



Dementia and the Brain-Breathing Connection

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The Burden of Dementia

Alzheimer's disease and other dementias is a scourge upon the world. In the U.S. alone, Alzheimer's (AD) affects 5 million people. When considering that AD is only one of several important dementias and that dementia is vastly underdiagnosed, the actual numbers are likely twice as high. When you then add in those with pre-clinical dementia or Mild Cognitive Impairment, a total exceeding 15 million Americans is not out of the question.

Dementia is a growth industry. As the population ages and as the Baby Boomers and Generation X individuals reach prime dementia age over 70, these numbers will mushroom. The economic burden on society, through the cost of the disease, associated medical problems, caregiving costs and lost productivity is astounding. But you already know this. It is part of every talk at every conference about dementia that you attend and part of the fundraising and consciousness raising efforts of the Alzheimer's Association.

Past Efforts at Etiology and Treatment

Many potential causes of dementia have been considered, including beta amyloid aggregation, hyperphosphorylated tau proteins, disrupted microtubules, acetylcholine deficiency, glutamate excitotoxicity, glial cell abnormalities, BACE 1, gamma secretase, astrocyte damage and potentially dormant infections acquired in early life that are triggered by aging. But, the treatments to date are limited to three cholinesterase inhibitors and an NMDA receptor agonist (Memantine) which, while clearly beneficial, does not alter disease progression.

No new dementia treatments have emerged successfully from phase 3 clinical trials in this century. Those companies who have invested millions of dollars in monoclonal antibody treatments (bapineuzumab and solanezumab, etc.) have discovered that clearing amyloid does not improve cognition in people, as it had in mice. The current hope is that these agents might prove to be effective if introduced at an earlier, preclinical stage.

A New Thought

But what if a major reason for these drug trial failures has been right under our noses this entire time, literally, in the form of the air that we breathe or fail to breathe, particularly while we sleep? What if hypoxia, due to obstructive sleep apnea (OSA) or sleep disordered breathing (SLB), is the missing piece in this puzzle?

First, why should this piece be missing? After all, many much brighter and better-educated people than we have spent their careers and millions of research dollars searching unsuccessfully for the elusive answer. But what if they were limited not by their intelligence, experience or financial support, but by their perspective? Maybe they are the dementia equivalent of the blind men and the elephant. In this tale, a band of blind men encounter an elephant and each, because of his visual limitation, incorrectly believes that the elephant resembles a snake, a tree trunk, a palm frond or a mountain. In the world of dementia, maybe our specialization and theoretical isolation have blinded us to seeing a larger picture. Notably, no phase 3 drug study has even tested for hypoxia, let alone used it as a potential moderator variable between groups. While many dementia drugs have worked

in mice, the mouse model of AD cannot take hypoxia, as it exists in humans, into account. Mice who are heterozygous for HIF1A do not respond to hypoxia as humans do and those who are entirely deficient for HIF1A do not survive.

Linking Oxygen Deprivation and Cognitive Change

Our review of the literature shows that there have been both animal and human models linking oxygen deprivation with cerebral amyloidogenesis and tau hyper-phosphorylation, two primary features of AD. In clinical practice, we have known for years that hypoxic injury causes memory failure in patients with COPD, CHF and CVA, as well as those who survive electrocution, choking, drowning, and other respiration-interrupting traumas. But it was not until the early 1980's that we find serious scientific thought connecting breathing deficits and cognition, typified by a small study by Reynolds et al. [1] which reported a nearly a 10-fold greater prevalence of OSA in their Alzheimer's subjects in comparison to matched controls.

It was then another 20 years before Ancoli-Israel et al. [2] demonstrated improvements in cognition related to even brief CPAP treatment of OSA. At around the same time, Yaffee et al. [3] showed significantly higher levels of cognitive decline in older women with OSA.

Our Experience

In our practice, we began to look at the brain-breathing association 10 years ago. We found extremely high rates of hypoxia and obstructive sleep apnea in patients presenting for evaluation of cognitive problems. In one series of more than 600 consecutive patients, the prevalence of either condition exceeded 60% [4]. In a subsequent case study [5], a 57 year old Army veteran diagnosed with AD on the basis of PET scan hypo-perfusion and impaired neuropsychological function improved to a normal PET scan perfusion and intact neuropsychological test scores following an OSA diagnosis and adherent CPAP treatment. Despite his initial findings, CPAP had apparently reversed his AD. This is consistent with the findings of Zimmerman et al. [6], relating degree of CPAP adherence to improvement in verbal memory of impaired patients.

Recent Evidence of Brain-Breathing Relationships

Much more recently, Osorio et al. [7] demonstrated an earlier age of cognitive decline in those with sleep disordered breathing. A meta-analysis of 19 studies [8] revealed significant negative relationships between OSA

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and neuropsychological scores for attention, verbal memory, nonverbal memory, working memory, concept formation, executive function, verbal reasoning, perception, processing speed, and construction ability. Another very recent report of 750 patients by Bubu [9] found that moderate to severe OSA doubled the risk of AD a decade later.

Oxygen as a Target and a Treatment

Oxygen saturation represents not only a potential cause for cognitive loss and dementia, but also a target for intervention that may prevent decline in preclinical cases and an intervention for currently demented patients. In our practice, we investigated the cognitive outcomes of 300 dementia outpatients in which hypoxia and OSA were assessed and treated (enhanced treatment group) and compared them with a demographically similar group of 225 (standard care) in which oxygen status was not assessed [10]. The majority of patients in both groups took dementia medications and at similar levels. We found a statistically higher level of cognition in the enhanced treatment group vs. the standard care group at six months into treatment and persisting for two years.

Next Steps

Based on these converging findings, from a variety of researchers and clinicians, we propose that clinicians and researchers use hypoxia and OSA as a variable in their clinical evaluation for cognitive loss, as an intervention in treatment and as an element in their research designs for emerging drugs.

This will require increased vigilance by health care providers to the signs and symptoms of hypoxia and OSA. Detection must go past a simple “do you sleep ok?” question or the moderately sensitive Epworth Sleepiness Scale and Stop-Bang questionnaire. In addition to the classic questions involving snoring and fatigue, clinicians should look for multiple episodes of nocturia, evening dozing while sitting, and morning fatigue. They should be suspicious when patients have known apnea-related conditions, such as obesity, large neck size, GERD, type II diabetes, ADHD, depression, PTSD, a-fib, erectile dysfunction, and hypertension. Patients with cognitive complaints or objective cognitive loss deserve special attention because of the high comorbidity between impaired cognition and sleep disordered breathing.

In many cases, inexpensive overnight pulse oximetry can focus attention to the at-risk subset that deserves polysomnography. In addition, because of the bidirectionality of impaired cognition and OSA, a brief, digital test of cognition can identify those with cognitive loss who are at higher risk for OSA [11]. We have developed two iPad versions of the Memory Orientation Screening Test (MOST) called mdMOST® and CogniSense™. Each version takes only 5 min, yields a value reflecting cognitive level and produces a detailed narrative that serves as a strong starting point.

The Fiscal Pay-Off

Because the cost of dementia and associated medical problems is so high, there is enormous societal financial benefit for diagnosing any condition that produces or accelerates cognitive loss and can be corrected or improved. The cost of polysomnography and CPAP treatment together is less than the annual cost of a single memory medication, let alone the cost of a brief hospital stay.

To make such an approach truly successful, we need to employ psychologists and other behavioral specialists to help patients accept and tolerate CPAP treatment. CPAP adherence rates are estimated to

be below 50% [12], with many patients being resistant, confused or too anxious to tolerate treatment. The adherence for patients experiencing cognitive loss is probably even lower. We have addressed this problem in our practice by developing a small-group behavioral intervention called CPAP Success that uses cognitive behavioral principles and at-home practice sessions. In five pilot groups composed of 4 dementia patients and their partners, meeting for 3-4 weekly 1 h treatment sessions, 80% of patients achieved successful CPAP adherence at 3 months from treatment inception. More work needs to be done in this area and may require practitioner- and vendor-reimbursement incentives to succeed.

A New Direction

In looking to the future, we encourage pharmaceutical companies with dementia drugs in Phase 2 and Phase 3 trials to test for hypoxia and apnea in their study patients and to include this as a potential moderator variable in their studies. By doing so, they may reduce variance in test subjects' response to treatment that may blur a clinically significant between-group difference. If so, they may find greater success for their emerging dementia drug treatments.

In the meantime, we encourage clinicians to assess for hypoxia and OSA more diligently in their middle-age and older patients and to persuade those with even “mild” clinical findings to accept treatment. By improving sleep disordered breathing in patients with cognitive deficits, we may improve their thinking.

Editor's notes

1. Much of the theoretical synthesis in this editorial is the creative product of the second author.
2. MOST and mdMOST are registered trademarks of Clionsky Neuro Systems, Inc.
3. CogniSense is a trademark of Quest Diagnostics, Inc.

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