discrepancies in methods between the current study, the Wisconsin cohort study, and recent task force recommendations—all three of which define apneas identically and hypopneas similarly—were most likely too small to affect the robust findings in the current study. Furthermore, the more conserva-
tive use of an AHI >10 to identify OSA in our sample, which was composed mostly of men, still showed that the frequency of OSA was nearly twice the frequency of an AHI >5 among men in the Wisconsin study.

Possible explanations for the observed association between CH and SDB include selection bias, shared genetic or biologic risk factors, shared environmental risk factors, convergence of risk factors through some common biologic mechanism, and an underlying unidirectional causal relationship. Selection bias may have had an important effect on our results. Although most subjects were identified through medical records or advertisements that did not mention sleep, snoring, or SDB, persons concerned about their sleep after an initial phone conversation with investigators may have been more willing to come to an initial appointment and to participate. To the extent that this bias did occur, however, we might also have expected to find other common sleep disorders (e.g., psychophysiologic insomnia and periodic limb movement disorder) among large proportions of our subjects, and we did not.

If a valid association between CH and SDB does exist, a third variable—genetic, biologic, or environmental—could potentially increase the risk of both conditions. CH patients, in comparison with control patients with or without other types of headaches, have been reported to have characteristic facial appearances, tall stature, and high rates of cigarette and alcohol use. Certain craniofacial features, smoking, and alcohol are all likely to be risk factors for SDB. The potential influence of unstudied third variables cannot be discounted in the current observational study, but such influence is somewhat less likely given the finding that measures of SDB severity were associated with the reported timing of CH during the first half of the night. Many potential third variables, such as facial structure, would be no more likely to trigger CH during one part of the night than any other, and other variables, such as smoking or alcohol, might be expected to exert their strongest effect during wakefulness, when exposure is maximal.

An association between SDB and CH could reflect a unidirectional causal relationship. Whereas we have no ready explanation for how CH could cause SDB, several features of SDB—including hypoxemia, hypercapnia, large swings in intrathoracic pressure, and abrupt changes in sympathetic tone—could trigger vascular changes thought to underlie CH. Few CHs during sleep were recorded in this study, and the potential influence of different SDB-related variables was therefore impossible to observe directly. We did find an independent association between extent of hypoxemia and timing of CH in the first half of the night (i.e., close to the onset of sleep and SDB, possibly with a refractory period during the second half of the night) and we therefore speculate, along with previous authors, that hypoxemia may be a key trigger of CH. Nitroglycerin-induced hypoxemia can trigger CH during active cluster periods, spontaneous oxygen desaturation may precede CH during wakefulness, and supplemental oxygen often aborts CH. A counter argument is that transient hypoxemia, induced in one study of CH patients by administration of pure nitrogen, produced a normal ventilatory response, but the hypoxemia generated was not sufficient to induce CH in any of the subjects.

We found that maximal end-tidal carbon dioxide levels, and not hypoxemia, were more extreme in subjects with active as opposed to inactive CH. Perhaps a decreased ventilatory response to hypercapnia prolongs apneic events and worsens hypoxemia. One study of patients with CH failed to demonstrate a decreased ventilatory response to a single inhaled tidal breath of 13% carbon dioxide, but the number of subjects was small and no tests were performed during sleep.

Finally, the results of this study have important implications for clinicians who see patients with CH. Although SDB was common in our sample, no subjects had received this diagnosis before they enrolled in this study. Clinicians should have a high index of suspicion for undiagnosed SDB in their patients with CH. Many CH patients with SDB do not describe excessive daytime sleepiness, but neither do most individuals in the community who have more than five apneic events per hour of sleep, and the risk for SDB can be assessed by other symptoms, signs, and tests if necessary. Identification of SDB is important because treatment may reduce associated morbidity and mortality, including comorbid CH. In the current study, treatment was not required or provided by the research protocol and few subjects chose to receive a therapy not yet proven to benefit their main complaint, which in many cases was in remission. However, two of three subjects with active CH whose SDB was treated by nasal continuous positive airway pressure at home showed moderate to complete improvement in their headaches.

References


