Alzheimer disease prevention

New optimism

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Summary

Alzheimer disease (AD) poses a major threat to medicine and society, but recent epidemiologic data indicate declining incidence of the disease. This development may be due to prevention of many cases by attention to modifiable risk factors. Meanwhile, all treatment efforts using drugs targeting amyloid have failed. In contrast to the assumption of recent decades that sporadic AD is primarily a genetic disease in which neuritic plaques and neurofibrillary tangles are mainly responsible for clinical features, it is now time for a more nuanced approach that considers the role of environmental factors preceding dementia onset and the appearance of aggregated proteins. This view of AD has important implications for medical care and health policy, and for counseling individuals to adopt lifestyle strategies that can be effective for prevention.

A 68-year-old retired accountant complains of frustrating memory lapses for the past year. He remains functional in all his usual activities, and his neurologic examination, including detailed mental status testing, is normal. Concerned about his mother, who was diagnosed with Alzheimer disease (AD) at age 75 and died without an autopsy, he asks if there is anything he can do to lower his risk of the disease.

For many decades, AD has been portrayed as an impending scourge of our society with strong genetic determinants and aggregated proteins that are responsible for dementia.¹ The aging of the population in industrialized countries has led to predictions that increasing numbers of people will be afflicted with this disease, and the influential amyloid hypothesis has stimulated enormous effort devoted to discovery of drugs intended to rid the brain of amyloid and cure the disease.² Yet despite widespread and well-justified concern about the AD epidemic, recent evidence has suggested that the age-specific incidence rate of AD is actually declining. One explanation for this decline may be that some cases formerly regarded as AD are now more accurately diagnosed as other degenerative dementias such as dementia

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with Lewy bodies and frontotemporal dementia, but the epidemiologic data have suggested that the decline in AD incidence is real. Five recent studies, 2 from the United States and 1 each from the Netherlands, Sweden, and England, all report declining incidence or prevalence of dementia among people born later in the first half of the 20th century.³ These studies are applicable to AD, as well as dementia broadly considered, because the great majority of dementia cases, particularly in late life, involve mixed neuropathology, most often a combination of AD and vascular changes.^{3,4} Alternatively stated, these findings indicate that all-cause dementia, typically related in the elderly to combined morbidities among which AD is a major contributor, has decreased. Plausible explanations for the decline in AD and dementia are control of cerebrovascular risk factors, better education, and improvements in economic well-being.³ The new findings suggest that evidence justifying preventive measures for AD, recently considered insufficient to support firm conclusions,⁵ has gained strength. Given the failure of all amyloid-based therapies thus far, most recently the 2 monoclonal antibodies bapineuzumab⁶ and solaneuzumab,⁷ the time has come to reconsider whether stronger emphasis on environmental or lifestyle modifications may be salutary.

Cerebrovascular disease

The most convincingly supported environmental factors that influence the risk of AD involve those that predict cerebrovascular disease: hypertension, diabetes, obesity, hyperlipidemia, metabolic syndrome, unhealthy diet, smoking, and physical inactivity.^{2,8,9} Neurologists are well aware of the importance of these factors in the etiopathogenesis of ischemic heart disease, stroke, and vascular dementia, but recent findings have steadily supported their effect on AD risk as well.^{2,8,9} The statement that “what is good for the heart is good for the brain” can now be made with additional enthusiasm.

Hypertension This well-recognized cerebrovascular disease risk factor clearly increases the risk of AD, most notably when present in midlife.^{2,8,9} Remarkably, treatment of hypertension can have the opposite effect. Of the 7 randomized controlled trials (RCTs) that have examined the benefits of antihypertensive treatment on dementia risk, 3 showed a beneficial effect.⁸ One study, the Syst-Eur trial of cognitively normal hypertensive adults 60 years or older who used nitrendipine alone, or in combination with enalapril or hydrochlorothiazide, demonstrated a specific reduction in AD risk over 3.9 years of follow-up.¹⁰ Nitrendipine, a calcium channel blocker taken by all treated subjects, may exert preventive effects on AD by virtue of suspected neuroprotective properties as well as antihypertensive effects.¹⁰ The Syst-Eur study is thus the only RCT ever to show a preventive effect for AD using medication of any kind.¹⁰ Some caution is warranted in view of other studies using antihypertensive agents that have not shown a preventive effect on cognitive decline¹¹ and dementia,¹² but limitations of these studies include substantial subject dropout¹¹ and relatively short follow-up.¹²

Diabetes Most work has been done on type 2 diabetes mellitus, and this disease has been found in longitudinal studies to almost double the risk of AD.^{8,9} The relationship between diabetes and AD is complex, as some but not all studies have found that diabetic patients have higher counts of neuritic plaques and neurofibrillary tangles than normal controls.⁸ Treatment trials using rosiglitazone and pioglitazone have shown improved cognitive function in some patients with AD or mild cognitive impairment (MCI)⁸ but no antidiabetic medication has yet been shown to have a preventive effect on AD.⁹

Obesity Midlife obesity, defined as a body mass index (BMI) of 30 or higher, has been shown to increase the risk of AD.^{8,9} This relationship is thought to be driven primarily by central (abdominal) obesity.⁸ Reduction of body weight has not yet been shown to lower the risk of AD.⁸ Interestingly, however, there is some evidence that low body weight may also increase this risk, suggesting that a U-shaped relationship may exist between BMI and cognitive performance.⁸ In light of these observations, maintenance of normal body weight in midlife would seem to be advisable.

Diet is a complex issue, but a “Western” diet with higher intake of red meat, high-fat dairy products, and refined grains has been associated with cardiovascular disease and obesity.

Hyperlipidemia Whereas data are conflicting about the relationship between hyperlipidemia and AD, midlife hyperlipidemia clearly increases the risk of cerebrovascular disease, which in turn increases the risk of AD.⁸ Statin drugs are widely prescribed for hyperlipidemia, and could plausibly lower AD risk by addressing this midlife risk factor while cognition is normal.^{13,14} RCTs of statins for prevention of AD have thus far been disappointing, but investigation of the possibility that statins may help lower AD risk continues.⁸

Metabolic syndrome Many of the cerebrovascular risk factors are interrelated and often occur in the same individual, and one construct intended to capture these comorbid conditions is the metabolic syndrome. Whereas varying definitions of this syndrome have been advanced, a combination of hypertension, type 2 diabetes, abdominal obesity, and hyperlipidemia is typically implied by this descriptor, and the metabolic syndrome has been shown in many studies to be associated with cognitive decline and AD.^{8,9}

Unhealthy diet Diet is a complex issue, but a “Western” diet with higher intake of red meat, high-fat dairy products, and refined grains has been associated with cardiovascular disease and obesity.¹⁵ In contrast, epidemiologic findings have suggested that adherence to the Mediterranean diet—one high in fruit, vegetables, whole grains, fish, and olive oil, with little red meat and low to moderate wine intake—can lower the risk of AD.¹⁶ As for alcohol in particular, the many potential hazards of drinking should always be considered, but a meta-analysis of 15 prospective studies found that light to moderate alcohol consumption reduces the risk of AD.¹⁷

Smoking Smoking remains a controversial issue, with some studies showing an increased risk of AD among smokers and some showing a decreased risk.^{8,9} Several early case-control studies showed a lower risk, but more recent prospective, longitudinal studies have found the risk of AD to be higher in smokers.^{8,9} Studies conducted with tobacco industry affiliation have tended to find a protective effect of smoking while studies performed with no such affiliation have more often shown an increased risk of AD among those who smoke.^{8,9}

Physical inactivity Physical activity improves aerobic fitness, with higher cerebral blood flow, oxygen extraction, and glucose utilization.⁸ Many studies of healthy older people have disclosed that aerobic exercise can improve aspects of cognitive function including processing speed and attention,^{8,9} and additional benefits may accrue from reduction of risk associated with hypertension, diabetes, and obesity.⁹ Conversely, physical inactivity has been shown to increase the risk of AD.⁹ Studies are under way to determine whether physical activity reduces the incidence of AD.⁹

Depression

An association has often been noted between late-life depression and AD.^{8,9,18} The mediation of this relationship is not well understood, as depression has been interpreted as an AD risk factor, or, alternatively, a prodromal sign of the disease.⁹ The high prevalence of cerebrovascular disease in older people favors the former interpretation because it can produce structural lesions leading to both depression and cognitive impairment.^{9,18} As depression is reversible in most cases, vigorous efforts are warranted to detect and treat this common mood disorder at

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an early stage. Treatment of depression may also improve the motivation to help facilitate reduction of other AD risk factors.

Traumatic brain injury

Repetitive brain trauma as a cause of dementia has recently received increased attention because of the newly described syndrome of chronic traumatic encephalopathy (CTE), previously known as dementia pugilistica, but studies over many years have documented that traumatic brain injury (TBI) is also a risk factor for AD.¹⁹ The cellular mechanism most often postulated in TBI is diffuse axonal injury in the white matter leading to proteopathy, which in turn may result in the widespread tauopathy of CTE, or the amyloid deposition characteristic of AD.¹⁹ A history of acute, single-injury TBI has been detected in 20%–30% of patients with AD, and as early as 2 hours after severe TBI, β -amyloid has been found to increase in the temporal cortex.¹⁷ While much remains to be learned about the relationship of TBI to both CTE and AD, avoidance of TBI, whether in civilian or military life, is surely to be sought in any case.

Cognitive inactivity

The idea that high education exerts a protective effect on AD has often been supported,^{8,9} and it has also become apparent that occupational engagement in adulthood and a socially integrated lifestyle also exert some protective effects against AD.²⁰ Thus cognitive activities appear to be protective not only in early in life but also continuing well into adulthood. These findings invoke the notion of cognitive reserve, which implies that people with higher education and occupational engagement are able to cope with incipient brain disease for a longer time.^{8,9,20} It follows that cognitive activity sustained into late adulthood, whether in an occupational setting, or afterward, may add protective effects with regard to the development of AD.

Sleep disorders

Sleep and its disorders are receiving long overdue attention in neurology, and the effect of sub-optimal sleep on cognition is a much studied topic. While AD is recognized as a cause of disrupted sleep, the possibility that the disease may in some way result from sleep disorders deserves attention. Obstructive sleep apnea, for example, is thought to produce deficits in executive function, attention, and memory, particularly if coupled with the *APOE* $\epsilon 4$ allele,²¹ and is associated with MRI white matter hyperintensities.²² Large epidemiologic studies have not directly linked sleep disorders with dementia incidence or prevalence, but insomnia has been associated with a higher risk of AD.²³ Moreover, shorter sleep duration and poorer sleep quality have been correlated with higher cortical amyloid as measured by Pittsburgh compound B PET,²⁴ and, in rodent studies, sleep has been found to clear amyloid from the brain.²⁵ Thus indirect evidence may support the hypothesis that sleep disturbance increases AD risk, providing another reason to strive for normal sleep.

What do these risk factors have in common?

AD is a complex disease, and plausible hypotheses about its origin include oxidative stress and inflammation as well as amyloid toxicity. Another hypothesis, which could unite the risk factors discussed above, is primary involvement of cerebral white matter. The role of white matter disease in the pathogenesis of dementia is increasingly appreciated,²⁶ and all the risk factors

Table Preventive medicine: Modifiable risk factors implicated in Alzheimer disease

Hypertension	Smoking
Diabetes	Physical inactivity
Obesity	Depression
Hyperlipidemia	Traumatic brain injury
Metabolic syndrome	Cognitive inactivity
Unhealthy diet	Sleep disorder

discussed above appear to involve some form of white matter disturbance.^{2,8,9,18–20,22,27–30} Whereas these studies do not establish a causal link between white matter change and AD, each offers support for the hypothesis. Most convincing is the role of white matter in the relationship between cerebrovascular disease and AD.^{2,8,9} Longitudinal MRI studies have found that ischemic white matter hyperintensities precede the onset of both AD²⁷ and MCI,²⁸ and epidemiologic data have shown an association between decline in dementia incidence and less prominent small vessel disease.²⁹ White matter changes are also implicated in depression,¹⁸ TBI,¹⁹ and sleep disorders,²² and cognitive inactivity may hinder the maintenance of white matter structure and function by reducing activity-dependent myelination.³⁰ Taken together, these observations suggest that the early neuropathology that is increasingly suspected to develop many years before the clinical manifestations of AD may originate in the cerebral white matter.³¹ An intriguing approach to etiopathogenesis has postulated the myelin model of AD, in which primary white matter disease related to ischemia and other insults leads to cortical plaques and tangles as byproducts of failed myelin repair.³¹ This model posits that cortical neuropathology is important in determining the clinical phenomenology of AD, but is not the primary disturbance, which begins in the white matter before neurobehavioral deficits become apparent.³¹ While the brains of older people with dementia typically show mixed neuropathology, suggesting that several mechanisms lead to dementia, the most common combination includes AD and vascular changes.⁴ Since ischemic white matter hyperintensities precede the onset of AD²⁷ and MCI,²⁸ treatment of cerebrovascular disease could help prevent AD through an effect on ischemic white matter.⁴ Much more work is needed, but the idea that white matter neuropathology may trigger subsequent pathophysiologic events that culminate in AD has growing preliminary support.^{27–31}

Offering advice

Neurologists are regularly faced with questions about recommendations to help reduce the risk of AD. Most of these inquiries come from middle-aged or older adults, with no clear history of familial AD, whose major concern is what can be done to lower the chance of developing sporadic AD. Many popular options exist, such as the online brain-training program Lumosity, which has attracted some 40 million enthusiasts, but cognitive training has not been shown to affect AD risk.⁵ Similarly, vitamins, minerals, and dietary supplements—including vitamin E and *Ginkgo biloba*—have insufficient evidence to support their use.⁵ The best advice neurologists can give on AD prevention is to follow the steadily accumulating epidemiologic and medical data on risk reduction strategies (table). A reasonable discussion can point out that despite areas of uncertainty, promising interventions are available that may preserve brain health in aging. While not notably different from advice any reasonable physician would offer to adults in almost any medical setting, these recommendations are backed by growing evidence with respect to AD, and they impose no undue hazard. Counseling should acknowledge the understandable concern harbored by many older people about genetic aspects of the disease, most notably the increased risk conferred by 1 and especially 2 copies of the *APOE* ε4

allele, but a focus on environmental risk factors, and their mitigation, can offer a welcome opportunity for personal action in response to the threat of AD. Emerging information on these risk factors, while encouraging, should be tempered by the absence of firm evidence that lifestyle changes can prevent AD, but research now underway will provide more information on the etiopathogenesis of this very complicated disease, as well as prospects for prevention. Details of how to go about controlling blood pressure, blood glucose, blood lipids, and body weight, avoiding smoking and head injury, and maintaining physical activity, a healthy diet, normal mood, cognitive stimulation, and restorative sleep will vary among individuals, but these principles can often alleviate the ominous sense of peril that lingers in the minds of many who have been led to expect the genetic inevitability of AD.

DISCUSSION

The projected increase in numbers of those affected and the absence of effective medical intervention have made AD one of the most discouraging problems in medicine, but this situation appears to be improving. While amyloid-based drug therapies continue to fail, strategies that rely on mitigation of risk factors are steadily succeeding. These new findings may have profound consequences. A recent epidemiologic review concluded that up to half of all AD cases worldwide can be attributed to potentially modifiable risk factors.⁹ Low education and smoking were cited as the greatest contributors to AD risk worldwide, while in the United States, physical inactivity contributed to the largest proportion of AD cases.⁹ Hypertension, diabetes, obesity, and depression were also found to be powerful AD risk factors.⁹ Although large-scale RCTs and detailed observational studies are needed to gather more data about the impact of risk factor reduction on the incidence and prevalence of AD, this challenging disease must now be conceptualized as involving nurture as well as nature. While much remains to be learned about etiopathogenesis, recent data compel a reconsideration of the widespread assumption that sporadic AD is predominantly a genetically mediated disorder attributable principally to amyloid toxicity. Instead, the disease should be recognized as having significant environmental determinants that can be gainfully modified.^{9,31,32} Successful interventions may involve both medical care—treatment of hypertension, diabetes, obesity, depression, and the like—and public health measures, such as policies expanding access to education and encouraging smoking cessation, physical exercise, and avoidance of TBI. Advances in these areas should be welcome. In parallel with these ideas, the amyloid hypothesis of AD remains alive, and eradication of amyloid before dementia onset has come to be seen as another potential approach to prevention. Participation in a clinical trial of an anti-amyloid drug may therefore be another option, particularly for an adult with an autosomal dominant AD gene mutation. Meanwhile, neurologists can offer sound advice to patients, families, and others interested in lifestyle changes that may preserve cognitive function or help prevent the development of AD. In contrast to the recent past, cautious optimism could be warranted.

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