Obstructive Sleep Apnea and its Association with Stroke: A Brief Review

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Abstract

Obstructive sleep apnea (OSA) has been associated with many of the known risk factors for stroke including hypertension, diabetes and atrial fibrillation. There is also a large body of literature that suggests that OSA and stroke are independently associated. In this review, we will discuss the literature supporting OSA not only a risk factor for stroke, but also show how untreated OSA has been associated with worse outcomes in those who suffer from stroke and OSA.

Keywords: Obstructive sleep apnea; Sleep disordered breathing; Stroke

Sleep Disordered Breathing (SDB) Described In Patients Who Have Had Stroke

SDB encompasses both central sleep apnea (CSA) and obstructive sleep apnea (OSA). Both have been described in stroke, though OSA is more prevalent and seems to have more impact on stroke outcomes. The prevalence of SDB is higher among stroke patients than the average population. A meta-analysis found the prevalence of SDB to be 63% in patients with stroke or transient ischemic attack (TIA) [9,10]. One of the first observational studies did not define as AHI>10. Patients with recurrent strokes had a higher percentage of SDB than initial strokes (74% compared to 57% p = 0.013). Only 7% of patients had predominantly central sleep apnea (CSA) with the majority being obstructive [1]. Central apneas appear to be more common acutely after a stroke and then decrease by three months [2].

While there is a growing body of evidence that OSA is associated with an increased risk for stroke, some sleep disordered breathing might also occur secondary to stroke. The brain stem is responsible for control of breathing. Case reports exist of both OSA and CSA after lesions to this area [3-6]. A particular lesion site has not been associated with SDB in prospective studies. However, among stroke patients, those with SDB have more bulbar weakness than those without SDB [7]. A recent cross-sectional study found that there was an increased prevalence of hypoglossal nerve dysfunction in patients with acute ischemic stroke. They were unable to show that the hypoglossal dysfunction was associated with more severe SDB [8]. Even though both CSA and OSA can be described in stroke, OSA is more commonly seen and is thought to have a strong association with risk for stroke as well as increased morbidity and mortality in those who have suffered from stroke.

Is OSA a risk factor for stroke?

Large cross-sectional studies have shown associations between OSA and prevalent stroke with a dose response relationship according to severity of AHI [9,10]. One of the first observational studies did not show a significant risk of stroke in those with AHI >=20 after adjustment for confounding risk factors. However subsequently, numerous large scale observational cohorts have supported a robust association of presence of OSA and incident stroke [11-15]. The Busselton Sleep Cohort is the longest published cohort to date. In this 20 year prospective cohort, 393 patients who had no history of prior stroke were prospectively followed. Moderate to severe OSA was found to have a hazard ratio of 3.7 (1.2, 11.8) for incident stroke when controlled for age, gender, obesity, smoking status, cholesterol, hypertension, diabetes, angina, and a history of cardiovascular disease [15]. There have been two recent meta-analysis conducted on prospective studies looking at OSA as risk factor for stroke. Dong et al. [16] looked at 10 prospective cohort studies and found that the relative risk for stroke in those with moderate-severe OSA compared to the controls was 2.02 (1.40-2.90). Li et al. [17] looked at 11 prospective cohorts and found the relative risk was 2.06 (95% CI 1.53-2.79).

Until recently, the effects of OSA and its treatment on cardiovascular outcomes in women was unknown. The Sleep Heart Health Study followed 5,422 subjects with untreated OSA with no prior history of stroke for a median of 8.7 years. They showed a positive association of OSA and incident stroke in men with a linear trend (p=0.016). Those in the highest quartile (obstructive AHI of >19) had an adjusted HR of 2.86 (1.10-7.39) [12]. In women, however, incident stroke was not associated with obstructive AHI quartiles. They did find, that an obstructive AHI>25 in women was associated with an increased risk for incident stroke. A recent publication followed 967 women specifically for a median of 6.8 years. The control group consisted of those with an AHI<10 and those with an AHI ≥ 10 were diagnosed with OSA and classified as either CPAP-treated (adherence ≥ 4 hours/day) or untreated (adherence<4 hours/day or not prescribed). Untreated OSA showed a strong association with incident stroke (adjusted HR 6.44, 95% CI 1.46-28.3). CPAP use appeared to reduce this risk as the CPAP-treated group showed now association with incident stroke (adjusted HR 2.76, 95% CI 3.5-5.62) [18].

Does the presence of OSA affect stroke outcome?

In addition to the growing support for OSA as a causal factor for stroke, there is growing evidence that co-morbid OSA may affect stroke outcomes. The literature suggests that those who have stroke...
and untreated OSA have higher morbidity and mortality compared to those without OSA. Higher desaturation indices post stroke have been associated with lower functional scores on the Barthel index and higher mortality at one year [19]. This suggests that OSA may play a role with those outcomes. Other studies have found increased mortality at one and 6 months in those with acute stroke and OSA [20,21]. Turkington et al. [21] found severity of OSA was independently associated with death with an OR of 1.07 (95% CI 1.03-1.12) as well as the length of the respiratory events, with respiratory events of 15 seconds having the most impact [21]. Parra et al. [22] looked at two year survival in a prospective study of 161 subjects with first ever stroke or TIA and found that the AHI was an independent risk factor for mortality [22]. Similarly, Dyken et al. [23] found in a prospective study those with stroke had higher incidence of OSA and at 4 years, the patients who had stroke and died all had OSA. Sahlin et al. [24] took a more long term look at mortality in 132 patients with stroke and OSA (defined as AHI of >=15) over 10 years. OSA was found to be an independent risk factor for death after adjusting for other confounding factors such as age, sex, BMI, smoking, hypertension, diabetes, and atrial fibrillation as well as Barthel index of daily living.

OSA has also been associated with other post stroke outcomes such as length of stay, worse functional outcomes, and recurrent cerebrovascular events. Kaneko et al. [25] looked prospectively at 61 patients with acute stroke admitted to the rehabilitation unit. Sleep studies were conducted on all patients and it was found that those with OSA (defined as AHI of >=10), had lower functional ability despite similar stroke severity as well as longer stay in the hospital and the rehabilitation center. Rola et al. [26] looked at 91 patients with stroke or TIA and SDB (defined as an AHI of >=5). It was found that presence of SDB was associated with higher risk of recurrent cerebrovascular events but interestingly, not mortality or functional outcome at 2 years [26]. The SDB group was mostly obstructive but those with central sleep apnea were included as well. Perhaps including patients with CSA and very mild OSA contributed to the lack of significant difference for mortality and functional outcome.

**Does treatment of OSA affect stroke outcomes?**

The gold standard treatment of OSA is continuous positive airway pressure (CPAP). The literature suggests that presence of OSA is associated with increased morbidity and mortality in those with stroke. One should then ask, "Does treating OSA improve these outcomes?" Both observational and randomized trials have addressed this. Observational trials suggest that CPAP treatment does improve mortality and decreases rate of recurrent vascular events in those with stroke and OSA compared to those stroke patients with untreated or sub optimally treated OSA. Martinez-Garcia et al. [27] looked at 166 patients and found that those with ischemic stroke and OSA (AHI>=20) intolerant of CPAP had higher mortality after adjusting for confounding factors compared to those with OSA who tolerated CPAP (HR 1.58; 95% CI 1.01-2.49) [27]. The same group also looked at risk of recurrent vascular events. They found that at 18 months, those intolerant of CPAP had 5 fold increase risk of new vascular events (odd ratio 5.09) after adjusting for other risk factors [28]. Similarly, at 7 years, they found that those who did not tolerate CPAP had increased risk of new vascular events, particularly ischemic stroke, compared to those who tolerated CPAP [29].

Randomized controlled trials have suggested benefits of CPAP use in those with ischemic stroke and OSA in terms of functional recovery in the short term but not as robust for long term function. The same holds true for mortality and recurrent vascular events. It is important to note, though, that the randomized trials have smaller number of subjects with shorter follow up compared to observational trials mentioned above. Minnerup et al. [30] looked at CPAP use the first 7 nights after stroke onset in 25 patients. The study randomized patients to CPAP or a control group and found a trend to improved stroke scores in those on CPAP that reached statistical significance in those with good CPAP use [30]. Ryan et al. [31] conducted a 4 week randomized study addressing the effects of CPAP on functional outcomes in stroke patients. They showed the patients randomized to CPAP had improved scores on stroke impairment testing and motor components on functional testing compared to those not on CPAP [31]. Bravata et al. [32] found CPAP to be beneficial to reduce recurrent vascular events in both TIA and stroke patients with OSA. They randomized 70 patients with transient ischemic attack (TIA) to treatment with auto CPAP or standard of care. Those with OSA and no CPAP use had higher incidence of vascular events at 90 days [32]. The same group found that stroke patients with OSA on CPAP had greater improvement in stroke severity as measured by the National institute of health stroke scale (NIHSS) at 30 days compared to those without CPAP [33]. These studies, while showing benefit for functional recovery and recurrent vascular events, have been short term with longest study being 3 months long. Parra et al. [34] looked at short and long term recovery in those with stroke and OSA. Patients with ischemic stroke and OSA (AHI>=20) were randomized to CPAP vs conventional treatment. They found neurological function was improved in the CPAP group at one month compared to control group but not at two years [34]. Survival was not statistically different between the two groups but time to next cardiovascular event was longer in the CPAP group. Overall, randomized trials suggest that there is some improvement in function and recurrent events after suffering from TIA/stroke in those with treated OSA compared to untreated OSA in the short term setting but long term benefit is not well described.

**Conclusion**

The current literature supporting OSA as an independent risk factor for stroke as well as poorer outcomes in those with recent stroke is quite strong. Observational data show a strong benefit of CPAP for recurrent vascular events and mortality that seems compelling but has not been described in randomized controlled data so far. Randomized studies demonstrate CPAP intervention seems to have some short term benefit on functional recovery and recurrent vascular events but long term data supporting this is lacking. The shorter duration of the randomized trials and number of subjects may play a role in the discrepancy between their results and those of observational trials. From the literature as it stands so far, it is important to screen patients with stroke for OSA and treat them appropriately as not treating them may cause the patient to incur further morbidity and mortality. However, there is recognition that large, long term, randomized trials would be helpful to further delineate the benefit of CPAP on stroke outcomes.

**References**