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# The Brain in Obstructive Sleep Apnea: the Chickens Coming Home to Roost?

Commentary on Kim et al. Obstructive sleep apnea as a risk factor for cerebral white matter change in a middle-aged and older general population. SLEEP 2013;36:709-715.

Garun S. Hamilton, MBBS, PhD[1,2]; Fergal J. O'Donoghue, MBBCh, PhD[3,4]

*[1]Monash Lung and Sleep, Monash Medical Centre, Clayton, Victoria, Australia; [2]Monash University, Clayton, Victoria, Australia; [3]Institute for Breathing and Sleep, Austin Health, Heidelberg, Victoria, Australia; [4]University of Melbourne, Parkville, Victoria, Australia*

Brain white matter hyperintensities (white matter disease [WMD]) seen on Proton Density, T2 weighted or FLuid Attenuated Inversion Recovery (FLAIR) MR scanning are extremely common with advancing age.[1-3] Typically they occur in periventricular areas or deep white matter (most commonly frontal, less commonly parieto-occipital, and rarely brainstem or basal ganglia). WMD is graded by the extent and confluence of these lesions. Early confluent or confluent changes tend to progress over time[3-5] and are strongly associated with development of stroke, cognitive impairment—especially executive function,[3,5-9]—and dementia.[10] The association with stroke persists even after adjustment for conventional vascular risk factors, suggesting either that WMD reflects the total effect of these risk factors better than the presence or absence of each factor alone, or alternatively that other risk factor(s) which are not conventionally recognized may play a role.[3,10] It is tempting to speculate that obstructive sleep apnea (OSA) may be such a missing risk factor. Indeed WMD has been proposed as a useful intermediate marker in the search for risk factors for stroke and dementia.[10] Pathologically these lesions correspond to areas of myelin pallor, gliosis, and tissue rarefaction with myelin and axonal loss, termed "leukoaraiosis"; they are thought to be due to small vessel ischemia.[2,3] Focal lesions tend to have a more diverse etiology[3] and have a lower propensity to progress radiologically or to clinical neurological impairment.[5,11]

OSA is known to cause many of the risk factors for both stroke and WMD.[2,10,12-14] OSA is also a known risk factor for stroke in both cross-sectional and longitudinal studies,[15-20] and is also associated with cognitive impairment,[21-24] though the literature is not uniformly positive on the latter issue, particularly in the elderly.[25-27] It has been postulated that OSA may also be a risk factor for WMD, and that the presence of WMD may indicate a population of OSA patients at particular risk of stroke and cognitive impairment, who therefore would be a potential target for intensified therapy.

Several neuroimaging studies have previously addressed these questions, with varying results. An early case control study failed to find any association between OSA and WMD.[28] Harbison et al. found in 78 acute stroke patients an independent association between WMD severity (presumed to predate the stroke) and apnea-hypopnea index.[29] Two publications from the Sleep Heart Health Study failed to demonstrate that OSA was a risk factor for incident WMD in either brainstem[30] or cerebral cortex.[31] In those studies, patients had two MR scans mean (SD) 5.0 (0.6) years apart, with a polysomnogram 3.6 (0.8) years after the first scan. Thus no truly cross-sectional (i.e., simultaneously acquired) data were available, and the timing of any incident WMD in relation to the PSG was uncertain. Only a small number of patients showed deterioration over the period of study, which may have impacted on likelihood of finding associations. However associations *were* found between arousal index and brainstem WMD progression[30] and between central apnea index and cerebral WMD progression.[31] Subsequently Eguchi et al.[32] demonstrated that nocturnal hypoxemia was an independent risk factor for silent cerebrovascular disease in a community sample (n = 146) selected for high cardiovascular risk factors. Cerebrovascular disease included both lacunae and WMD as a composite outcome. Nishibayashi and coworkers[33] found increases in presence and severity of both lacunae and WMD in moderate and severe OSA in 192 middle-aged clinic-referred patients. Most recently Kiernan et al.[34] found a high prevalence of WMD in an OSA population (n = 62) but no relationship was found with severity.

The study by Kim and colleagues[35] in this month's issue of Sleep is, therefore, the first population-based cross-sectional study to examine the association between OSA and WMD. In 503 subjects aged 40-69 in 2001 at recruitment to the Korean Genome and Epidemiology Study (KoGES), they found a significant increase in WMD across control, mild, and moderate to severe OSA groups. Furthermore they showed a significant increase in severity of OSA across groups with increasing severity of WMD. Moderate to severe OSA was associated with over twice the risk of any WMD compared to a control group with no OSA, after adjustment for relevant covariates. The study is, therefore, a significant step forward in defining an association between the two pathologies.

Nevertheless, the evidence for OSA as a causal factor in WMD in the community remains inconclusive. Despite the strengths of the work of Kim and colleagues, it is not clear how exactly the cohort who had both MR scanning and PSG were derived. It is therefore difficult to know how representative they are of the parent population of almost 11,000 who were randomly telephoned in 2001. In one respect they differed markedly, being 71% female. This may also explain the very low rates of smoking. (In 2009, 44% of Korean males and 7% of Korean females smoked daily.[36])

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Address correspondence to: Dr. Fergal O'Donoghue, Institute for Breathing and Sleep, Bowen Centre, Austin Health, Studley Road, Heidelberg, Victoria, Australia; Tel: 61 3 94963688; Fax: 61 3 94965124; E-mail: fergal.odonoghue@austin.org.au

A second issue is the question of the clinical significance of the white matter lesions they observed. Not all white matter hyperintensities carry the same prognosis.[3] It is not possible to tell whether a score of 3 represents isolated focal lesions in 3 of the 10 brain regions analyzed, or a single confluent (grade 3)[37] lesion in one area.

Lastly this study does not answer the old "chicken or egg" question, to continue the analogy of Gozal[38] and of Morrell.[39] It remains possible that WMD is the cause rather than the consequence of OSA (i.e., the egg rather than the chicken). The independent association of moderate to severe OSA with presence of WMD after controlling for covariates tends to favor the chicken,[35] but this remains an association, and no comparable analysis in search of evidence to favor the egg was reported.

Replication of the findings of Kim et al.[35] is now needed, and they are in an ideal position to further investigate the links between OSA and WMD longitudinally in future. Certainly there is a need for further longitudinal data, to determine the influence of OSA on incident WMD and subsequent clinical sequelae, and also the effects of treatment. An Australian population-based study, Snore-ASA (Australian Clinical Trials Registry Number ACTRN12612000891820) is also currently investigating this issue, as well as the influence of aspirin on cognitive decline and WMD progression in OSA and non-OSA populations. Given the high prevalence of stroke, cognitive decline, and OSA in the swelling ranks of the elderly, delineating the potential role of OSA as a modifiable risk factor for WMD and cognitive impairment is of paramount importance. Kim and colleagues have taken an important step in that direction, but much remains to be done.

## CITATION

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## DISCLOSURE STATEMENT

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## REFERENCES

1. Grueter BE, Schulz UG. Age-related cerebral white matter disease (leukoaraiosis): a review. Postgrad Med J 2012;88:79-87.
2. Pantoni L, Garcia JH. Pathogenesis of leukoaraiosis: a review. Stroke 1997;28:652-9.
3. Schmidt R, Grazer A, Enzinger C, et al. MRI-detected white matter lesions: do they really matter? J Neural Transm 2011;118:673-81.
4. Fazekas F, Kleinert R, Offenbacher H, et al. Pathologic correlates of incidental MRI white matter signal hyperintensities. Neurology 1993;43:1683-9.
5. Garde E, Lykke Mortensen E, Rostrup E, Paulson OB. Decline in intelligence is associated with progression in white matter hyperintensity volume. J Neurol Neurosurg Psychiatry 2005;76:1289-91.
6. Vermeer SE, Den Heijer T, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM. Incidence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. Stroke 2003;34:392-6.
7. Breteler MM, van Amerongen NM, van Swieten JC, et al. Cognitive correlates of ventricular enlargement and cerebral white matter lesions on magnetic resonance imaging. The Rotterdam Study. Stroke 1994;25:1109-15.
8. Longstreth WT Jr, Manolio TA, Arnold A, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. Stroke 1996;27:1274-82.
9. Black S, Gao F, Bilbao J. Understanding white matter disease: imaging-pathological correlations in vascular cognitive impairment. Stroke 2009;40(3 Suppl):S48-52.
10. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ 2010;341:c3666.
11. Schmidt R, Enzinger C, Ropele S, Schmidt H, Fazekas F. Progression of cerebral white matter lesions: 6-year results of the Austrian Stroke Prevention Study. Lancet 2003;361:2046-8.
12. Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. Lancet 2009;373:82-93.
13. Li Y, Veasey SC. Neurobiology and neuropathophysiology of obstructive sleep apnea. Neuromolecular Med 2012;14:168-79.
14. Ovbiagele B, Saver JL. Cerebral white matter hyperintensities on MRI: Current concepts and therapeutic implications. Cerebrovasc Dis 2006;22:83-90.
15. Arzt M, Young T, Finn L, Skatrud JB, Bradley TD. Association of sleep-disordered breathing and the occurrence of stroke. Am J Respir Crit Care Med 2005;172:1447-51.
16. Martinez-Garcia MA, Campos-Rodriguez F, Soler-Cataluna JJ, Catalan-Serra P, Roman-Sanchez P, Montserrat JM. Increased incidence of non-fatal cardiovascular events in stroke patients with sleep apnoea: effect of CPAP treatment. Eur Respir J 2012;39:906-12.
17. Martinez-Garcia MA, Campos-Rodriguez F, Catalan-Serra P, et al. Cardiovascular mortality in obstructive sleep apnea in the elderly: role of long-term continuous positive airway pressure treatment: a prospective observational study. Am J Respir Crit Care Med 2012;186:909-16.
18. Redline S, Yenokyan G, Gottlieb DJ, et al. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. Am J Respir Crit Care Med 2010;182:269-77.
19. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med 2005;353:2034-41.
20. Munoz R, Duran-Cantolla J, Martinez-Vila E, et al. Severe sleep apnea and risk of ischemic stroke in the elderly. Stroke 2006;37:2317-21.
21. Yaffe K, Laffan AM, Harrison SL, et al. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. JAMA 2011;306:613-9.
22. Sforza E, Roche F. Sleep apnea syndrome and cognition. Front Neurol 2012;3:87.
23. Aloia MS, Arnedt JT, Davis JD, Riggs RL, Byrd D. Neuropsychological sequelae of obstructive sleep apnea-hypopnea syndrome: a critical review. J Int Neuropsychol Soc 2004;10:772-85.
24. Cooke JR, Ayalon L, Palmer BW, et al. Sustained use of CPAP slows deterioration of cognition, sleep, and mood in patients with Alzheimer's disease and obstructive sleep apnea: a preliminary study. J Clin Sleep Med 2009;5:305-9.
25. Boland LL, Shahar E, Iber C, Knopman DS, Kuo TF, Nieto FJ. Measures of cognitive function in persons with varying degrees of sleep-disordered breathing: the Sleep Heart Health Study. J Sleep Res 2002;11:265-72.
26. Sforza E, Roche F, Thomas-Anterion C, et al. Cognitive function and sleep related breathing disorders in a healthy elderly population: the SYNAPSE study. Sleep 2010;33:515-21.
27. Quan SF, Chan CS, Dement WC, et al. The association between obstructive sleep apnea and neurocognitive performance--the Apnea Positive Pressure Long-term Efficacy Study (APPLES). Sleep 2011;34:303-14B.
28. Davies CW, Crosby JH, Mullins RL, et al. Case control study of cerebrovascular damage defined by magnetic resonance imaging in patients with OSA and normal matched control subjects. Sleep 2001;24:715-20.
29. Harbison J, Gibson GJ, Birchall D, Zammit-Maempel I, Ford GA. White matter disease and sleep-disordered breathing after acute stroke. Neurology 2003;61:959-63.
30. Ding J, Nieto FJ, Beauchamp NJ Jr, et al. Sleep-disordered breathing and white matter disease in the brainstem in older adults. Sleep 2004;27:474-9.
31. Robbins J, Redline S, Ervin A, Walsleben JA, Ding J, Nieto FJ. Associations of sleep-disordered breathing and cerebral changes on MRI. J Clin Sleep Med 2005;1:159-65.

32. Eguchi K, Kario K, Hoshide S, Ishikawa J, Morinari M, Shimada K. Nocturnal hypoxia is associated with silent cerebrovascular disease in a high-risk Japanese community-dwelling population. Am J Hypertens 2005;18:1489-95.
33. Nishibayashi M, Miyamoto M, Miyamoto T, Suzuki K, Hirata K. Correlation between severity of obstructive sleep apnea and prevalence of silent cerebrovascular lesions. J Clin Sleep Med 2008;4:242-7.
34. Kiernan TE, Capampangan DJ, Hickey MG, Pearce LA, Aguilar MI. Sleep apnea and white matter disease in hypertensive patients: a case series. Neurologist 2011;17:289-91.
35. Kim H, Yun CH, Thomas RJ, et al. Obstructive sleep apnea as a risk factor for cerebral white matter change in a middle-aged and older general population. Sleep 2013;36:709-15.
36. OECD Health at a Glance 2011 Tobacco consumption among adults. http://dx.doi.org/10.1787/888932523899 OECD. Accessed April 12th 2013
37. Wahlund LO, Barkhof F, Fazekas F, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke 2001;32:1318-22.
38. Gozal D. The brain in sleep-disordered breathing: is it the chicken or is it the egg? Am J Respir Crit Care Med 2002;166:1305-6.
39. Morrell MJ, Glasser M. The brain in sleep-disordered breathing: a vote for the chicken? Am J Respir Crit Care Med 2011;183:1292-4.