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Review Article

How to Control the Rising Ocean of Dementias in the United States

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Abstract

Effective treatment of vascular risk factors early in midlife is critical for the prevention of dementias. Despite therapeutic progress, currently there is no treatment for neurodegenerative dementias, but progression of mild cognitive impairment (MCI) can be slowed down with appropriate treatment of hypertension, hyperlipidemia, diabetes and other cardiovascular conditions, as well as with the use of vitamin B-group supplements (cobalamin, folic acid, pyridoxine), Mediterranean diet with extra-virgin olive oil, and regular exercise. To date, only some vascular forms of dementia, Hashimoto encephalopathy, and normal-pressure hydrocephalus (NPH) can be effectively cured. Abnormal sleep, mainly from obstructive sleep apnea, is a major, treatable, and usually overlooked risk factor for late-life dementias, including most vascular dementias, Alzheimer's disease and NPH.

Keywords: Alzheimers disease; Cobalamin; Dementia; Exercise; Folate; Frontotemporal dementia; Hypertension; Lewy body disease; Mediterranean diet; Obstructive sleep apnea; Olive oil; Parkinson's disease; Pyridoxine; Sleep; Vascular dementia; Vitamin B

Late-life Dementias

Dementia is the loss of cognitive functions associated with advancing age. Patients begin by misplacing objects and forgetting names, struggling with word-finding, getting lost in familiar streets, become unable to use the TV remote control or the microwave oven and finally they have to depend on the spouse for basic activities of daily living. The loss of independence is the frontier that defines dementia. Alzheimer's disease (AD) is the most common cause of dementia and according to the Alzheimer's Association more than 6 million Americans older than 65 years suffer from AD. Given that aging is the main cause of dementia, and people over 85 years are the fastest growing age group in the USA, we are confronting what we now characterize as the "rising ocean of dementias." This is in contrast with the metaphor of a tsunami first alluded to more than a decade ago with terms such as a "silver tsunami." We feel that a tsunami is a mischaracterization of the increasing burden of dementias. A tsunami brings massive volumes and then returns to normal levels rapidly. What the world is experiencing now is more akin to rising ocean levels. Slowly but surely, the case numbers are steadily rising and overcoming the health care delivery system. Already it costs more to take care of dementia patients than cancer or cardiovascular disease [1]. There are, however, some signs indicating that we may be able to slow down the rising tides.

The most important advance has been the recognition that cerebral blood vessels and cerebral circulation are the critical component for the development of dementias after 75 years of age [2-5]. Toledo and colleagues [6], at the National Institutes of Health (NIH), studied 4629 brains from patients with neuropathologically-confirmed AD and other forms of neurodegenerative dementia and found vascular pathology in 80% of the cases. Lesions included atherosclerosis of the Circle of Willis, ischemic leukoencephalopathy, arteriolosclerosis, large infarcts, lacunes, multiple microinfarcts, and hemorrhages. It is clear that the most frequent form of dementia is mixed dementia resulting from the combination of cerebrovascular lesions and neurodegeneration [7,8]. For these reasons, it is critical to determine the presence of all vascular risk factors in patients presenting vascular cognitive impairment [9]. In addition to advancing ageing, some of the commonest vascular risk factors [2,3,5,7,8,10] include the following: smoking, midlife arterial hypertension, hyperlipidemia, diabetes mellitus type 2, evidence of atherosclerosis involving peripheral vascular disease, coronary artery disease, congestive heart failure, atrial fibrillation, hyperhomocysteinemia, silent lacunar strokes, history of stroke, obesity, sedentary life style, markers of inflammation such as C-reactive protein (CRP), infectious agents causing gingivitis, and obstructive sleep apnea [11]. The availability of effective medications for the early control in midlife of blood pressure, lipids, and diabetes, has been shown to decrease the incidence of dementias [2,3,5,7], not only by preventing stroke and ischemic small-vessel white matter disease, but by slowing down brain degeneration.

The number of neurodegenerative conditions causing dementia extends beyond AD and includes, among others, Posterior Cortical Atrophy with cortical blindness plus dementia; Primary Progressive Aphasia and other forms of Frontotemporal dementia causing personality changes, hypersexuality, verbal and physical aggressiveness that in most cases requires psychotropics and institutional admission. Dementias with motor symptoms affecting posture, gait and fine hand movements, in addition to depression, visual hallucinations and other psychiatric manifestations, occur in Lewy body disease (LBD), Parkinson's disease (PD), Parkinson's disease dementia (PDD), Progressive Supranuclear Palsy, Multiple System Atrophy, and Corticobasal Degeneration [12]. Autonomic dysfunction, manifested as syncope due to orthostatic hypotension, urinary incontinence and severe constipation, is common in PD, PDD and LBD [13]. Recording of blood pressure sitting and standing should be obtained in the routine examination of all patients with dementia. The use of elastic travelers' socks or knee-high compression stockings helps to prevent syncope and its associated trauma.

Mild Cognitive Impairment (MCI): The approval by the Food and Drug Administration of two humanized monoclonal anti-amyloid beta (Aβ) antibodies, aducanumab [14] and lecanemab [15], and pending decision for donanemab [16], for the treatment of early AD increases the hope that safer and effective treatments to cure AD will become available in the near future. For this reason, it is critical to recognize MCI at the earliest possible stage of AD. The early diagnosis of MCI allows not only the treatment of accompanying cardiovascular conditions, but also the critical use of B-group vitamins including vitamin B12 (cobalamin), vitamin B9 (folic acid), and vitamin B6 (pyridoxine). The use of these vitamins in the MCI Optima trial in Oxford, UK [17,18] were confirmed to lower damaging homocysteine levels and to significantly slow down the progression of dementia by modulating the expression of methylated genes [19-21]. In addition, the positive effects of regular exercise, extra-virgin olive oil [22] and the Mediterranean diet [23] should be emphasized. The critical role of obstructive sleep apnea (OSA) is reviewed later.

Normal-pressure hydrocephalus (NPH**):** In addition to some forms of vascular dementia [24], Hashimoto's encephalopathy and other auto-immune encephalopathies [25,26], the only treatable form of dementia affecting gait is NPH described almost 60 years ago by Salomón Hakim –a Colombian neurosurgeon– and his colleagues in Boston [27,28]. NPH remains poorly understood and is frequently overlooked; its average age of onset is above 70 years. NPH is often diagnosed when greatly enlarged ventricles are unexpectedly found in a CT head obtained as a result of a fall, head injury and fractures in an elderly patient. The clinical syndrome accompanying ventriculomegaly consists of a typical triad of dementia, urinary incontinence and abnormal gait [29]. Patients complain of having poor balance, being unsteady, wobbly, staggering, and drunken. Very slow walking with short steps is typical. With eyes closed the ataxia, postural instability and unsteadiness of gait increase markedly. Shuffling and scuffing occur and turning becomes precarious and is usually done by pivoting in one leg; i.e., the so-called "compass sign." At this point, patients require a cane or a walker to ambulate and are at very high risk of hip fractures due to a tendency to fall and to the difficulty negotiating stairs and curbs. Parkinsonian-like features occur with difficulty initiating gait movements due to the feet being "glued" to the floor or "magnetized." Confirmation of the diagnosis of NPH requires a large-volume spinal tap [30] draining 50 mL of cerebrospinal fluid with demonstration by physical therapy of quantitative amelioration of gait and balance, return of bladder control, and cognitive improvement by neuropsychology testing. Positive results of surgical treatment with ventriculoperitoneal shunt occur in 80% of patients [31].

Obstructive Sleep Apnea causes idiopathic NPH: In 2018, we studied sleep disturbances in a prospective cohort of 31 consecutive patients with NPH confirmed by successful ventriculoperitoneal shunt [32]. Vascular risk factors in this cohort included hypertension, diabetes, hyperlipidemia, smoking, hyperhomocysteinemia, coronary disease, stroke, and excessive body weight. Using nocturnal polysomnography, we found OSA in 90% of patients with NPH. The sleep apnea-induced negative intrathoracic pressure opposes the CSF-venous return to the heart resulting in elevation of venous pressure in the superior vena cava and internal jugular vein system. The end result of untreated OSA is intracranial venous hypertension leading to a reduction of the normal drainage of CSF into the cranial venous sinuses with progressive accumulation of CSF inside the ventricles, ventriculomegaly and symptomatic NPH [33]. Furthermore, of major importance in OSA is the loss of the normal drainage of metabolic brain debris into the recently described glymphatic (glia-lymphatic) circulation [34] that occurs during deep sleep (delta and REM sleep) [35]. According to Nedergaard [35] the glymphatic system has three sequential components: i) a

para-arterial extracellular influx of CSF resulting from pulsation of arteries in the subarachnoid space; ii) an intracellular trans-astrocytic path mediated by aquaporin-4 (AQP4) water channels; and, iii) a para-venous clearance route draining CSF and interstitial fluid into lymphatics of the head and neck. This glymphatic system is found throughout the brain and removes 40 to 80% of large proteins and solutes during sleep [34,35]. Cortical brain biopsies in NPH patients showed reduced density of AQP4 water channels in astrocytic end-foot membranes [36]. Also, intrathecal gadobutrol MRI in subjects with NPH showed delayed clearance of the CSF tracer confirming the importance of reduced glymphatic circulation [37]. OSA causes a large number of metabolic and clinical complications in internal medicine and neurology [38]. In addition to the interruption of glymphatic function because of the absence of delta-REM sleep, other detrimental vascular effects of sleep apneas include recurring hypoxemia (low arterial SaO2), hypercapnia (elevated arterial CO2), and respiratory acidosis, leading to activation of carotid and aortic chemoreceptors, reflex contractions of respiratory muscles in chest and abdomen causing severe increase in negative intrathoracic pressure, along with pulses of sympathetic (adrenergic) activity manifested by outbursts of arterial hypertension, tachycardia, peripheral vasoconstriction, hyperglycemia, and hypercoagulability along with release of other stress-induced hormonal and inflammatory responses [38] leading to the recurrent arousals from deep sleep and frequent awakenings typical of OSA. In addition to increasing the risk of stroke, OSA induces subcortical ischemic small-vessel white matter disease leading to vascular cognitive impairment. OSA is also a significant risk factor for sudden death, and for a number of cardiopulmonary problems such as atrial fibrillation, cardiac arrhythmias and pulmonary hypertension [38]. However, it should be emphasized that positive effects of continuous positive air pressure (CPAP) treatment for OSA include control of cardiovascular problems such as severe hypertension and arrhythmias, as well as cognitive improvement and decrease of subcortical white matter ischemic lesions. CPAP also improves cognition in patients with OSA and AD [11].

Conclusion

Sleep has become the central factor in the prevention and treatment of dementias because loss of REM sleep resulting in glymphatic failure allows the accumulation of environmental pollutants including ultrafine particles (UFP<1μm) associated with early dementia, as well as Aβ, phosphorylated tau, TDP-43 and α-synuclein. Contrariwise, a 6% reduction in brain Aβ accumulation occurs with each additional hour of night-time sleep [39]. The circadian rhythm dependence on glymphatic function during sleep to prevent Aβ accumulation, prior to the development of cognitive decline or dementia, might be responsible for the increasingly frequent association of decrease in social sleep time, OSA and AD [11]. In 2005, Jennifer Wilson proposed in *Annals of Internal Medicine* [40] to consider sleep as a vital sign. Implementing this proposal by asking simple questions about sleep on every patient seeking medical attention will have enormous Public Health benefits. Regarding MCI, dementia and NPH, the nocturnal polysomnogram should become a compulsory test in the evaluation of every patient suspected of becoming demented. These simple but critical tests should help decrease the menacing rising ocean tide of dementia.

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Conflict of Interest

No Conflict of interest.

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