Sleep-Disordered Breathing as a Risk Factor for Cerebrovascular Disease

A Case-Control Study in Patients With Transient Ischemic Attacks

Nigel McArdle, MD; Renata L. Riha, MD; Marjorie Vennelle; Emma L. Coleman; Martin S. Dennis, MD; Charles P. Warlow, MD; Neil J. Douglas, MD

Background and Purpose—The evidence that obstructive sleep apnea/hypopnea (OSAH) is a risk factor for ischemic cerebrovascular disease is inconclusive. We explored this relationship in transient ischemic attack (TIA) patients because they are less likely than stroke patients to have OSAH as a consequence of cerebrovascular disease.

Methods—We performed a case-control study among 86 patients with TIA from a hospital neurovascular clinic, matched for age (±5 years) and sex with controls from the referring local family practice registers.

Results—Forty-nine of the 86 matched pairs were male and the body mass index was similar among cases and controls. Hypertension or increased fibrinogen levels (eg, by first leading to hypertension associated with a hypercoagulable state and may decrease cerebral perfusion and alter cerebral autoregulation. High rates of snoring have been reported before stroke and transient ischemic attacks (TIAs). However, OSAH and stroke have many shared risk factors, including male sex, increasing age, obesity, alcohol consumption, and smoking, and OSAH has not been proven to be an independent risk factor for or on the causal pathway to ischemic stroke (eg, by first leading to hypertension or increased fibrinogen levels).

Conclusion—OSAH does not appear to be strongly associated with TIAs. (Stroke. 2003;34:2916-2921.)

Key Words: cerebral ischemia, transient cerebrovascular disorders sleep apnea syndromes

Stroke is the second leading cause of death in the world and a major cause of disability. The vast majority of strokes are ischemic and risk factors include hypertension (which is considered the most important), cigarette smoking, diabetes mellitus, embolism from the heart, high plasma fibrinogen and cholesterol levels, increasing age, male sex, and heavy alcohol consumption. However, not all strokes can be explained by these risk factors and there is some evidence to suggest that obstructive sleep apnea and hypopneas (OSAH) may also play a part. OSAH has not only been associated with hypertension but may also be associated with a hypercoagulable state and may decrease cerebral perfusion and alter cerebral autoregulation. High rates of snoring have been reported before stroke and high rates of OSAH have been found after strokes and transient ischemic attacks (TIAs). However, OSAH and stroke have many shared risk factors, including male sex, increasing age, obesity, alcohol consumption, and smoking, and OSAH has not been proven to be an independent risk factor for or on the causal pathway to ischemic stroke (eg, by first leading to hypertension or increased fibrinogen levels). There is evidence that stroke results in pharyngeal dysfunction and OSAH. Pharyngeal dysfunction (at least in terms of video-fluoroscopic aspiration) is common after cerebral and brain stem strokes. Further, the high rate of OSAH soon after cerebral and brain stem stroke declines over a few months suggesting that acute stroke is a common cause of this irregular breathing. Hence one cannot study whether OSAH predisposes to cerebrovascular disease by examining OSAH frequency after stroke. On the other hand, patients with TIA are unlikely to have OSAH as a consequence of cerebrovascular disease, unlike patients with completed stroke and persisting neurological deficits. Only 1 relatively small study has examined the prevalence of OSAH among TIA patients (n=32) and this reported an increase in OSAH compared with a (nonindividually) matched control group (n=25). We, therefore, performed a larger study of the prevalence of OSAH among TIA patients and carefully matched community controls. We hypothesized that if OSAH is a risk factor for ischemic stroke, then it should also be a risk factor for TIA, which is, essentially, only a mild ischemic stroke defined arbitrarily as lasting <24 hours.

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Subjects and Methods
A matched case-control study recruited patients with cerebral TIA attending the neurovascular clinics at a large teaching hospital (Western General Hospital, Edinburgh) and controls from the referring family practitioners’ registers.

Recruitment of Cases
Patients were diagnosed with TIA, by a stroke physician with many years of clinical and research experience (MD), if they had acute symptoms of focal neurological dysfunction confined to the carotid or verteobasilar artery territories lasting <24 hours. Patients with transient monocular blindness were excluded, as their etiology may be somewhat different. If there was any doubt about the diagnosis, further investigations such as CT/MRI brain imaging were performed. Patients in whom a TIA mimic was possible (eg, hypoglycemia, migraine, tumor attack, or focal epilepsy) were excluded. Patients were also excluded if they had had a previous stroke (but not previous TIA).

Recruitment of Controls
In the United Kingdom each person registers with a single local family practitioner, and the resulting family practitioner registers were used by an independent (governmental) body (the Caldecott Guardian), with no access to clinical details, to obtain matched controls. This body randomly selected controls from the referring family practice matched for age (±5 years) and sex. The body first approached the family practitioner, who could exclude controls with serious/terminal illness (eg, terminal malignancy or dementia). This body then approached potential controls by post. The information sheet indicated that we needed a control group as part of an investigation into a possible association between sleep and stroke. Potential controls were told that they would need to complete a health questionnaire and undergo tests including assessment of sleep pattern and breathing during sleep. If the potential control did not respond or agree to participate, a further potential control was approached. Those with a history of a previous stroke or TIA were excluded.

Patients and controls were excluded for inability to give written informed consent (eg, language difficulties), or for serious/terminal illness. No patient or control had received treatment for OSAH.

Sleep Studies
The primary focus in our study was the apnea/hypopnea index (AIH), which is the standard measure of the severity of OSAH, and is defined as the frequency of apneas plus hypopneas (irregular breathing events) per hour of sleep. All participants underwent full overnight polysomnography in the Edinburgh Sleep Centre or in their home (6 patients and 1 control) with the Compumedics S or P (portable) system, respectively (Compumedics Ltd). In all participants we recorded a number of channels to assess the pattern of breathing (nasal/oral airflow [thermostor], chest/abdominal wall movement [inductance plethysmography], oxygen saturation), sleep stage (electro-encephalogram, electro-oculogram, chin electromyography [EMG]), and other relevant parameters (ECG and tibialis anterior EMG). All studies were scored on the same equipment by a sleep technician, blinded to case/control status, using standard criteria. Hypopneas were defined by >50% decrease in thoraco-abdominal amplitude for ≥10 seconds in the presence of continued nasal/oral airflow. Standard nocturnal oxygen desaturation indices were calculated, including the average desaturation occurring in conjunction with respiratory events, and the frequency of desaturations >4%. TIA patients were studied when stable, at least 1 month after their last TIA.

Other Data Collected
At the time of the sleep study a research nurse, blinded to case/control status, collected the following data:

Blood pressure (BP), using the appropriate cuff size, with the participant supine for >5 minutes. The average of 2 readings taken 2 minutes apart was recorded on the study evening was reported. A validated electronic blood pressure recording device was used (Omron 711, AutomaticIS, Omron-Matsusaka Ltd). Weight (kilograms) and height (meters) [body mass index (BMI)=weight/(height)^2] were recorded and a 12-lead ECG, morning fasting blood glucose, and fibrinogen taken.

A self-administered in-house questionnaire asked about vascular risk factors for TIA and symptoms of the OSAH syndrome. Daytime sleepiness was assessed using the Epworth sleepiness score (ESS), which consists of 8 questions asking about the propensity to daytime sleepiness in situations of varying sleep-inducing potential (each question scores 0 to 3, total=0 to 24). Higher ESS scores indicate greater daytime sleepiness.

Data from the questionnaire and measurements at the time of the study were also combined to assess the prevalence of the following risk factors: hypertension (defined as treatment for hypertension or measured hypertension on the study evening [at 2 cutoffs: BP >140/90 or >160/100]), diabetes (treatment for diabetes or fasting blood glucose >7.0mmol/L), and myocardial infarction (history of myocardial infarction or pathological “Q” waves on the ECG in a pattern consistent with a past myocardial infarction).

The study was approved by the Local Ethics Committee and written informed consent obtained from all subjects. Controls were offered £50 (US$70) to cover their expenses.

Statistical Analysis
Statistical analysis was undertaken using SPSS (release 10.0/Windows;SPSS). Matched comparisons were made using McNemar’s (dichotomous), paired t test (parametric), or Wilcoxon’s (nonparametric continuous) test. All tests used 2-tailed significance, with P<0.05.

Results
The study was undertaken between February 1999 and August 2001. A total of 129 consecutive eligible patients with TIA were asked to participate, of whom 94 (73%) were recruited; the remainder declined, usually because of perceived inconvenience. Decliners (23/35) completed the questionnaires by post and were older (71 years) than those who participated (66 years, P=0.02) and more often smoked but were similar on all other risk factors. Those who declined had similar rates of witnessed apneas and snoring but less daytime sleepiness (mean ESS: declined 4, participants 7, P=0.001).

Of the 94 TIA patients enrolled in the study, 87 were successfully matched with controls. Controls could not be found for the remaining 7 TIA cases after between 3 to 7 potential controls were approached for each case. One matched pair was subsequently discarded, as the control subject did not sleep at all. To obtain the final 86 controls, 158 potential controls were approached, of whom 72 declined to participate.

Data are presented on these remaining 86 (49=male) pairs.

Vascular Risk Factors
All participants were white and had a similar BMI (Table 1). Hypertension, myocardial infarction, and a history of raised cholesterol and of ever smoking were significantly more common in those with TIA (Table 1). The fibrinogen level was also significantly higher in the TIA group. Diabetes and a history of claudication were found among TIA patients about twice as often as in controls, but the overall prevalence in the study was low and the difference was not statistically significant (Table 1).

Breathing Indices During Sleep
There was no significant difference between the TIA patients and the controls in the primary outcome—the number of
apneas and hypopneas per hour slept (Table 2 and the Figure). The mean and 95% confidence interval of the difference in AHI between TIA and control was 0.3 (−4.0 to 4.7). At least mild sleep-disordered breathing (AHI ≥15)20 was present in 43 (50%) TIA and 52 (60%) control subjects. Nor was there any difference in EEG arousal frequency between the 2 groups. However, the TIA group had statistically greater nocturnal oxygen desaturation than controls, but only by 1% (Table 2). The awake saturation was also slightly lower and the 4% desaturation index higher (Table 2). Sleep efficiency (time slept/total sleep study time) was lower in the TIA group due to a decrease in stage 2 sleep (TIA 179 standard deviation [SD] 49, control 198 SD 45 minutes, \( P = 0.012 \)). No significant differences were found across the other sleep stages between the groups. OSAH symptoms of snoring, witnessed apneas, and choking were not significantly different between cases and controls. The ESS was 7 SD 4 for the TIA group and 6 SD 4 for controls \( (P = 0.3) \). The obstructive sleep apnea/hypopnea syndrome, defined as AHI ≥5 with excessive daytime sleepiness (ESS >10), was present in 10 (12%) TIA and 11 (13%) control subjects \( (P = 1.0) \). Subgroup analysis of the 79 matched pairs where both were studied in the Sleep Centre did not change the primary outcome (AHI: TIA 22.0 SD 17.3, control 20.9 SD 14.8, \( P = 0.6) \).

**Discussion**

We report the first individually matched case-control study of OSAH in TIA patients without prior stroke. There was no evidence of an increase in OSAH in TIA patients compared with community-matched controls; both groups had relatively high frequencies of irregular breathing during sleep. Furthermore, symptoms of OSAH were no more common in the TIA group. Nocturnal oxygenation was marginally lower among TIA patients, but the significance is unclear. This could represent differences in arousal thresholds to hypoxemia in TIA patients, but this will require further study. Traditional risk factors for stroke including myocardial infarction, hypertension, raised cholesterol, and cigarette smoking were significantly more common in the patients with TIA. The prevalence of diabetes in the study group was low, but there was a trend to an association with TIA. Our study strongly

<table>
<thead>
<tr>
<th>TABLE 1. Clinical Characteristics of Transient Ischemic Attack and Control Groups</th>
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<tbody>
<tr>
<td>Characteristic*</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Serum fibrinogen, g/L</td>
</tr>
<tr>
<td>Characteristic†</td>
</tr>
<tr>
<td>Cigarette consumption, pack-years</td>
</tr>
<tr>
<td>Alcohol consumption, g/wk</td>
</tr>
<tr>
<td>Characteristic‡</td>
</tr>
<tr>
<td>History of hypertension</td>
</tr>
<tr>
<td>Hypertension,§ treatment or BP &gt;140/90</td>
</tr>
<tr>
<td>Hypertension,§ treatment or BP &gt;160/100</td>
</tr>
<tr>
<td>Myocardial infarction§ history or ECG changes</td>
</tr>
<tr>
<td>Diabetes mellitus,§ treatment or fasting glucose</td>
</tr>
<tr>
<td>History of increased cholesterol</td>
</tr>
<tr>
<td>History of leg claudication</td>
</tr>
<tr>
<td>Ever smoker</td>
</tr>
</tbody>
</table>

Group comparisons by * paired t, †Wilcoxon’s, or ‡McNemar’s test.
§Denotes prevalence of disease at the time of study: hypertension (treatment for hypertension or measured hypertension, at 2 cutoffs: BP >140/90 or >160/100); myocardial infarction (history of myocardial infarction or ECG changes of past myocardial infarction); diabetes mellitus (treatment for diabetes or fasting blood glucose >7 mmol/L).
SD indicates standard deviation; IQR, interquartile range; BP, blood pressure measured on the study evening; ECG, electrocardiogram.
suggests OSAH is not a risk factor for TIA, but further studies are required to determine whether there may be an interaction in some subgroups of patients.

Previous studies looking at OSAH among patients with TIA include case reports, retrospective reviews, uncontrolled prevalence studies,17,25,26 and 1 case-control study by Bassetti and Aldrich.14 This last study found a prevalence of OSAH (defined as AHI/H11022 10) of 69% in 32 patients with TIA compared with 13% in 25 "healthy" controls. Patients with TIA had a mean AHI of 23 events/hour slept and minimum overnight saturation of 80/H1100612% compared with 5 events/hour slept and 90/H110065%, respectively, among controls. Their controls were “healthy volunteers” rather than a random community sample and were not individually matched to the patients. Although their controls were similar in age and sex to the patients, there was a trend to greater obesity in the TIA group (BMI: TIA 30, control 26 kg/m2), which would predispose them to more apneas and hypopneas. Our study sought controls from the same community environment by recruiting from the same family practitioner as the index TIA patient. Further, our study has more than twice the number of TIA participants and 3 times the number of controls. The 95% confidence interval for the difference in AHI between patients and controls in our study is narrow, indicating that the study was well powered to detect a clinically significant difference in our primary outcome variable. A power calculation27 on our data gives a power of 94% at P/H110050.05 to detect a minimal clinically significant difference in AHI between TIA and matched controls of 7.5 events/hour (based on guidelines of OSAH severity20). As part of the Sleep Heart Health Study, a cross-sectional assessment was made of the association between sleep-disordered breathing and self-reported vascular disease in the community.7 After adjustment for confounders, that study showed a weak increased risk (OR=1.58, 95% CI 1.02 to 2.46, P=0.03, parsimonious model) of self-reported stroke comparing highest to lowest AHI quartiles. However, that study cannot exclude OSAH occurring as a result of stroke and made no specific allowance for confounding due to socioeconomic factors.

Although we found a high prevalence of OSAH among community controls, our results are compatible with previous cross-sectional studies that have shown that this is not

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TIA Mean±SD</th>
<th>Control Mean±SD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apnea/hypopnea index (events/hour slept)</td>
<td>21±17.0</td>
<td>21±14.4</td>
<td>0.9</td>
</tr>
<tr>
<td>Arousal index (events/hour slept)</td>
<td>33±15.5</td>
<td>34±13</td>
<td>0.6</td>
</tr>
<tr>
<td>Total sleep time, min</td>
<td>283±75</td>
<td>305±73</td>
<td>0.04</td>
</tr>
<tr>
<td>Sleep efficiency index, %</td>
<td>62±16</td>
<td>67±15</td>
<td>0.02</td>
</tr>
<tr>
<td>Epworth sleepiness score</td>
<td>7±4</td>
<td>6±4</td>
<td>0.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TIA Median (IQR)</th>
<th>Control Median (IQR)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awake SaO2, %</td>
<td>96 (95–97)</td>
<td>97 (96–98)</td>
<td>0.03</td>
</tr>
<tr>
<td>Minimum nocturnal SaO2, %</td>
<td>89 (86–92)</td>
<td>91 (87–93)</td>
<td>0.06</td>
</tr>
<tr>
<td>Average nocturnal desaturation, %</td>
<td>3 (2–3)</td>
<td>2 (1–3)</td>
<td>0.03</td>
</tr>
<tr>
<td>&gt;4% Desaturation index, n/h</td>
<td>12 (4–36)</td>
<td>6 (1–23)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TIA No. (%)</th>
<th>Control No. (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of snoring</td>
<td>54 (63)</td>
<td>61 (73)</td>
<td>0.6</td>
</tr>
<tr>
<td>History of witnessed apneas</td>
<td>9 (10)</td>
<td>10 (12)</td>
<td>1.0</td>
</tr>
<tr>
<td>History of nocturnal choking</td>
<td>11 (13)</td>
<td>14 (17)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

SD indicates standard deviation; IQR, interquartile range; SaO2, oxygen saturation.

Plot of the apnea/hypopnea index in transient ischemic attack patient and control groups.
unusual in the healthy older population. Our hypopnea definition is the currently recommended definition, but is less conservative than used by some and so will tend to give higher AHI values than those laboratories. Ancoli-Israel, using a similar hypopnea definition, reported 62% of those aged ≥65 years had an AHI ≥10 (compared with our 60% with AHI ≥15). Duran and colleagues, using a more conservative hypopnea definition, reported that 25% of men and 16% of women aged 60 to 70 years have an AHI ≥15.

In the current study, overnight oxygenation was lower in the TIA group and this may mean that apnea/hypopnea that causes more severe hypoxemia is a separate risk factor for TIA. However, the difference in the median overnight oxygen desaturation between the 2 groups was very small (1%) and its clinical significance is unclear.

There are a number of shared risk factors for TIA and OSAH, which could confound the association between these conditions. The well-recognized shared risks were, however, matched for in the study design (age, sex) or of similar prevalence (obesity, alcohol consumption) in the TIA and control groups. Cigarette consumption was more prevalent in the TIA group, and adjusting for this would lead to an even higher estimate of OSAH among the control group. Hypertension is a strong risk factor for TIA and stroke and has been postulated to be on a causal pathway between OSAH and TIA/stroke. However, the increased prevalence of hypertension in our TIA patients must have been because of something other than OSAH, since OSAH was not associated with TIA.

Potential Selection Bias Among Cases
We did not succeed in recruiting all consecutive TIA patients. However, the patient recruitment was relatively high for such a time-consuming study, and questionnaire information suggested that the TIA participants were similar to nonparticipants on most risk factors. Those who declined were older and spending a night away from home presented a problem for some elderly patients; this was partly overcome in some who were willing to have home studies. In fact, the TIA patients who declined had fewer OSAH symptoms, and this would have prejudiced our results in favor of finding increased sleep-disordered breathing in the TIA participants, but this was not what we found. Virtually all patients presenting with a definite TIA to the neurovascular clinic during the study period were referred to our study. Although no record was kept, we estimate that <10 patients were not referred because they were overlooked or they stated they did not want to be involved in research.

Potential Selection Bias Among Controls
One weakness of the study is that 72 controls declined to participate, thus potentially biasing toward the recruitment of more symptomatic participants. However, in the recruitment process no mention was made of snoring or daytime sleepiness and no suggestion given that results of tests would be made available to the participants. The controls were approached by an intermediary body, and it was not ethically possible to pursue those who declined. However, comparisons with middle-aged and elderly community controls reported in the literature suggest that our controls had little, if any, bias to symptoms of OSAH. A survey of sleepiness in 188 members of the healthy UK population (mean age 49, SD 16 years) found that all had an ESS ≥14. Our study of older community controls (mean 66, SD 10 years) found that only 3% had an ESS >14. This is compatible with North American data in which 7% to 8% of those aged over 65 had an ESS >14. The percentage of reported snoring in our controls was 73%, compared with 63% in a control population of those aged ≥65 years. “Any” reported witnessed apneas in our study controls occurred in 12% and choking episodes at least 3 times/month in only 4% (data not shown), compared with a stricter definition of “breathing pauses 3 days/week” in 6% of a community population sample of 30- to 70-year-olds.

One of the strengths of the study is that controls were recruited from the same family practice as the cases, thus obviating socioeconomic confounders. As the study participants were all white, there should be no bias due to any higher disease prevalence from ethnic minorities. Recruitment of controls proceeded in a blinded fashion and no details apart from age and sex of the case were available to the intermediary body or the family practitioner.

Recall Bias
Recall bias may occur among patients who have recently diagnosed illness (TIA). However, we included unrelated questions (eg, about migraine) to help obscure the study hypothesis. But despite this potential recall bias, the TIA patients still did not have more sleep-related symptoms than the controls. Further, the main outcomes of the study were objective.

Mechanism of the Transient Ischemic Attack
The diagnosis of TIA used standard clinical definitions. Perhaps our TIA patients were atypical of the generality of cerebrovascular disease patients because we had to exclude those who had had a stroke before they were seen. Also, TIA is a heterogeneous condition due to several possible mechanisms and our group data may hide subgroups in whom abnormal breathing during sleep is important.

In conclusion, our study has not shown an increase in apneas and hypopneas during sleep in TIA patients.

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