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Sleep Fragmentation, Cerebral Arteriolosclerosis, and Brain Infarct Pathology in Community-Dwelling Older People

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Abstract

Background and Purpose—While several forms of sleep disruption are associated with stroke, few studies have examined the relationship between sleep and histopathological measures of cerebrovascular disease. We tested the hypothesis that greater sleep fragmentation is associated with a higher burden of cerebral vessel and infarct pathology at autopsy.

Methods—We used ordinal logistic regression models to relate sleep fragmentation measured by actigraphy to the severity of arteriolosclerosis, atherosclerosis, and cerebral amyloid angiopathy, and the number of macroscopic and microscopic infarcts assessed by structured brain autopsy in 315 participants from the Rush Memory and Aging Project.

Results—Greater sleep fragmentation was associated with more severe arteriolosclerosis (odds ratio 1.27, 95% confidence interval 1.02–1.59, p=0.03 per 1 standard deviation greater sleep fragmentation) and more subcortical macroscopic infarcts (odds ratio 1.31, 95% confidence interval 1.01–1.68, p=0.04). These associations were independent of established cardiovascular risk factors and diseases, and a number of medical co-morbidities.

Conclusions—Sleep fragmentation is associated with arteriolosclerosis and subcortical infarcts in older adults.

Keywords

sleep; arteriolosclerosis; cerebral infarct; histopathology

INTRODUCTION

Sleep abnormalities are associated with imaging markers of cerebrovascular pathology and with clinical stroke[1, 2]. However, some cerebrovascular pathologies like arteriolosclerosis,

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DISCLOSURES

None

cerebral amyloid angiopathy, and microscopic infarcts, can only be quantified by histopathology and with few exceptions[3], their associations with sleep are unknown. This is important because these pathologies contribute not only to clinical stroke, but also to chronic progressive cognitive[4] and motor[5] impairment.

We tested the hypothesis that greater sleep fragmentation is associated with more severe arteriolosclerosis, atherosclerosis, and cerebral amyloid angiopathy and more macroscopic and microscopic pathological infarcts in older adults.

METHODS

For full details the Online Supplement

We studied 315 autopsied individuals with >=1 actigraphic recording from the Rush Memory and Aging Project, a community-based cohort study of aging with brain donation upon death.

Sleep fragmentation was assessed biennially by 10 days of ambulatory actigraphy using the metric k_{RA}[6]. As described in the Supplement, k_{RA} correlates strongly with polysomnographic measures of fragmentation including the arousal index ($R=+0.6$, $p<0.0001$) and sleep efficiency ($R=-0.6$, $p<0.0001$). The mean k_{RA} was 0.029 which at steady-state would correspond to 6.96 movement arousals per hour.

As in prior work with other risk factors[7], where an individual had >1 actigraphic measurement before autopsy, we took the average of all measurements. This best reflects the cumulative impact of sleep fragmentation, minimizing the effects of individual measurements, which could reflect acute or terminal illness. The average participant had 3 recordings.

We used an ordinal outcome of 0, 1, or >=2 infarcts to summarize the number of cortical and subcortical microscopic and macroscopic infarcts quantified histopathologically as previously described[8]. The severity of atherosclerosis, arteriolosclerosis, and amyloid angiopathy were quantified by gross and histopathological examination of the Circle of Willis and specific brain regions, and summarized using 4-point semi-quantitative scales as previously described[8, 9].

Additional actigraphic and clinical covariates were quantified as described in the Online Supplement.

We used ordinal logistic regression models to relate sleep fragmentation to the severity of each vessel pathology, or the number of subcortical or cortical infarcts, adjusting for potential confounders as described in the Online Supplement.

RESULTS

The mean age at death of the 315 participants was 90.4 years; 70% were female (Supplemental Table I). 29% had a clinical stroke. 61% of participants had >=1 moderate to severe vascular pathology.

Each 1 standard deviation (SD) higher sleep fragmentation was associated with nearly 30% higher odds of more severe arteriolosclerosis (Table 1). By contrast, sleep fragmentation was not associated with the severity of atherosclerosis or amyloid angiopathy.

Each 1 SD higher sleep fragmentation was also associated with >30% higher odds of having more subcortical macroscopic infarcts (Table 2); by contrast sleep fragmentation was not associated with cortical macroscopic infarcts (Column 2), with microscopic infarcts (Columns 3–4), or with clinically evident strokes (OR 0.95; 95% CI 0.72–1.22, p=0.69). Associations were similar for lacunar (>=1mm; OR 1.30; 95% CI 1.00–1.68) and non-lacunar (<1mm; OR 1.36; 95% CI 0.96–1.88) infarcts.

Adjusting for arteriolosclerosis attenuated the association between sleep fragmentation and subcortical infarcts by less than 5%, indicating that arteriolosclerosis does not account for this association (Supplemental Table II).

The associations between sleep fragmentation and arteriolosclerosis (Supplemental Table III) and subcortical infarcts (Supplemental Table IV) remained significant after adjusting for potential confounders including date of actigraphy and time of autopsy; total daily rest and activity; cardiovascular risk factors and diseases; and several medical co-morbidities including Alzheimer's pathology, pain, depression, and heart failure. In models adjusted for pulmonary and renal function, the associations between sleep fragmentation and arteriolosclerosis were minimally attenuated. Similarly, in models adjusted for circadian irregularity, dementia, coronary disease, and renal function, the associations with subcortical infarcts were minimally attenuated. Dementia did not modify the associations with arteriolosclerosis (p=0.29) or subcortical infarcts (p=0.86).

DISCUSSION

Our findings may be interpreted three ways: 1) One possibility is that cerebrovascular pathology causes sleep fragmentation. We previously showed that cell loss in the intermediate nucleus is associated with sleep fragmentation[10]. However, the hypothalamus and other sleep centers represent a tiny volume of the brain and hypothalamic infarction is unusual because of its rich blood supply[11]. Moreover, although individuals with clinical stroke symptoms should be the most likely to have stroke-induced sleep fragmentation, the associations were independent of clinically evident stroke. 2) Although the associations between sleep fragmentation and cerebrovascular pathology were independent of established risk factors, an unmeasured latent variable may have predisposed to both. 3) Sleep fragmentation may contribute to cerebrovascular pathology. In support of this, other forms of sleep disruption are associated with physiological risk factors for cerebrovascular pathology including diurnal and nocturnal hypertension[12, 13] and abnormal glucose processing[12], among others, which may be mechanisms linking sleep fragmentation to cerebrovascular pathology.

This study had limitations. First, it was observational, limiting determination of causality. Second, although we showed that k_{RA} correlates strongly with polysomnographic measures, and unlike polysomnography is well tolerated, does not perturb sleep, and can record over

days, it does not directly measure brain electrical activity. Third, actigraphy does not distinguish between causes of sleep fragmentation. We adjusted for several of these in our analyses, including clinical stroke, heart disease, dementia, depression, pain, and pulmonary and renal function. However, sleep apnea, which is common in stroke patients[14], was not specifically measured, nor were periodic limb movements in sleep. This is relevant given our finding that in sleep apnea patients, k_{RA} may be a marker of sleep apnea severity (Online Supplement). Fourth, while key covariates were objectively quantified, including physical activity, BMI, blood pressure, pulmonary function, and renal function, others were self-reported including heart disease, smoking, and diabetes.

Notwithstanding these limitations, these data show that greater sleep fragmentation is associated with more arteriolosclerosis and macroscopic subcortical infarct pathology. Further work is needed to clarify whether these are consequences or causes of sleep fragmentation, the role of specific contributors to sleep fragmentation (e.g. sleep apnea), and underlying biological mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Sleep Fragmentation and Vessel Pathology

	OR for More Severe Vascular Pathology (95% CI) p-value		
	Arteriolosclerosis	**Atherosclerosis**	**Amyloid Angiopathy**
Age at Death (/year)	1.04 (1.00–1.07) 0.05	1.06 (1.02–1.10) 0.001	1.03 (1.00–1.07) 0.08
Male Sex	0.53 (0.33–0.85) 0.01	1.31 (0.80–2.13) 0.28	0.65 (0.65–1.71) 0.83
Education (/year)	1.04 (0.97–1.13) 0.26	0.91 (0.84–0.98) 0.02	0.97 (0.90–1.05) 0.46
Sleep Fragmentation (/1SD)	1.27 (1.02–1.59) 0.03	1.15 (0.92–1.42) 0.22	1.10 (0.88–1.37) 0.42

Table 2

Sleep Fragmentation and Number of Infarcts

	OR for Greater Number of Infarcts (95% CI) p-value			
	Macroscopic		Microscopic	
	Subcortical	Cortical	Subcortical	Cortical
Age at Death (/year)	1.04 (1.00–1.09) 0.06	1.00 (0.95–1.06) 0.95	1.00 (0.95–1.06) 0.96	1.03 (0.98–1.08) 0.21
Male Sex	0.98 (0.54–1.75) 0.96	1.83 (0.90–3.66) 0.09	0.67 (0.29–1.42) 0.32	1.01 (0.53–1.87) 0.98
Education (/year)	0.87 (0.79–0.96) 0.01	0.98 (0.87–1.10) 0.73	0.95 (0.84–1.07) 0.41	0.98 (0.89–1.08) 0.72
Sleep Fragmentation (/1SD)	1.31 (1.01–1.68) 0.04	0.94 (0.65–1.29) 0.72	0.87 (0.58–1.22) 0.45	1.14 (0.86–1.48) 0.36