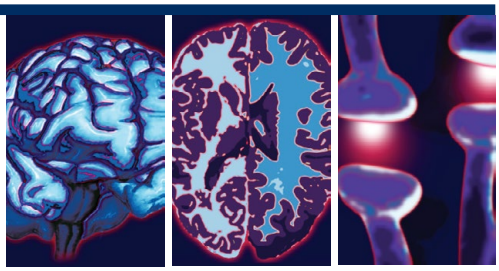
Review



Alzheimer Disease: The Burden on Mortality, Preclinical Alzheimer Disease Affects on Healthy Aging Functional Connectivity Studies, and New Evidence on Extrinsic and Intrinsic Risk Factors.

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Abstract

Alzheimer disease is the most common form of dementia and has a significant impact on mortality in the senior population. A vast amount of information has emerged over the past decade especially in regards to the underlying genetics and the significance of intrinsic and extrinsic risk factors. The importance of identifying risk factors may provide critical information to prioritize those patients that may benefit from implementing preventative factors. The methods used in this review was a PubMed search using the words "Alzheimer disease", "mortality", and "risk factors"; this was further refined by selecting articles from 2015-2012. Additional background references were added prior to 2012 as deemed appropriate. The results of this review was that Alzheimer-related mortality is underreported, loss of default mode network functional connectivity is due to Alzheimer pathology rather than healthy aging, and three new AD risk factors were identified.

Key Words: Alzheimer disease; Dementia; hyperlipidemia; hypertension; Intracranial artery stenosis; Arteriosclerosis

Introduction

Alzheimer disease (AD) is the most common age-related dementia, which is a very critical public health concern that has an enormous impact within the growing senior population [1]. The Center for Disease Control (CDC) and the Leading Causes of Death 2012 (updated August 2015) has enumerated AD as the sixth leading cause of death in women and the ninth leading cause of death in men, in the United States [2]. However, the actual mortality numbers may be underappreciated.

It is important to characterize, in more detail, the risk factors of AD. This should include both types of factors, i.e., extrinsic- factors that can be modified and intrinsic- factors that cannot be modified (Table 1). Secondly, protective factors need to be identified and implemented in the clinic in an effort to stymie the progression of the underlying pathology of AD, ideally prior to the diagnosis of dementia.

Dementia secondary AD can manifest several mental and cognitive abnormalities which are attributable to the underlying pathophysiology. Due to substantial progress in scientific research, more is known about the neuropathological abnormalities and biomarker alterations that are involved in AD, which heralds decades before symptoms emerge [3-8]. Conversely, a smaller amount is understood in regards to the subtle cognitive changes that may possibly occur prior to the patient manifesting obvious clinical

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Table 1. Intrinsic and extrinsic AD risk factors.

Intrinsic AD risk factors
• Age
• Family History- genetics
• History of traumatic brain injury
• Neurotic personality*
Extrinsic AD risk factors
• Stress
• Poor sleep
• Hypertension
• Other vascular risk factors, e.g., intracranial artery stenosis*
• Obesity and sedentary lifestyle
• Dyslipidemia
• Diabetes and metabolic syndrome (insulin resistance)
• Low level of education
• Elevated levels of homocysteine and C-reactive protein
• Lifestyle, e.g., alcoholism and drug use
• Environmental/occupational exposures, e.g., pesticides, aluminum, and copper
• Vitamin D deficiency*
*Newly identified AD risk factors that will be discussed in this article

symptoms. In this review article, the burden of AD on mortality, the preclinical AD effects on previous healthy aging functional connectivity studies, and new information on extrinsic and intrinsic AD factors will be surveyed.

The Burden on mortality: Is the prevalence of AD being underreported?

Worldwide, it is estimated that over 46 million individuals have AD dementia. This number was recently refined by the workgroup from the World Alzheimer Report 2015 [9]. In the United States, it has been estimated that there are 4.7 million individuals over the age of 65 with AD dementia. This number was assessed from the 2010 U.S. mortality, education, and new U.S. Census Bureau estimates [10].

In 2010, it was approximated in the US that AD dementia accounted for 83,494 deaths [11]. The method in which this number was tabulated is primarily devised from death certificates. It has been suggested, in a 15-year epidemiological study, that this particular method leads to the underreporting of the actual number of AD dementia-related deaths [12]. To further solidify the results of this research, a recent cohort study demonstrated that an even larger number of the deaths, which was 503,400 individuals, were attributable to AD dementia in 2010 [13]. This is a significant discrepancy.

Thus, there are a large number of individuals worldwide with AD dementia, and based on the World Alzheimer Report 2015, that number will continue to grow in the future [9]. Additionally, AD dementia results in a notable contribution to mortality annually, and this number has been shown to be underestimated [12, 13].

Preclinical AD effects on healthy aging functional connectivity studies

It has been demonstrated that the deposition of amyloid can impede the functional connectivity of the default mode network (DMN) [14, 15]. In addition, a major AD risk factor gene, the APOE ε4 phenotype, has also been shown to disrupt the functional connectivity of the DMN [16, 17]. Therefore, it is critical to acknowledge that the pathological factors and genes found in AD can adversely affect DMN functional connectivity and in the future researchers in this area should account for this.

This acknowledgement is significant because several studies using resting-state functional MRI (rs-MRI) have reported that a decrease in functional connectivity is associated with healthy aging [18-21], but all of these studies (and possibly others not referenced) neglected to control for individuals with undiagnosed preclinical AD. A recent study, using two groups of cognitively normal individuals, which were compared to one group with CSF biomarker evidence of preclinical AD; all of whom were examined using rs-MRI, demonstrated that preclinical AD accounts for a substantial fraction of the earlier reported effects of aging on the functional connectivity of the DMN [22]. According to this study, after the removal of the effects of detectable AD pathology, there remained nonzero effects of normal healthy aging on DMN functional connectivity.

These findings highlight the complexities involved in studying functional connectivity in the human brain. They also force into deliberation the pathological factors and biomarker status of preclinical AD subjects, all of which must be taken into consideration in these types of studies. In this case, the earlier studies [18-21] have overestimated the effects of what is considered healthy aging on the functional connectivity of the DMN.

Screening, Risk Factors, and the Prevention of AD

The current evidence proposes not to perform routine unprovoked screening in older adults. In general, the Alzheimer's Association recommends clinicians to be aware of, and look for, ten warning signs, which collectively should

increase the index of suspicion of early dementia **(Table 2)** [23]. When cognitive impairments are inferred and confirmed a diagnostic evaluation should be implemented. In addition, the consideration of existing risk factors should also play a pivotal role in the clinical assessment of the potential for developing dementia.

There are three main risk factors that are considered non-modifiable (intrinsic factors): age, genetics, and traumatic brain injury. There are six major risk factors that are potentially modifiable (extrinsic factors): depression, diabetes mellitus (type two), hyperlipidemia, hypertension, smoking, and low level of educational attainment.

Taking these risk factors into consideration, there are three categories of potential protective factors against AD [24, 25]: 1) Dietary- high intake of fish, vegetables, monounsaturated fatty acids, folic acid; low intake of saturated fat, regular intake of vitamin C, regular intake of turmeric (a herbaceous perennial plant of the ginger family), and following a Mediterranean diet. 2) Behavioral- increased cognitive activities, social engagement, and increased physical activities. 3) Medications- moderate alcohol consumption and NSAIDs. In addition to the risk factors and potential protective factors reviewed here, newer intrinsic and extrinsic factors have been identified, which will be discussed in the next section.

Identifying populations that are at risk is important because therapeutic strategies for AD must be implemented as early as possible, e.g., prevention of disease progression. Finally, refining the ability to predict the risk of impending deterioration will be especially valuable in patients with mild cognitive impairment (MCI); the transitional stage between normal cognitive function and dementia, as novel treatments are being developed.

Two newly identified extrinsic AD RISK FACTORS: Intracranial artery stenosis and vitamin D deficiency

During the course of AD pathogenesis and development, vascular (and degenerative) lesions coexist, interact, and intensify cognitive damage [26, 27]. This is due, in part, to the severe aftereffects of inefficient blood supply to the brain, which can be caused by vascular distortions and mechanical obstructions of major intracranial blood vessels.

Table 2. Ten Warning Signs that Should Increase the Suspicion of AD Dementia [23].

1. Memory loss which disrupts daily life
2. New difficulties in planning or problem solving
3. Episodes of confusion- mostly with place and time
4. New difficulties with words- speaking or writing
5. New difficulties completing familiar tasks
6. New difficulties with understanding visual images and spatial relations
7. Lose of the ability to retrace steps and misplacing objects
8. Decreased or poor judgement
9. Withdrawal from work or social activities
10. Changes in mood or personality

Intracranial artery stenosis (IAS) is the narrowing of any artery in the brain, which is usually caused by a buildup of plaque, i.e., arteriosclerosis. The narrowing of arteries can restrict blood flow to associated areas of the brain and can increase the risk of stroke; and even death. Treatments typically entail controlling or removing the plaque buildup and/or preventing the formation of blood clots with blood-thinners.

The correlation between vascular risk factors, e.g., hypertension, dyslipidemia, diabetes mellitus, obesity, and smoking; and the development of AD is still not clearly understood. IAS and its involvement in the AD progression pathway may be by way of promotional mechanisms, a synergistic role, or it may maintain a completely independent component.

In a recent prospective study of 423 patients with MCI, using a CT angiography as a method to conduct follow-up evaluations of stenosis in major intracranial arteries, demonstrated that the presence of IAS increased the risk of progressing to AD dementia after being diagnosed with MCI [28]. This study suggested that IAS promotes the progression from MCI to AD dementia in patient populations whom have underlying AD pathology. This is significant because IAS and other vascular risk factors can be successfully managed, and perhaps in these cases, more aggressively.

Another extrinsic AD risk factor is vitamin D. Many associate vitamin D with healthy bones and osteoporosis. However, vitamin D has many cellular functions in the neuron, e.g., modulation of neurite growth, proliferation, differentiation, and calcium signaling. More recently, it has been implicated as a neuroprotective agent, and it may affect neurotransmission and synaptic plasticity [29].

In addition to performing several vital neurobiological functions, several recent studies have demonstrated a correlation between low serum vitamin D concentrations and an

increase in all-cause dementia, AD dementia, and cognitive impairment [30-34]. One way that vitamin D deficiency may be correlated to AD is that it has also been linked to vascular dysfunction and increased risk of ischemic stroke [35]. Vascular risk factors were discussed earlier in this section, in particular to significance of IAS, so in a way these two risk factors may be related. A second cellular pathway in which vitamin D may be correlated to AD risk, is that vitamin D has been found to stimulate phagocytic macrophages that clear amyloid plaques from the brain [36, 37].

Consequently, we can clearly see a multitude of mechanisms and biochemical pathways in where vitamin D potentially contributes to the healthy neuro-cognition of the human brain. Also, a correlation between low serum vitamin D concentration and AD dementia has now been established in several studies [30-34]. Hence, we can now recognize vitamin D deficiency as an extrinsic AD risk factor and that vitamin D supplementation in this particular population serves as a potential protective factor.

A newly identified intrinsic AD risk factor: Personality

Personality is defined as an individual's unique variation on the general evolutionary design for human nature, expressed as a developing pattern of dispositional traits, characteristic adaptations, and integrative life stories complexly and differentially situated in culture [38]. It may strike one as odd to see personality listed as a risk factor for a neurodegenerative disease. However, a recent article which performed a 38-year follow-up on 153 women with dementia, found an increased risk associated with midlife neuroticism [39]. Neuroticism is a personality trait associated with anxiety, fear, moodiness, worry, envy, frustration, jealousy, and loneliness. Moreover, according to this study, extraversion, which is a personality trait that is primarily concerned with the act of directing one's interest outward or to things outside the self; was associated with no impact on AD dementia risk.

Conclusion

The scientific knowledge base of AD continues to explode; it seems on a monthly basis, especially in regards to the etiopathogenesis. This review has highlighted several new issues that should be considered when preforming initial and follow-up visits with AD patients. First, the mortality associated with AD dementia has been grossly underappreciated. Secondly, decrease in the functional connectivity of the brain is not a result of healthy aging; rather it is significantly correlated to AD pathology and genetics. Thirdly, identifying patient populations that are likely to develop AD dementia by establishing the patient risk factors is important because there are many potential protective actions involving diet, behavior, and medication that can be clinically utilized. Another example of a protective factor that was reviewed in a previous article discussed using melatonin as a therapeutic intervention in patients with MCI and AD dementia [39]. Finally, new AD risk factors may continue to emerge, and it is important for the clinician to be mindful of these risk factors when evaluating patients and their potential chance of developing AD dementia.

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