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Leukoaraiosis on MRI in Patients with Minimally Symptomatic Obstructive Sleep Apnoea

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Key Words
Leukoaraiosis · Obstructive sleep apnoea · Magnetic resonance imaging · Hypertension

Abstract
Background: Obstructive sleep apnoea (OSA) is associated with hypertension, nocturnal blood pressure (BP) surges, and increased risk of stroke. It may therefore also be associated with a higher risk of developing leukoaraiosis. Only few data about the prevalence of leukoaraiosis in patients with OSA, and any association between degrees of severity of either condition, exist. ***Methods:*** We studied patients who were part of a clinical trial (MOSAIC) in minimally symptomatic OSA. All patients had brain MRI (T2, FLAIR) at baseline. A single observer assessed the images for the presence and severity of leukoaraiosis (ARWMC-score). We related the extent of leukoaraiosis to the severity of OSA (measured by oxygen desaturation index [ODI]) and the presence of other vascular risk factors. ***Results:*** 183 patients (156 men, 85.2%; mean age ± SD = 57.7 ± 7.4 years; median oxygen desaturation index = 9.6, interquartile range = 4.6–16.0) took part in the study. Although 135 (74%) patients had some leukoaraiosis, this was generally mild. We confirmed the well-known risk factor associations between leukoaraiosis, increasing age ($p < 0.0001$) and hypertension ($p = 0.003$), but we did not find any association between OSA and leukoaraiosis ($p = 0.33$), despite both conditions being associated with increasing current BP and a history of hypertension. ***Conclusion:*** Our data confirm the well-known association between leukoaraiosis, age and increasing BP. However, we found no association between OSA and leukoaraiosis despite some shared risk factor associations. Our findings suggest that OSA is not a strong independent risk factor for leukoaraiosis. Confounding by hypertension may explain any apparent association in previously reported studies of patients with severer OSA.

Introduction

Leukoaraiosis or 'age-related white matter changes (ARWMC)' are commonly observed on CT or MRI brain examinations in the elderly [1]. These lesions are thought to be due to chronic ischaemia from damage to the small penetrating vessels, endothelial dysfunction, and disruption of the blood-brain barrier [1]. Hypertension and increasing age are the best established risk factors [1–3]. Clinically, leukoaraiosis is associated with

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cognitive decline, gait disturbance and increased stroke risk [1, 4, 5]. With an ageing population, the prevalence of leukoaraiosis and its consequences is set to increase. It is therefore important to identify potentially treatable risk factors to try and reduce its occurrence.

Obstructive sleep apnoea (OSA) with daytime symptoms affects 2–4% of men and 1–2% of women. Minimally symptomatic OSA (without excessive daytime sleepiness) is considerably more prevalent [6, 7]. Severe OSA is associated with the development of endothelial dysfunction, hypertension, atherosclerosis, stroke and myocardial infarction [7–10]. OSA may therefore also be a risk factor for leukoaraiosis by promoting endothelial dysfunction and the development of hypertension, which could lead to white matter changes.

Only few studies exist of the relationship between OSA and leukoaraiosis [11–14]. These were done in patients with already established cerebrovascular disease [11, 12], or in patients with severe OSA [13, 14], and results were conflicting. If there was an association between leukoaraiosis and the more common milder degrees of OSA, OSA treatment might reduce the development of leukoaraiosis in a considerable number of people, and treatment trials might be justified. We studied the prevalence and risk factor associations of leukoaraiosis in the largest cohort to date of patients with minimally symptomatic OSA and MRI of the brain.

Methods

This study is a substudy of the MOSAIC trial (Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular Trial) [15], which studied the effect of continuous positive airway pressure (CPAP) therapy in patients with minimally symptomatic sleep apnoea on sleepiness and vascular risk factors. Patients were randomised to 6 months of CPAP therapy or no intervention. Two of the study centres conducted an MRI substudy of OSA and leukoaraiosis. This was prespecified in the study protocol, and all patients from these two centres underwent MRI brain scanning in addition to the general study assessment. As our aim was to study the association of OSA and leukoaraiosis independently of any treatment, and as MRI scanning was done at baseline, prior to any study intervention, we studied all patients as a single, combined cohort, regardless of treatment allocation. These results are reported in the current paper. The trial was registered (ISRCTN 34164388) and approved by all the local ethic committees of the participating centres (REC No. 05/Q1604/159).

Participants

Patients were eligible to enter the study if they were aged 45–75 years, had no history of concerning daytime somnolence, but had newly diagnosed, proven OSA on a cardiorespiratory sleep study, performed as the routine diagnostic investigation in the participating centre. The qualifying severity was defined as an oxygen desaturation index (ODI) >7.5, i.e. patients had to have at least 7.5 dips of >4% SaO_2 per hour in their original diagnostic sleep study. We used the ODI instead of the apopnea-hypopnea index (AHI) for several reasons: first, the ODI, but not the AHI, can be obtained from home oximetry. To standardise the study ODI (which could thus be different from the entry ODI), all patients underwent a home oximetry study with a specific oximeter (Konica-Minolta, Japan). Second, the ODI is more reproducible than the AHI [16]; third, hypoxia and re-oxygenation are thought to be one of the main provokers of potential damage from OSA [7], and fourth, in epidemiological studies the ODI is a better predictor of vascular associations than the AHI [17]. The ODI therefore seemed to be the best measure to identify any association between OSA and leukoaraiosis.

Clinical Assessment

All patients underwent a detailed standardised assessment at study entry. This included height, weight, neck, waist and hip measurements. Blood pressure (BP) was monitored by home measurements (M7, Omron, Japan). These were made weekly in triplicate at the same time of day throughout the 6-month follow-up period. All patients had fasting blood tests, including cholesterol, glycosylated haemoglobin (HbA1c) and insulin levels.

MRI Scan

All patients with no contra-indications underwent brain MRI scanning (GE Sigma Twin Speed 1.5 T) at baseline and after 6 months. Sequences included axial fast spin echo T2-weighted (TR 6,160 ms, TE 105 ms, slice thickness 3 mm, matrix 384 × 256) and fast spin echo fluid-attenuated inversion recovery (FLAIR) images (TR 8,820 ms, TE 131 ms, slice thickness 3 mm, matrix 256 × 192). All scans were reviewed by an experienced observer (U.G.S.) blinded to OSA severity. In patients who were scanned twice, the 2 scans were assessed separately and at least 1 month apart. We used the ARWMC score, a well-validated score to assess the extent of white matter disease in 10 areas of the brain [18], with a maximum total score of 30. We used the ARWMC score rather than volumetric analysis, as we expected the degree of white matter changes in this cohort of relatively young individuals to be mild. While volumetric analysis may appear to offer higher precision, the relevance of minor differences between scans is uncertain, and will include some background noise. The visual semi-quantitative assessment with the ARWMC score helped to identify relevant differences between scans and offered a more robust analysis.

Statistical Analysis

Values are presented as absolute numbers, percentages, means (with standard deviation, SD) or medians (with interquartile range) as appropriate, unless otherwise stated. For the BP measurements, we calculated the mean systolic and diastolic BPs from the weekly measurements over the study period, as well as the VIM (variance independent of the mean) for the systolic BP. This is a measure of BP variability which is independent of the mean absolute BP measurement [19]. To assess the association of the severity of leukoaraiosis with clinical risk factors, we divided the ARWMC scores into quartiles. For each of the clinical variables, we performed an ANOVA for trend (continuous variables) or a χ^2 test (categorical variables) across quartiles. For variables associated at the $p < 0.05$ significance level in the univariate analysis,

Table 1. Risk factor association for leukoaraiosis, assessed by ARWMC score

	Total (n = 183)	Quartile 1 (n = 48)	Quartile 2 (n = 51)	Quartile 3 (n = 48)	Quartile 4 (n = 36)	p_{het}	p_{lin}
Male sex	156 (85.2)	41 (85.4)	42 (82.4)	42 (87.5)	31 (86.1)	0.906	0.754
Age, years	57.7±7.4	53.6±6.4	57.1±5.9	58.0±7.8	63.8±5.8	<0.0001	<0.0001
Current smoker	24 (13.1)	5 (10.4)	7 (13.7)	5 (10.4)	7 (19.4)	0.594	0.355
Diabetes mellitus	27 (14.8)	3 (6.3)	7 (13.7)	10 (20.8)	7 (19.4)	0.184	0.045
Hypertension	82 (44.8)	16 (33.3)	22 (43.1)	18 (37.5)	26 (72.2)	0.002	0.003
Height, cm	176.0±7.6	176.3±7.3	175.9±7.9	176.5±7.6	175.3±7.7	0.893	0.699
Weight, kg	97.2±16.4	93.4±15.5	97.0±16.7	100.6±13.8	98.5±20.0	0.230	0.084
BMI	31.5±4.9	30.6±5.3	31.4±5.1	32.1±3.8	32.3±5.7	0.434	0.108
Waist-hip ratio	0.968±0.057	0.954±0.062	0.956±0.055	0.981±0.054	0.988±0.049	0.007	0.001
Neck circumference, cm	42.9±3.5	42.1±3.3	42.7±3.8	43.4±3.4	43.3±3.4	0.251	0.061
ODI							
Median	9.6	12.5	8.7	7.5	12.1	0.104	0.327
Interquartile range	4.6–16.0	5.1–22.5	5.1–14.9	3.2–14.3	7.8–16.6		
SBP, mm Hg	130.2±11.7	128.1±10.9	126.2±10.8	132.4±11.9	135.2±12.7	0.002	0.001
DBP, mm Hg	80.8±7.6	81.4±8.6	78.6±7.4	81.2±6.4	82.4±7.3	0.114	0.330
VIM SBP	8.9±2.9	7.8±2.4	9.0±2.8	9.2±2.9	9.8±3.1	0.011	0.001
Total cholesterol, mmol/l	5.17±1.11	5.30±1.19	5.22±0.93	5.33±1.08	4.83±0.87	0.133	0.115
HbA_{1c}, %	5.95±0.80	5.85±0.79	5.94±0.67	6.10±1.01	5.89±0.67	0.460	0.498
Insulin level, pmol/l	94.7±60.5	84.9±49.1	98.1±60.4	91.5±54.5	107.3±79.2	0.377	0.167

Results are expressed as means ± SD or as absolute number (percentage); p_{het} = p for heterogeneity; p_{lin} = p for linear trend; SBP = systolic BP; DBP =diastolic BP; VIM = variance independent of the mean; HbA_{1c} = glycosylated haemoglobin. First quartile: ARWMC score 0; second quartile: scores 1–2; third quartile: scores 3–4; fourth quartile: score >4. To determine associations with the ARWMC-score, we used the χ^2 test for categorical variables, ANOVA for continuous variables, and the non-parametric Kruskal Wallis test and independent samples median test for the ODI. History of hypertension and of diabetes present if recorded in the family physician's medical records or patient on medication.

we performed a stepwise backward multiple logistic regression comparing the top quartile of the ARWMC score versus the other three categories combined. To assess the association of the ODI with any of the clinical risk factors, we divided the cohort into quartiles and performed an ANOVA for trend (continuous variables) or a χ^2 test (categorical variables) across quartiles. All statistical analyses were performed with SPSS version 18®.

Results

There were 238 participants in the two centres conducting the MRI substudy. Of these, 183 (156 men, mean age ± SD = 58 ± 7 years) underwent MRI scanning at baseline, while 55 patients refused scanning or had a contra-indication. The baseline characteristics of the scanned patients are given in table 1.

The analyses in this paper are based on the ARWMC score obtained from the FLAIR images, as FLAIR has the highest sensitivity for detecting white matter lesions. ARWMC scores from the FLAIR scans were slightly higher (mean ± SD = 2.4 ± 2.6) than from the T2-weighted scans (1.9 ± 2.5, $p < 0.0001$, paired t test), but highly correlated (Spearman's $\rho = 0.90$, $p < 0.0001$).

157 patients (86%) had MRI scanning at baseline and at 6 months. Readings showed no significant difference between scans, and were highly correlated (intraclass correlation coefficient = 0.92, 95% confidence interval = 0.89–0.94, $p < 0.0001$) confirming high intrarater reliability, and lack of lesion progression over 6 months. Given the absence of progression and high agreement between first and second scans, we averaged the readings where available to increase the robustness of our data. To eliminate any potential effect of CPAP treatment or time, we also performed the analysis with only the baseline scans. Results were virtually identical.

The prevalence of leukoaraiosis in this population was low, and the extent of disease mild. Forty-eight patients (26%) had no disease, 90 patients (49%) had very mild changes with an ARWMC score of 1–2, and only 36 patients (20%) had a score of >4. Imaging examples are given in figure 1. Table 1 shows the association of disease severity with baseline characteristics. Increasing

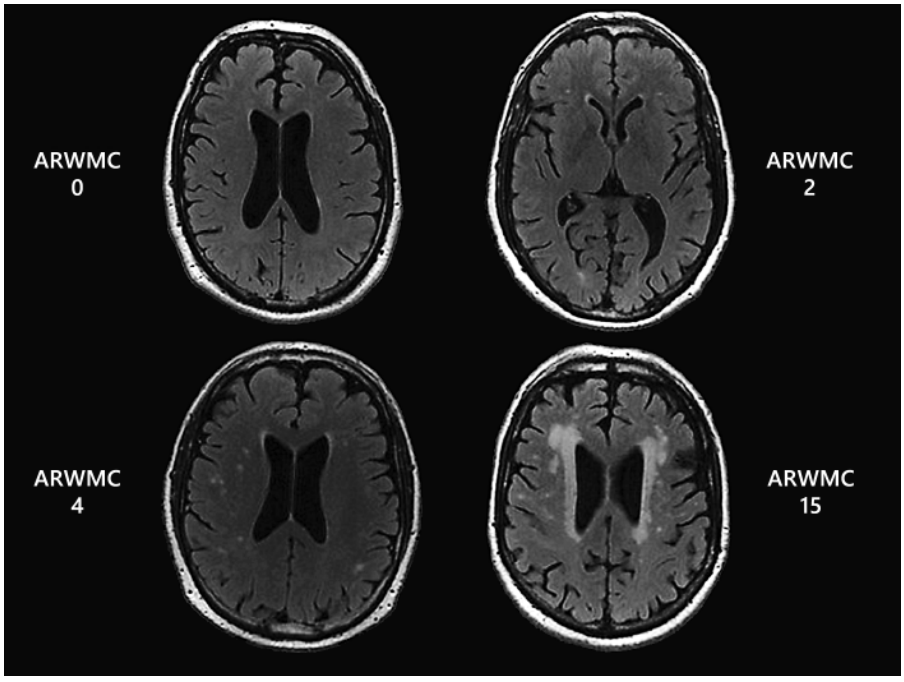

Fig. 1. Examples of FLAIR scans of study participants with different degrees of leukoaraiosis. The ARWMC score is shown next to the images, and reflects examples for each of the quartiles used in the analysis (table 1).

Table 2. Multivariate logistic regression of variables associated with ARWMC score, using a backward stepwise procedure

Characteristic	OR	95% CI	p
Age (per year)	1.16	1.08–1.24	<0.0001
History of hypertension	2.82	1.19–6.69	0.019

OR = Odds ratio; CI = confidence interval. Variables included were those showing a statistically significant association ($p_{lin} < 0.05$) in the univariate analyses: age, mean systolic BP, variance independent of the mean of the systolic BP, waist-hip ratio, history of hypertension.

severity of leukoaraiosis showed a strong association with age, history of hypertension, systolic BP, variability (VIM) of systolic BP and waist-to-hip ratio. Cholesterol levels were lower in the most severe category of leukoaraiosis. This may be explained by higher statin use in these patients (39 vs. 28% in quartiles 1–3, p = 0.34). In the multivariate logistic regression analysis (table 2), only age and history of hypertension remained significantly associated with leukoaraiosis. Patients with hypertension had a higher BMI (32.8 ± 4.9 vs. 30.5 ± 4.7, p = 0.003) and a higher waist-hip ratio (0.98 ± 0.06 vs. 0.96 ± 0.05, p = 0.007) than non-hypertensive patients.

Increasing severity of leukoaraiosis was not associated with increasingly severe OSA in any analysis. Absolute ARWMC scores and ODI showed no significant correlation (Spearman's ρ = –0.015, p = 0.85). A binary logistic regression analysis comparing the quartile of patients with the most severe disease versus all other patients combined, or versus patients with no leukoaraiosis, did not show ODI as a predictor of severe disease (odds ratio = 1.01, 95% confidence interval = 0.98–1.04, p = 0.65, and odds ratio = 0.99, 95% confidence interval = 0.96–1.03, p = 0.75). In a multivariate analysis including ARWMC score, age, systolic and diastolic BP and BMI, ODI and leukoaraiosis were not associated.

Table 3 shows risk factor associations across increasing degrees of severity of OSA. As expected, weight, BMI, waist-hip ratio and neck circumference were all associated, as were history of hypertension, systolic and diastolic BP, but systolic BP variability and age were not.

Discussion

Our study confirms the widely accepted risk factor associations for leukoaraiosis with age and hypertension. We found no independent association between leukoaraiosis and OSA, but both were associated with increasing BP and waist-hip ratio.

Table 3. Risk factor associations of OSA measured by the ODI

	Total (n = 183)	Quartile 1 (n = 48)	Quartile 2 (n = 44)	Quartile 3 (n = 46)	Quartile 4 (n = 45)	p_{het}	p_{lin}
Male sex	156 (85.2)	40 (83.3)	37 (84.1)	39 (84.8)	40 (88.9)	0.880	0.462
Age, years	57.7±7.4	55.8±6.8	57.5±7.6	59.7±7.1	57.9±7.6	0.083	0.071
Current smoker	24 (13.1)	7 (14.6)	4 (9.1)	7 (15.2)	6 (13.3)	0.826	0.929
Diabetes mellitus	27 (14.8)	6 (12.5)	7 (15.9)	7 (15.2)	7 (15.6)	0.965	0.710
Hypertension	81 (44.3)	19 (39.6)	14 (31.8)	22 (47.8)	26 (57.8)	0.080	0.034
Height, cm	176.0±7.6	178.2±8.1	175.0±7.1	175.2±8.2	175.5±6.5	0.140	0.106
Weight, kg	97.2±16.4	95.5±13.9	92.2±15.7	100.1±16.4	100.9±18.3	0.063	0.039
BMI	31.5±4.9	30.2±4.0	30.3±4.8	32.8±5.1	32.6±5.2	0.021	0.006
Waist-hip ratio	0.968±0.057	0.956±0.057	0.959±0.056	0.982±0.055	0.977±0.055	0.073	0.023
Neck circumference, cm	42.85±3.50	41.9±3.3	42.9±3.9	43.2±3.4	43.4±3.3	0.187	0.042
ARWMC score	2.3±1.1	2.7±2.3	2.5±2.3	3.1±2.7	2.9±3.5	0.779	0.500
SBP, mm Hg	130.4±11.7	128.2±10.6	127.2±12.7	134.0±13.0	131.2±10.7	0.031	0.048
DBP, mm Hg	82.1±7.6	80.4±8.3	80.7±7.9	85.0±6.5	82.5±7.0	0.014	0.034
VIM SBP	8.9±2.9	8.1±2.6	9.4±2.9	9.2±3.0	9.0±2.9	0.169	0.184
Total cholesterol, mmol/l	5.17±1.11	5.01±1.08	5.37±1.21	5.37±0.98	4.94±1.11	0.113	0.829
HbA_{1c}, %	5.95±0.80	5.98±0.83	5.82±0.53	5.99±0.92	6.01±0.89	0.668	0.662
Insulin level, pmol/l	94.7±60.5	88.4±48.7	87.4±55.9	89.0±53.4	114.4±78.1	0.095	0.049

Results are expressed as means ± SD or as absolute number (percentage); p_{het} = p for heterogeneity; p_{lin} = p for linear trend; SBP = systolic BP; DBP = diastolic BP; VIM = variance independent of the mean; HbA_{1c} = glycosylated haemoglobin. Participants were divided into quartiles according to the ODI. The median ODI (and interquartile range) in the different quartiles was: first quartile, 3.0 (1.9–3.7); second quartile, 7.4 (6.0–8.0); third quartile, 12.9 (11.4–14.7); fourth quartile, 27.0 (21.2–41.1).

In this cohort, 26% of the participants had no leukoaraiosis, and the degree of leukoaraiosis in the remainder was generally mild. This may partly have been due to the relatively young mean age of 58 years. While we had no control group, other studies offer some comparison to the prevalence of leukoaraiosis in populations without OSA. In the Rotterdam Scan Study only 5% of patients aged 60–90 years were completely free of disease [20]. This percentage was highest in the 60- to 70-year-olds, of whom 13% had no subcortical lesions and 32% had no periventricular lesions, although the authors do not comment on how many had no lesions at all. In the Cardiovascular Health Study [21], approximately 30% of participants with a mean age of 75 years had no, or only mild, leukoaraiosis. While no direct comparison is possible, the prevalence of leukoaraiosis in our cohort appears similar to these general populations of a similar age range, suggesting that OSA is not a strong risk factor for this condition.

Our study confirms the strong association of increasing age and a history of hypertension with leukoaraiosis. As others, we also found an association of leukoaraiosis with current systolic BP and its variability, and with diastolic BP, which was highest in the patients with the most severe disease [1, 22–24]. In the multivariate analysis current systolic BP was no longer associated with leukoaraiosis. This indicates that a history of hypertension is more strongly associated with leukoaraiosis than current BP (influenced of course by current treatment), and that long-standing BP changes are required for leukoaraiosis to develop. This is further supported by the lack of disease progression over the 6-month study period.

OSA and leukoaraiosis were both associated with increasing waist-hip ratio in the univariate analysis. Obesity is an important risk factor for OSA [7], and the association with waist-hip ratio was expected. However, the association of waist-hip ratio with leukoaraiosis was surprising. It was absent in the multivariate analysis, and may simply reflect a higher rate of obesity in hypertensive subjects. Alternatively, obesity may promote the release of inflammatory mediators, which induce vascular damage and may lead to leukoaraiosis [25].

OSA and leukoaraiosis were not associated with each other, although both were associated with hypertension. A possible explanation is the different temporal relationship of either condition with hypertension: whereas OSA

as an aetiological factor would precede the development of hypertension, leukoaraiosis would follow, and any effect of OSA on leukoaraiosis via hypertension would have a delay, often of many years. This is difficult to identify in a cross-sectional study. Our findings suggest that to identify any association between OSA and leukoaraiosis, long-term follow-up studies would be required. Furthermore, if any association between OSA and leukoaraiosis was due to confounding by hypertension, treatment trials of OSA could consider BP rather than leukoaraiosis as an outcome measure. Indeed, several studies have already shown that treatment of OSA with CPAP leads to a modest but significant reduction in BP [10, 26]. However, it is still unknown if this is reflected in any reduced risk of stroke or leukoaraiosis.

Previous studies of leukoaraiosis and OSA have shown conflicting results. One study of 78 stroke patients showed that sleep-disordered breathing was more common after stroke in patients with leukoaraiosis than those without [11]. Another study showed that sleep-disordered breathing was more common in multi-infarct dementia than other types of dementia [12]. As both studies included only patients with already established cerebrovascular disease, it is unclear if this caused the disordered breathing, or if the breathing disorder was pre-existing, possibly promoting cerebrovascular injury. The Cardiovascular Health Study found that patients with progressive leukoaraiosis had a higher prevalence of central, but not of obstructive sleep apnoea [27]. This study emphasises the importance of distinguishing different types of breathing disorder, and confirms our finding that OSA is not associated with leukoaraiosis. Two other small studies of patients with moderate to severe OSA had conflicting findings: whereas one study found a higher prevalence of silent brain infarction in patients than in healthy controls [14], the other did not [13].

A potential limiting factor of our study is that we used standard imaging sequences, and assessed visible white matter changes, as we felt this would provide the clinically most robust data. However, the extent of disease in our cohort was mild. Changes in normal-appearing white matter in OSA patients have been reported with other MRI methods, e.g. magnetic resonance spectroscopy [28] or diffusion tensor imaging [29]. More complex newer imaging sequences, specifically in more mildly affected patients, may form an important approach in future research of the effects of OSA on the brain.

Conclusion

We found no association between OSA and leukoaraiosis in this large patient cohort. However, we identified hypertension as a possible mechanism by which OSA could promote the development of leukoaraiosis. Confounding by hypertension may explain any apparent association in previously reported studies of patients with more severe OSA.

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