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Obstructive Sleep Apnea, Apolipoprotein E e4, and Mild Cognitive Impairment

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Memory complaints within the context of obstructive sleep apnea (OSA) are common. Neuropsychological studies have previously documented reduced performance on tests sensitive to executive function and vigilance (1-4), memory (5-7), and other cognitive skills (8) in patients with OSA. Similar cognitive deficits in patients with traumatic brain injury are worse when there is concurrent OSA (9). Impaired vigilance may have consequences. For example, patients with OSA may be at greater risk for motor vehicle accidents possibly reflecting impaired attention skills or falling asleep while driving (10). Treatment with continuous positive airway pressure (CPAP) (1,4,6,7) and medication (11) partially reverse some of the cognitive changes, and CPAP appears to do so in a dose-related manner (7).

The e4 allele of apolipoprotein E (APOE) is a major risk factor for Alzheimer's disease (AD) that generally begins with memory loss and increases in incidence and prevalence exponentially with advancing age (12). APOE e4 carriers have abnormal metabolic patterns that topographically overlap AD-susceptible brain regions prior to the development of memory loss (13), and age-related memory decline is accelerated in late middle age APOE e4 carriers, even in the absence of symptomatic memory impairment (14). Further, in late middle age APOE e4 carriers memory and executive skills decline respectively in the face of fatigue (15) and anxiety (16) more than their matched e4 noncarrier counterparts, suggesting that APOE e4 carrier status results in reduced ability to cognitively withstand physical or emotional stress. While prevalence varies between populations globally, roughly 20% of North Americans and Europeans are APOE e4 carriers, so it is a common allele (17). APOE e4 has been associated with OSA in adults (18) and children (19), especially in the setting of cognitive problems (19).

The relationship between OSA and APOE e4 mediated cognitive decline is therefore a timely issue concerning not only Sleep Medicine, but Behavioral Neurology, Geropsychiatry, and Gerontology as well; in this regard, the study of Cosentino and colleagues (20) is an important addition to the growing body of evidence that OSA is itself detrimental for cognition, especially among those at greater risk for AD due to their APOE e4 carrier status. Memory loss, especially in anyone over the age of 60 years, invariably raises concern about possible AD. AD is a progressive neurodegenerative dementia for which there is no effective cure or disease modifying therapy. Even the impact of symptomatic therapy is modest at best. Diagnostic evaluation is generally aimed at disclosing potentially reversible etiologies of the dementia syndrome, and while textbooks and review articles appropriately list metabolic, infectious, structural, and other causes, few mention OSA. In part this makes sense since OSA does not cause dementia. Unfortunately, this is also misleading because many patients who ultimately

prove to have AD present at an early stage of disease, termed “Mild Cognitive Impairment” (MCI).

MCI was originally conceived as a relatively circumscribed amnesic syndrome, bad enough to cause symptoms and impair psychometric performance, but not bad enough to cause any functional disability (21). The definition of MCI has since been revised to include essentially any pattern of cognitive impairment that is not severe enough to cause functional disability. The “conversion rate” to dementia of patients originally presenting with MCI is roughly 15% per year (21), so MCI itself raises fear of future dementia even though not all patients ultimately prove to have AD. While OSA does not cause dementia, it could be considered to cause the syndrome of MCI. Cosentino and colleagues have once again demonstrated that OSA is itself detrimental for memory and frontally mediated executive tasks, and that APOE e4 may have a further detrimental effect in the setting of OSA (20). Such findings could qualify as MCI in at least some of these patients. OSA is potentially reversible with treatment, and so deserves to be considered in patients with MCI.

A strength of Cosentino et al’s study is that it includes a relatively large number of polysomnographically confirmed OSA patients, although the numbers are probably not high enough to reliably determine the relative APOE allele frequency differences between OSA patients and controls if they indeed exist as previous research has suggested (18). In their substudies of APOE e4 carriers and matched noncarriers with and without OSA, their numbers reduce to levels that lack sufficient power to show potential differences in memory scores, yet disclose a difference on the Corsi spatial span test not found in the larger sample. This suggests the possibility that the Corsi difference may be driven by a subset of individuals with exceptionally lower scores, and it would be of interest to determine whether there were other notable characteristics of these individuals such as more severe OSA, or other comorbid problems. The authors note the higher prevalence of obesity, diabetes and cigarette smoking in the OSA group, and certainly the effects of cerebrovascular disease, for example, must be considered.

Whether OSA is itself sufficient to produce MCI is simply a marker of a vulnerable patient due to the entire “package” of daytime somnolence, disordered sleep, subclinical (or clinical) cerebrovascular and cardiovascular disease, psychoactive medication (for comorbid depression and anxiety [22]); unmasking early AD in genetically susceptible patients remains uncertain. For now, however, it is important to recognize the association between OSA and cognitive impairment so that patients with MCI undergo appropriate screening (and treatment) for OSA and to address the cognitive and psychological issues that adversely affect the quality of life in patients with OSA.

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