Case Control Study of Cerebrovascular Damage Defined by Magnetic Resonance Imaging in Patients with OSA and Normal Matched Control Subjects

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Study Objectives: To assess whether MRI detectable evidence of silent cerebrovascular disease is more prevalent in patients with obstructive sleep apnea (OSA) when compared to carefully matched control subjects.

Design and Setting: Case-control study of patients with OSA attending a specialist sleep clinic and matched control subjects drawn from the normal community.

Participants: Forty-five sleep clinic patients with moderate to severe OSA and excessive daytime sleepiness, matched to 45 control subjects without excessive sleepiness or evidence of OSA on a sleep study. Matched variables included age, body mass index (BMI), alcohol and cigarette consumption, treated hypertension, and ischaemic heart disease.

Interventions: N/A

Measurements and Results: All subjects underwent 24-hour ambulatory blood pressure recordings (before treatment in OSA patients) and sagittal T₁, axial T₂, and coronal dual echo cerebral MRI imaging to detect clinically silent abnormalities related to hypertensive cerebrovascular disease; areas of high signal foci in deep white matter (DWM), lacunae, and periventricular hyperintensity. Lacunae/high signal foci in DWM and/or periventricular hyperintensity were present in 15 (33%) OSA subjects and 16 (35%) controls, despite significant increases in mean daytime diastolic blood pressure (4.6mmHg, p<0.05), and both nighttime diastolic (7.2mmHg, p<0.001) and systolic blood pressures (9.2mmHg, p<0.05) in OSA subjects. These data exclude more than a 17% excess prevalence of MRI detected minor cerebrovascular disease in the OSA patients, with 95% confidence.

Conclusions: Sub-clinical cerebrovascular disease is prevalent in both clinic patients with OSA and their matched control subjects. Despite the increased arterial blood pressures, there is, however, no apparent excess of MRI-evident subclinical cerebrovascular disease in patients with OSA compared to appropriately matched control subjects.

Key words: Sleep apnea; sleep apnea; stroke; cerebrovascular disease; hypertension

INTRODUCTION

OBSSTRUCTIVE SLEEP APNEA (OSA) IS CHARACTERIZED BY THE REPEATED PARTIAL OR COMPLETE INTERRUPTION OF AIRFLOW DURING SLEEP DUE TO PHARYNGEAL COLLAPSE, provoking arousals from sleep to restore pharyngeal muscle tone and airflow. In patients with severe OSA a typical night is characterized by hundreds of apneic episodes and associated arousals from sleep leading to severe sleep fragmentation and daytime sleepiness. Coincident with each sleep arousal is an associated surge in blood pressure caused by activation of the brainstem cardiovascular control mechanisms and increases in sympathetic activity. There is also an overall rise in blood pressure in OSA, particularly at night and these changes improve with effective nasal continuous positive airway pressure (nCPAP) treatment compared to control.

Despite these blood pressure changes, it is unclear how OSA relates to long-term vascular risk. The high prevalence of confounding variables such as age, obesity (and particularly upper body obesity), alcohol and cigarette consumption, obscure the role of OSA in vascular risk. Secondly, the physiology of blood pressure disturbance in OSA differs from that of essential hypertension and may be of differing prognostic importance. Well-controlled studies of end organ vascular damage are needed to clarify these important issues.

Attempts to look at the prevalence of OSA in patients following stroke have found a high frequency of sleep disordered breathing, which is associated with a poor outcome from the stroke. However, these studies are limited by the fact that the cerebrovascular incident per se is likely to alter both central and upper airway control, as evidenced by its considerable resolution some months after the acute event. Other investigators have used snoring as a marker of upper airway obstruction, and found an association between previous habitual snoring and stroke, but satisfactory conclusions are again limited by subjective information regarding upper airway obstruction and inadequate control for confounding variables.

Magnetic resonance imaging (MRI) of the brain can visualize three types of lesions related to hypertensive cerebrovascular damage and provides a tool to assess cerebrovascular damage and stroke risk. These lesions are lacunae, high signal foci in deep white matter (DWM), and periventricular white matter abnormalities. Lacunae are small, deep infarcts from penetrating arteries and stroke risk. These lesions are lacunae, high signal foci in deep white matter (DWM), and periventricular white matter abnormalities. Lacunae are small, deep infarcts from penetrating arteries and are found frequently on brain computerised tomography (CT) scans in subjects investigated for acute stroke, away from the area of acute damage. Hypertensive
small vessel disease is thought to play an important aetiologic role in the development of high signal foci and periventricular white matter lesions.30,31 The severity of these types of cerebral lesion seen on MRI is closely correlated with each other.32 An increasing number of lacunae and high signal foci in DWM on MRI appear to be associated with increasing age,32-35 increased ambulatory blood pressure,32,36 (particularly asleep blood pressure32,33), carotid atherosclerosis,37 peripheral vascular disease,37 left ventricular hypertrophy on electrocardiography33,34 impaired performance on a cognitive cube drawing test,38 and poor outcome from major depression in the elderly.39 Once these areas of ischaemic damage appear on MRI, they remain visible and act as cumulative markers of hypertensive cerebrovascular damage.

We have performed a case-control study of cerebral MRI in 45 patients with moderate or severe OSA, and compared them with 45 closely matched control subjects from the general population. Ambulatory 24-hour blood pressure recordings were performed in both populations, to explore the association of lacunae and periventricular white matter lesions, OSA and blood pressure. A more detailed description of the 24-hour blood pressure data has been published elsewhere.6

METHODS

Subjects

Patients with OSA were identified prospectively through the Oxford Regional Sleep Clinic. The clinic draws its referrals from general practice, ear nose and throat services and tertiary hospital referrals in approximately equal proportions. All patients were men aged between 30 and 80 years, with excessive daytime sleepiness and proven obstructive sleep apnea. The presence of OSA was established by a one-night sleep study recording body movement and heart rate as markers of sleep disturbance, with arterial oxygen saturation measurements (SaO2) and snoring as markers of respiratory impairment (Visi-Lab system, Stowood Scientific Instruments, Oxford, UK).40 In addition, a video recording of the whole night is available to confirm that abnormalities seen on the tracings are due to OSA. The severity of OSA was quantified from the number of >4% falls in arterial saturation per hour of study, and for entry to this trial a severity of >10 per hour of >4% falls in SaO2 was required. Excessive daytime sleepiness for this trial was defined as an Epworth Sleepiness Score (ESS) of ≥10.

Control subjects were identified from the register of a general practice in Bicester, Oxfordshire, as potential matched control subjects for the patients with OSA according to the matching criteria described below. Sleep studies were performed in the control subjects’ own homes using RM50 portable monitors (Parametric Recorders, London, UK). The RM50 records oxygen saturation from a finger probe, snoring via a throat microphone, body position via a sensor in a chest box (held on by one chest band), chest movements and heart rate (from 3 ECG electrodes). Analysis of these signals for this study provided the following derivatives:- the number of >4% falls in oxygen saturation per hour of study,41 minimum and mean oxygen saturation overnight, numbers of snores per hour of study and the number of heart rate rises per hour of study across the whole study.32,42 Control subjects were excluded when they exhibited >5 per hour of >4% falls in arterial saturation (SaO2) during the night of the recording.

Matching

Controls were matched to OSA patients by age (± 10%), BMI (± 5%), alcohol (> or <10 units/week), smoking (never versus ex/current), treated hypertension, ischaemic heart disease (documented history of angina and/or previous myocardial infarction) and diabetes. A control subject for each patient with OSA was selected by matching for all these variables. Venous blood was collected for cholesterol measurement and serum was stored at -70°C for later analysis in all patients.

Subjects in both groups were excluded if they had a previous history of stroke, or suffered from claustrophobia, exceeded the maximum allowable MRI scan weight of 127kg, or had a cardiac pacemaker, internal hearing devices or intracranial vessel clips, making MRI examination inappropriate. Patients with OSA for whom we could not identify suitable matching control subjects were also excluded from the study.

Ambulatory Blood Pressure Recordings

Twenty-four hour ambulatory blood pressure recordings were performed as an out-patient during subjects’ normal activities, and before the patients with OSA started any treatment, using a validated ambulatory recorder (TM2420, Takeda-A&D, Japan).44-46 Machines were programmed for cuff inflation and measurements every 30 minutes throughout the 24-hour period, and blood pressure was analysed (systolic and diastolic means) for the overall 24-hour period, daytime (from waking until bedtime) and nighttime (from retiring to bed until waking).

Magnetic Resonance Imaging

Cerebral MRI was performed in all 90 subjects using a superconducting magnet with field strength of 1.5T (Siemens Vision, Germany). The brain was imaged with sagittal T1 (6mm-thick slices), axial T2 (5mm-thick slices), and coronal dual echo (6mm-thick slices). Based on our previous pilot work,47 we estimated that a study of 45 patient/control pairs would be required to exclude a difference in lesion prevalence of 25% at the 5% level with 80% power.

Two experienced neuroradiologists (PA and ZCT), blinded to the clinical status of the patients, scored the MRI scans. Images were evaluated by consensus scoring, for the presence and number of lacunae and high signal foci in the deep white matter (DWM) (none, 1—5, or greater than 5), and for periventricular hyperintensity (none, minor, moderate or severe). Lacunae were defined as well-defined lesions greater than 3mm, but less than 10mm diameter, and with low intensity on T1-weighted images, but high intensity on T2-weighted and proton density images. These are typically located adjacent to the basal ganglia and thalamus. DWM lesions were defined as diffuse hyperintensities on T2-weighted images and proton density images, which were located in the white matter.

All subjects gave consent to take part in the study. Central Oxford Research Ethics Committee (number 94.086) approved the protocol for this study, and the Oxfordshire Health Services Research Committee financially supported it.

Analysis

The presence and number of lacunae/high signal foci in
DWM, and the degree of periventricular hyperintensity were compared between the OSA and control groups by chi-squared tests. Blood pressure was compared by paired t-tests. Statistical analysis was performed using the SPSS statistical software package (SPSS Software, SPSS Inc., Chicago, USA).

### RESULTS

#### Subjects

The demographics of the two groups are shown in Table 1. The severity of the sleep apnea in the patients ranged from 10.4 to 66.6 >4% SaO2 dips/hour, compared to control subjects, range 0 to 5/hour; p<0.001. The two patient groups were closely matched as intended. Three pairs had a matching history of ischaemic heart disease, and six pairs were matched for treated hypertension. Thirty-three pairs had a current or previous history of smoking and 12 pairs had never smoked. There was no difference in cholesterol levels between groups.

#### Ambulatory Blood Pressure

Compared to control subjects, OSA patients had significantly increased mean (SD) diastolic blood pressure (DBP) during both the daytime (87.4 [10.2] vs. 82.8 [9.1] mmHg, p<0.05) and nighttime (78.6 [9.3] vs. 71.4 [8.0], p<0.001), and higher systolic blood pressure (SBP) at night (119.4 [20.7] vs. 110.2 [13.9], p<0.05) (Table 1). There was an attenuated reduction in the normal nocturnal fall in systolic blood pressure, (day to night fall, 13.5mmHg vs. 21.0mmHg; p<0.005, OSA and control subjects respectively), indicating a reduction in nocturnal “dipping.”

### MRI Abnormalities

These results are displayed in Table 2. Both the patients with OSA and the matched control subjects showed frequent lacunae or high signal foci in DWM, and periventricular hyperintensity, the prevalence being 33% in patients with OSA, and 35% in control subjects. There was no significant difference in the presence or number of lacunae/high signal foci in DWM between the two groups even when subjects with known hypertension were excluded from the analysis. These results effectively exclude an excess prevalence of more than 17% in silent vascular events in the OSA sample, with 95% confidence.48

### DISCUSSION

This study reports the results of a case-control study of cerebral MRI in 45 male patients with moderate or severe OSA, compared with 45 closely matched control subjects from the general population, documenting the presence of lacunae, diffuse, and periventricular white matter lesions as markers of subclinical cerebrovascular disease. The two groups have been closely matched to control for the confounding variables likely to influence cerebrovascular morbidity, namely sex, age, obesity, smoking, alcohol, and serum cholesterol. Abnormalities on cerebral MRI were common in both groups of patients and, despite the increase in ambulatory blood pressures in OSA subjects, there was no increase in MRI evident subclinical cerebrovascular disease when compared to the control subjects.

OSA subjects presented to the sleep clinic and were identified by overnight sleep laboratory study, whereas the control subjects were identified from a GP register of community based subjects, and their absence of OSA confirmed on a home sleep study. Thus one potential criticism of this work is that because different sleep study technologies have been utilized in patients and the control

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**Table 1**—Demographic and ambulatory details of patients with OSA and control subjects

<table>
<thead>
<tr>
<th>Mean and (SD)</th>
<th>Patients with OSA (n=45)</th>
<th>Control subjects (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.7 (10.4)</td>
<td>52.2 (10.4)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>93.1 (10.1)</td>
<td>94.1 (10.3)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.74 (0.08)</td>
<td>1.75 (0.07)</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>30.9 (2.8)</td>
<td>30.5 (2.4)</td>
</tr>
<tr>
<td>Neck (cm)</td>
<td>42.8 (2.9)</td>
<td>41.9 (2.1)</td>
</tr>
<tr>
<td>Epworth Sleepiness Score</td>
<td>15.9 (3.1)</td>
<td>7.1 (3.2)</td>
</tr>
<tr>
<td>&gt;4% falls in arterial saturation (SaO2)/hour</td>
<td>29.1 (13.4)</td>
<td>1.7 (1.6)</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>6.2 (1.3)</td>
<td>6.0 (1.3)</td>
</tr>
<tr>
<td>Overall Systolic Pressure</td>
<td>128.2 (17.2)</td>
<td>123.9 (13.8)</td>
</tr>
<tr>
<td>Overall Diastolic Pressure</td>
<td>83.7 (9.5)</td>
<td>78.6 (8.8)</td>
</tr>
<tr>
<td>Daytime Systolic Pressure</td>
<td>132.9 (16.5)</td>
<td>131.2 (14.8)</td>
</tr>
<tr>
<td>Daytime Diastolic Pressure</td>
<td>87.4 (10.2)</td>
<td>82.8 (9.1)</td>
</tr>
<tr>
<td>Night-time Systolic Pressure</td>
<td>119.4 (20.7)</td>
<td>110.2 (13.9)</td>
</tr>
<tr>
<td>Night-time Diastolic Pressure</td>
<td>78.6 (9.3)</td>
<td>71.4 (8.0)</td>
</tr>
</tbody>
</table>

**Table 2**—Prevalence of MRI abnormalities in OSA subjects and the control group

<table>
<thead>
<tr>
<th>MRI abnormality</th>
<th>OSA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacunae / High signal foci deep white matter</td>
<td>12 (27%)</td>
<td>16 (35%)</td>
</tr>
<tr>
<td>Periventricular Hyperintensity</td>
<td>4 (9%)</td>
<td>3 (6.7%)</td>
</tr>
<tr>
<td>Prevalence of any abnormality</td>
<td>15 (33%)</td>
<td>16 (36%)</td>
</tr>
</tbody>
</table>
subjects, this may have blurred the distinction between the groups. For compliance reasons, we felt it was important to offer the normal subjects a sleep study at home using a reliable home monitoring system, rather than asking them to come into hospital. The Visi-Lab system we use for in-patient studies is also a reliable form of polysomnography, and if there was any doubt video recordings were always available to confirm that SaO2 abnormalities were due to obstructive events. In order to reduce any discrepancy between the systems, to actually quantify the OSA we used the >4% SaO2 dip rate which is computer-calculated using the same analysis algorithm in both systems.

In addition to these minor technical differences, there will be an inevitable further potential problem because of the considerable night-to-night variation in OSA severity, particularly in the mid-range, as well as the “first night” effect seen in laboratory sleep studies. Thus some OSA subjects, would on repeat monitoring tend to have fewer >4% falls in SaO2 overnight, and some of the controls subjects would tend to have more (examples of regression to the mean). This again might blur the distinction between the two populations. However, there are several reasons why this is unlikely to be a problem. First, they were clearly selected in different ways, clinic attenders with a history of OSA (sufficient to be referred for a specialist opinion) versus randomly chosen community subjects. Next, the patients and normal subjects had very different ESS scores that measure a perception of sleepiness over a period of time prior to study. Finally, the differences in nighttime blood pressure, measured on nights separate from the sleep study, further confirm that these are two different populations. Thus, although the two groups were studied once using different systems, the large difference in the mean number of >4% falls in SaO2 overnight, the very different ESS scores, and the different 24-hour BP profiles, clearly indicate that these are different populations.

The acute cardiovascular effects of OSA are well recognised. Each obstructive apnea and subsequent arousal is associated with an acute surge in blood pressure (often over 50mmHg), but it is not known whether these hundreds of blood pressure surges cause any significant end-organ damage. In addition to this nocturnal variability, there is evidence for an overall average elevation in nighttime blood pressure in OSA, with smaller effects during the day, which improve with nCPAP therapy. In addition, recent epidemiological studies have shown an independent association between OSA and hypertension. This study addresses the question of whether these blood pressure effects are important in producing silent cerebrovascular disease that may be a precursor of subsequent stroke. The result of this analysis of 45 patient control pairs excludes an excess prevalence of more than 17% in MRI detectable silent vascular events in the OSA sample, with 95% confidence.

It is interesting to compare the high MRI lesion prevalence in this study with that reported in normal populations. Cranial MRI has been performed in a large population-based study of cardiovascular disease of 1890 participants, aged 55 to 72 years at the time of MRI screening. Infarct-like lesions and white matter abnormalities were found in 15.3% of subjects and the prevalence of lesions increased with age, from only 7.9% in the 55—59 year-old group, to 22.9% in the 65—72 year-old group. The overall prevalence of lesions in our groups (mean age approximately 52 years) of 34% was therefore significantly greater than might have been predicted, and of similar frequency to reports on asymptomatic elderly subjects. Shimada et al. reported a 50% prevalence of silent lesions in a series of elderly patients (mean age 70 years), and Kawamoto et al. found lacunae in 41% of normotensive elderly patients. The mean age of subjects in our study was 52 years and clinical stroke is uncommon before the age of 60 years, thus it would require an extremely large trial if this was to be the outcome measure of interest. The MRI lesions seen in our study are known to be precursors of symptomatic cerebrovascular disease and there is an abnormally high prevalence in our control population when compared to the prevalence reported elsewhere in this age group. Unfortunately, from published literature it is not known whether the frequency of cerebrovascular abnormalities on MRI in our study is truly higher than expected, since no one has specifically studied subjects with the particular characteristics of patients with OSA. Our data does imply however that both patients with OSA and their matched control subjects are likely to be at high risk for later symptomatic cerebrovascular disease, and emphasizes the need for the active management of vascular risk in this population. Because the patients with OSA did not have an excess of cerebrovascular damage, these data emphasize the overall high cerebrovascular risk in patients with OSA.

Hypertension and stroke risk is associated with the MRI abnormalities described in this study. Shimada et al. showed in 73 subjects, that the number of lacunar infarcts correlated with age and with ambulatory blood pressure (ABP), particularly nocturnal systolic blood pressure, although there was no association with casual blood pressure readings. Similar studies have found that failure to reduce blood pressure at night (“non-dipping”) is a strong predictor of MRI-defined lacunae and white matter lesions, and the presence of lacunae is also associated with left ventricular hypertrophy on electrocardiography. Bots et al. also found an association between atherosclerosis, measured by ultrasonography of the common carotid arteries, and cerebral white matter lesions, and Inoue showed a relationship between increased blood pressure, microangiopathy and cerebral lesions in middle-aged diabetic patients, adding further support that asymptomatic multiple lesions are related to subclinical cerebrovascular disease. Lacunar infarcts are usually defined as lesions in the deep penetrating branch areas, whereas DWM lesions are within the subcortex. Clinico-pathological studies strongly support that both types of white matter lesions seen on MRI scans are associated with degenerative changes in arterioles that are related to atherosclerosis (arteriolosclerosis) in which hypertension may play a major role. Against this background, it is a little surprising that there was no apparent excess in our OSA subjects, despite their elevated blood pressure levels. This suggests that the pattern and causes of blood pressure disturbance in OSA may have a different significance for vascular risk from that seen in essential hypertension.

This report is the first case-controlled series of cerebral MRI in patients with OSA and carefully matched control subjects, which is sufficiently powered to cast light on the prevalence of silent cerebrovascular disease in these two populations and whether OSA is an independent predictor of these changes. One small series from Germany of 14 patients with OSA and 14 control subjects, only matched for age, found similar results, with no difference in the frequency of cerebral MRI abnormalities between the two groups.
In conclusion, we have found that subclinical cerebrovascular disease is common in both patients with OSA and carefully matched control subjects, implying that both groups may have a high risk of later stroke. This emphasizes the need for active steps to reduce overall vascular risk in these populations. Despite this overall high lesion prevalence, and a higher blood pressure in the OSA subjects, we found no apparent excess of MRI evident subclinical cerebrovascular disease in the patients with OSA when compared to the control subjects.

AKNOWLEDGMENTS

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