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History and experience: the direction of Alzheimer's disease

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Abstract

As the global population is projected to age substantially in coming decades, the number of individuals who will develop Alzheimer disease (AD) is expected to rise dramatically. We have come to understand that AD is likely to be multidetermined through interactions between heritable causal and susceptibility genes, environmental exposures, midlife health status, and lifestyle choices. In addition, mounting evidence suggests that the neuropathological processes characteristic of AD can be detected several years before the onset of clinical symptoms. Thus, AD is now considered to have presymptomatic, prodromal (mild cognitive impairment), and dementia phases. Through cerebrospinal fluid biomarkers, volumetric neuroimaging, functional neuroimaging, and cognitive stress tests, individuals at significant risk for developing dementia can now be identified with greater sensitivity and specificity. Consequently, there is growing attention to identify interventions to halt or delay the onset of AD. The biological capacities of neurogenesis and neuroplasticity and the related concepts of brain and cognitive reserve provide a rationale for developing techniques to maintain or enhance the cognitive abilities of older persons to sufficiently prevent dementia. This has led to the emergence of a new "brain fitness" commercial industry in which "products" are being marketed and sold to consumers to "keep your brain sharp." However, most available brain fitness products have scant scientific evidence to support their effectiveness. Nevertheless, ongoing research advances do support the potential for memory and other intellectual functions to be strengthened and maintained through cognitive training, physical exercise, dietary choices, social engagement, and psychological stress reduction.

Key Words: Alzheimer disease – Dementia – History – Prevention – Brain fitness.

With the projected aging of the global population, the prevalence of dementia is anticipated to rise from nearly 40 million persons today to approximately 118 million by 2050.[1] Today, Alzheimer disease (AD), the preeminent cause of dementia, is as much a part of the public health lexicon as cancer, stroke, and heart disease. With unusual exception when directly queried, adults from all walks of life will remark that indeed, they have known or loved an individual who had this disorder. However, this was not our experience through most of the 20th century. The public's recognition of the remarkable frequency with which dementia accompanies advancing age and that a neurodegenerative disorder, AD, is the major cause of the syndrome has especially come to light during the last 40 years.

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HISTORY OF AD

It was little more than a century ago that Dr. Alois Alzheimer (b. 1864-1915), a German physician, publically shared his original case of the disorder that, shortly thereafter, would endure to bear his name. In 1906, Alzheimer specifically reported on his treatment and the subsequent postmortem brain examination of a female patient, Frau Auguste Deter (Auguste D), who had dementia in midlife. She presented to Alzheimer as a 51-year-old married woman who expressed delusional jealousy and manifested depressive symptoms. She was confined to the state asylum in Frankfurt, where Alzheimer was then working. Her clinical syndrome was found to include hallucinations, paranoid ideation, and a tendency toward screaming and to be hostile. Enmeshed within this presentation of insanity was severe memory impairment along with other abnormalities in cognitive ability, including language disturbance.

The patient continued to rapidly deteriorate in the asylum and became bedridden and incontinent and was in a completely helpless state. After her death and when Alzheimer had already moved to Munich to continue his work under the tutelage of the prominent psychiatrist Emil Kraepelin, his colleagues in Frankfurt sent him Auguste D's brain for postmortem examination. Alzheimer's public lecture about the case

and the subsequent written report identify the presence of dramatic brain atrophy and abnormal microscopic deposits in and around the patient's neurons. These pathological findings included neuronal death, arteriosclerotic changes, extracellular plaques, and intracellular tangles of fibrils. Alzheimer reported "…scattered through the entire cortex, especially in the upper layers, one found miliary foci that were caused by the deposition of a peculiar substance in the cerebral cortex...."[2]

Alzheimer was not the first to have identified plaques, or as it was termed then, miliary sclerosis, as present in the brains of individuals with senile dementia. However, the unique nature of Auguste D's case, including the relatively early age of onset before 65 years (presenile), the rapid progression of cognitive deficit with behavioral change, and the severity of the neuropathological alterations that were evident, led Alzheimer to believe that he was describing a novel neurological condition. Other cases of this presenile dementia with similar neuropathological features of plaques and tangles subsequently appeared in the literature over the next few years.

It was in 1910 that Kraepelin,[3] in his *Handbook of Psychiatry, 8th Edition*, stated "…a particular group of cases with extremely serious cell alterations was described by Alzheimer…the clinical interpretation of this Alzheimer's disease is still unclear. Although the anatomical findings suggest that we are dealing with a particularly serious form of senile dementia, the fact is that this disease sometimes starts as early as in the late forties." This statement by Kraepelin is widely regarded to have been the first time that this specific neurodegenerative disorder causing senile dementia was named for Alzheimer.

After 1910 and through most of the next half century, senile dementia was widely thought to be caused by atheromatous degeneration of blood vessels with accompanying stroke and was a distinct condition from AD.[4] It was generally believed that "senility" was a distinct disorder from either AD or senile dementia and represented an expected, age-related deterioration in cognitive functioning. As more individuals, especially in Western societies, were living to advanced ages, the prevalence of cognitive failure was increasing. Notably, however, senile dementia was rarely mentioned as a cause of death in the elderly population. AD as the major cause of both cognitive failure and subsequent mortality was largely ignored. Adding to a lack of clarity throughout the first half of the 20th century were studies reporting that intraneuronal tangle pathology was found across a number of different neurological disorders and that seemingly cognitively healthy elderly individuals older than 65 years had postmortem pathological evidence of cerebral plaques and tangles.

Public recognition and advocacy

In 1948, Newton[5] published an article entitled "The Identity of Alzheimer's Disease and Senile Dementia and Their Relationship to Senility," in which he argued that both AD and senile dementia were progressive conditions with a cluster of similar clinical features that are indistinguishable from one another. He posited that the postmortem pathological hallmarks of these seemingly disparate clinical disorders were actually indistinguishable from one another. This argument was further supported by an epidemiological study published by Neumann and Cohn[6] in 1963, who reported on the incidence of AD in a large psychiatric hospital. Within a decade, AD would become recognized as the principal cause of senile dementia through the research findings of Blessed et al.[7] In a significant cohort of elderly individuals who had died with diagnoses of dementia and went on to postmortem brain examination, they were the first to demonstrate a significant correlation between the level of cortical burden of senile plaques and neurofibrillary tangles and the severity of dementia.

These findings were followed by a seminal editorial published in April 1976 in the *Archives of Neurology* by Robert Katzman,[8] entitled "The Prevalence and Malignancy of Alzheimer's Disease: A Major Killer." Through this article, the major public health impact of the disorder became more widely appreciated. In the United States, in the 1980s, the National Institutes of Health, through the National Institute on Aging, launched a concerted scientific effort in AD, including the creation of a specialized network of university-based research and care centers. During this historic period of increasing public awareness, the Alzheimer's Disease and Related Disorders Association (ADRDA) was formed to support affected families across the nation and to garner more resources to advance research into the causes and treatments of the illness. The association ultimately was rebranded as the Alzheimer's Association.

As federally funded neuroscience research continued to progress through the especially fertile period of the 1980s to advance our understanding of the pathogenesis of AD and to thus identify potential therapeutic targets, important strides were also being made to establish greater precision in the diagnosis of the disorder. In the fall of 1983, a workgroup was convened by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the ADRDA to develop standardized diagnostic criteria and to more fully describe the clinical presentation of AD. In 1984, the group published what was to become the dominant approach for the diagnosis of AD over the subsequent 27 years, the NINCDS-ADRDA criteria.[9] These criteria defined the diagnosis of AD as either "definite" (the most typical clinical syndrome, confirmed by either biopsy or postmortem histopathological confirmation), "probable" (the most frequently encountered clinical presentation including memory loss, at least two cognitive deficits, insidious onset and gradual progression of the severity of deficits, and the absence of other significant plausible causes in the setting of functional decline), or "possible" (an atypical or mixed etiological presentation). In addition, age of onset was described to be between 40 to 90 years of age.

Major late 20th century discoveries on pathogenesis

Cholinergic depletion

As the field progressed toward an enhanced understanding of the pathogenesis, diagnosis, and treatment of AD, several

especially noteworthy scientific developments occurred during the same period. In 1981, Whitehouse and colleagues[10] reported that the cholinergic basal forebrain (the nucleus basalis of Meynert) had all but disappeared in the brains of patients who had died of AD.

This finding would ultimately lead to the cholinergic depletion hypothesis of AD—that loss of cells in the cholinergic basal forebrain and diminished cholinergic neurotransmission were fundamentally responsible for the cognitive impairment associated with AD. However, subsequent research has suggested that this hypothesis was overly simplistic and failed to explain the early symptoms of the disorder.

Amyloid protein

In 1984, Glenner and Wong[11] reported on the purification and characterization of a novel cerebrovascular amyloid protein. They stated, in what was to be a landmark article, that "this protein may be derived from a unique serum precursor which may provide a diagnostic test for Alzheimer's disease and a means to understand its pathogenesis."[11] Although the specific diagnostic test they had hoped for has yet to materialize, their critical work did indeed help to establish cerebral amyloid metabolism, deposition, and clearance as perhaps the most vital areas of AD pathogenesis for continued study. Arguably, the presumed early and central role of amyloid in the cascade of pathological changes characteristic of AD would be seen by many to overly dominate the next quarter century of basic research efforts in the disorder.

τ Protein

In 1986, other research teams focused on characterizing the biological origin of paired helical filaments, which were known at the time to form neurofibrillary tangles, the most common intraneuronal abnormality of the cytoskeleton found in AD. The research groups of Grundke-Iqbal and colleagues[12] and Kosik et al[13] reported within a month of each other on the association of the hyperphosphorylated microtubule–associated τ protein as a major component of Alzheimer paired helical filaments. It was surmised at the time, and is still believed by many today, that the progressive accumulation of abnormal τ protein in Alzheimer affected neurons may lead to instability of the microtubular structure and the consequent loss of effective intracellular transport, and ultimately, neuronal death.[12,13]

As the years progressed, a number of other major areas of basic AD research activity emerged, including, but not limited to, neurochemical alterations, especially of the cholinergic system; inflammation; oxidative cell damage; apoptosis; mitochondrial dysfunction; gene expression; and the role of heritable factors.

Genetic mutations and the amyloid hypothesis

In 1987, the first causative Alzheimer gene mutation was reported by St George-Hyslop and colleagues.[14] This gene, located on chromosome 21, was associated with a comparatively rare, early-onset, familial form of the disease, which is now frequently called autosomal dominant AD or early-onset AD (with onset before 65 y of age). Although this gene was associated with an atypical version of AD, its function to code for the amyloid precursor protein (APP), the parent molecule from which amyloid-β is formed, represented a major advance in furthering our understanding of the disorder's potential genetic influences on pathogenesis.[14]

Two additional causative gene mutations would eventually be reported over the next few decades, presenilin 1 and presenilin 2. These genetic mutations would also ultimately be implicated in amyloidogenesis and the development of autosomal dominant, early-onset familial AD.[15] The link between AD and genetic mutations affecting the processing of APP would ultimately provide some of the strongest evidence supporting the amyloid hypothesis—the notion that some aspect of the protein's metabolism initiates a cascade of pathological events resulting in the characteristic plaques, tangles, and cognitive dysfunction associated with AD.[16]

In 1993, the first major susceptibility gene for the most typical form of the disorder, sporadic (late-onset) AD, the apolipoprotein ϵ 4 (APOE-e4) allele, was reported by Corder and colleagues.[17] This allele has been consistently demonstrated during the intervening years to be a strong risk factor for the development of AD in later life such that up to nearly 50% of affected patients are carriers. Possessing one copy of the allele increases the lifetime risk of AD by 3- to 4-fold; having two copies (homozygous condition) increases lifetime risk by 9- to 10-fold.

Pharmacological interventions

Cholinesterase inhibitors

During this same period in the 1980s, in the first multisite clinical trial of an AD-specific therapy, the cholinesterase inhibitor tacrine was collaboratively launched by the Warner-Lambert pharmaceutical company and the National Institute on Aging. The drug would eventually prove to have sufficient but modest efficacy and with acceptable levels of tolerability and safety to come to market in 1993 as the inaugural AD therapy, Cognex. Its indication was limited to mild- to moderate-stage clinical disease. Widespread use of the drug was significantly limited by its required four times per day dosing regimen; cholinergic side effect profile, especially gastrointestinal upset; and the observation of hepatic enzyme elevation in a significant number of treated patients.

As the search for effective pharmacological interventions continued, donepezil hydrochloride (Aricept) became the second cholinesterase inhibitor introduced for the treatment of mild to moderate AD in 1996. It required an improved once per day dosing regimen and had a significantly better tolerability profile than Cognex did. In 2000, rivastigmine (Exelon) and, in 2001, galantamine (Reminyl/Razadyne) were introduced as alternative cholinesterase inhibitors for the treatment of mild to moderate AD. In 2003, memantine (Namenda), with a noncholinergic mechanism of action affecting the glutamatergic system, was approved for the treatment of moderate to severe AD. Since that time, no new medications have been approved in the United States for treatment of the condition,

although the indication for donepezil was subsequently broadened to include moderate to severe AD.

Unfortunately, as a group, studies examining the effectiveness of cholinesterase inhibitors in improving the symptoms or slowing the rate of decline in AD have shown relatively modest benefits of this drug class.[18]

Antiamyloid and other treatments

Currently, more than 80 drugs are being investigated for AD therapy in various preclinical and clinical trial stages. These drugs vary in their main therapeutic properties. Many of the agents in development target amyloid-β, with some aiming to decrease its production, others targeted to limiting its aggregation, and others designed to increase the brain's ability to clear it (via immunotherapy). Another class of drugs in development is designed to decrease the aggregation or phosphorylation of τ. Still, other classes of drugs involve a combination of these therapeutic properties or target some other mechanism such as mitochondrial dysfunction, apoptosis, inflammation and oxidative cell damage.

Given the limited effectiveness of current pharmacological therapies in treating AD once clinical symptoms are apparent (tertiary prevention), many research groups have increasingly focused their efforts on the early identification of individuals in the early, preclinical stages of AD (secondary prevention) or even earlier in healthy individuals in middle adulthood who have an elevated risk for developing AD (primary prevention). Specifically, many now believe that the limited effectiveness of AD therapies to date may be because clinical trials have targeted individuals already showing symptoms of dementia, clinical features that are probably emerging after several years of amyloid accumulation and the other pathological changes underlying the disorder.[19,20]

As a result, an increasing view in the field is that the onset of dementia can be conceptualized as a relatively advanced form of brain failure that generally occurs after the pathological burden of AD, and neurofibrillary tangle formation is very well established in the affected brain with resulting neuronal dysfunction and cellular loss. Therefore, much work has commenced in recent years to better understand how to identify the disease in its earliest possible expression and then to target therapies before the clinical onset of dementia. It is hoped that this approach to treatment will yield improved results over the failures that have largely characterized AD clinical drug development since the introduction of the cholinesterase inhibitors and memantine.

Revision of diagnostic criteria

Since the time of the originally published NINCDS-ADRDA criteria in 1984, a number of vital research advances have led to what has recently been proposed as the need for a significant revision to the diagnosis of AD. The factors necessitating the revision include the increased appreciation that the histopathology that has characterized AD can occur across a broader clinical spectrum than previously understood to include persons with not only frank dementia but also mild cognitive impairment (MCI) and normal cognitive performance. These conditions are now seen along a clinical continuum in which AD also exists in a pathological, but preclinical, state. As stated earlier, we have come to understand that AD neuropathological change may begin several years and perhaps at least a decade before the onset of cognitive deficits.[21] These changes now have the potential to be detected preclinically through innovations in brain imaging and the identification of peripheral biomarkers.[22,23]

Imaging markers

Advances in structural imaging, particularly volumetric measurement of especially vulnerable brain regions in AD, such as the mesial temporal area including the hippocampus, may herald the development of the disease in the preclinical state. Positron emission tomography (PET) imaging demonstrations of impaired glucose utilization in critical neocortical areas for cognitive function also have the potential to identify the disorder in preclinical states. This technique can also be ultimately used to confirm AD in the setting of MCI or overt dementia. Imaging is now increasingly being used in research studies to directly detect the presence of amyloid deposition using PET tracers such as Pittsburgh compound B (PIB).[24]

Cerebrospinal fluid markers

Over the last decade, as imaging advances have been made, similar efforts have continued to identify reliable and valid serum and cerebrospinal fluid (CSF) markers indicative of AD pathology. Recently, results from the multisite Alzheimer's Disease Neuroimaging Initiative were released to show that there is a typical AD CSF biomarker profile. As compared with controls, patients with AD had decreased levels of CSF Aβ42 protein and increased levels of CSF total τ and phosphorylated τ. In reporting these results, De Meyer and colleagues[25] demonstrated that the AD CSF profile appeared in 90% of AD patients diagnosed by clinical criteria, 39% of normal controls, and 73% of research subjects meeting diagnostic criteria for MCI. After 5 years of follow-up, 100% of the MCI group that had the AD CSF profile went on to develop dementia, presumably due to AD. It is posited that the cognitively normal group showing the AD profile may be in a preclinical stage of the disorder and at risk for eventually developing MCI or dementia.[25] Work continues to develop greater reliability, validity, and standardization of these approaches before they will be readily available, through the creation of diagnostic algorithms, for routine clinical use.

Other factors

In addition, there are other reasons that have been posited to support the need for a revision of the 1984 NINCDS-ADRDA criteria. For example, other forms of dementia, such as dementia with Lewy bodies, primary progressive aphasia, behavioral variant frontotemporal dementia, and vascular dementia, are now more accurately clinically characterized and can be better distinguished from AD. New diagnostic criteria can also incorporate genetic factors including causative mutations.

Revised criteria would also acknowledge that although memory impairment is most commonly the central cognitive deficit of AD, other nonamnestic presentations can rarely but do occur with AD histopathology (eg, posterior cortical atrophy). Lastly, accumulated observations over the past few decades no longer support an arbitrary age cutoff for the probability of an accurate premortem diagnosis of AD.

Diagnosis of AD in 2011

In response to the growing need for a more comprehensive consideration of the full clinical continuum and biological spectrum of AD, a series of articles were published by the National Institute on Aging–Alzheimer's Association workgroups that detailed the recommendations for revised diagnostic guidelines for AD.[15,21,26,27] The recommendations incorporate many of the 1984 NINCDS-ADRDA criteria and still propose classification criteria for probable AD and possible AD based on behavioral indicators of cognitive function and objectively measured change in cognitive function. In addition, the recommendations also include categories intended for research purposes that incorporate biomarkers of AD—probable AD or possible AD with evidence of the AD pathophysiological processs.[27] Evidence of the AD pathophysiological process include biomarkers of amyloid-β deposition (low CSF Aβ42 or positive results on PET amyloid imaging) and neuronal degeneration or injury (elevated CSF τ, decreased fluorodeoxyglucose uptake on PET in the temporal-parietal cortex, or disproportionate atrophy on structural magnetic resonance imaging [MRI] in the medial-parietal cortex and medial-, basal-, and lateral-temporal cortex). A positive result for one of these biomarkers is indicative of intermediate probability of AD etiology; a positive result on both biomarkers is indicative of high probability of AD etiology.

However, McKhann and colleagues[27] noted that although "biomarker evidence may increase the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process…we do not advocate the use of AD biomarker tests for routine diagnostic purposes at the present time." That healthy older individuals without dementia can have both positive biomarkers and evidence of amyloid (PIB) burden undermines the use of these methods for clinical diagnosis of AD.

Toward earlier identification of preclinical AD and MCI due to AD

As repeatedly argued above, there is increasing acceptance that AD probably exists in preclinical and prodromal phases (eg, MCI). Even during the preclinical asymptomatic stage, there are mechanistic neuronal changes taking place, such as a functional disconnect between critical regions in large-scale neural networks (eg, the default mode network) that can be distinguished from healthy aging. Notably, a diagnosis of MCI due to AD (with possible or probable certainty) may be considered given evidence of change from an individual's previous level of cognitive function, as indicated by a clinician, an informant (eg, spouse, caregiver), or the patient.

Importantly, the subtle cognitive and/or neuropathological changes in preclinical or prodromal AD are still plausibly reversible at this stage. In contrast, the changes associated with subsequent stages of disease progression are less likely to be reversible. These include degradation in the microstructure of white matter tracts during the beginning signs of MCI and macrostructural changes such as volumetric brain atrophy that is evident on MRI in the final stage that qualifies as a progressive clinical dementia syndrome.[28] As such, a body of work has been conducted over the past several years to better understand the risk factors for the development of AD and putative strategies targeting primary, secondary, and tertiary prevention of the disorder.

Through the use of CSF biomarkers (low Aβ42, elevated τ), PET (Aβ deposition), volumetric neuroimaging, functional neuroimaging, genetic testing, and cognitive stress tests, individuals at significant risk for developing dementia due to AD can now be identified with greater sensitivity and specificity and at earlier ages than has been previously possible. The emerging ability to detect the disorder much earlier in its course has increasingly demanded more research emphasis on prevention and early intervention.

PREVENTION OF AD

Over the past few decades, great attention has been paid to identifying potentially important AD risk factors, with increasing efforts underway to identify potential targets for the prevention of age-related cognitive decline and dementia. A variety of factors have been shown to impact the likelihood that an individual will develop AD, including genetic load, hormonal status, cognitive stimulation, social engagement, body weight, cardiovascular health, diet, and exercise. As discussed in more depth below, some AD risk factors that may influence the risk of developing AD are associated with an assortment of disorders, including type 2 diabetes mellitus, atherosclerosis, hyperlipidemia, hypertension, cardiac disorders, cerebrovascular pathology, and body mass index.[29]

Risk factors

As discussed earlier, gene studies and observational or epidemiological studies have revealed a number of factors associated with increased risk of developing AD that vary in their degree of potential modifiability. Relative to factors like one's genetic profile and sex, many risk factors that have been identified have the potential to be altered by experience, including educational/occupational attainment, diet, a variety of leisure activities (cognitive stimulation, social engagement, physical exercise), and health status.

Genetics

A recent meta-analysis of studies predicting progression from MCI to AD with APOE-e4 genotyping found that "the APOE-e4 allele is a moderately strong predictor of progression from MCI to AD-type dementia. The risk is twice as high for APOE-e4 heterozygotes and four times as high for APOE-e4 homozygotes compared with non-carriers."[30] However, the authors concluded that, to date, there is limited value in using APOE genotyping for predicting progression to AD in clinical practice, as sensitivity and positive

predictive value were low (half of those without an APOE-e4 allele progressed to AD and 40% of those with an APOE-e4 did not progress to AD over a 3-y period).[30]

A family history of AD is a risk factor over and above the presence of APOE-e4 alleles as well. For example, even in cognitively normal, middle-aged adults who are APOE-e4 noncarriers, a family history of the disorder is associated with several putative preclinical AD CSF and neuroimaging biomarkers (levels of Aβ42 and τ in CSF, PIB mean cortical binding potential, and decreased fractional anisotropy from diffusion tensor imaging in the genu and splenium of the corpus callosum).[31] This suggests that those with a family history of AD may have biological evidence of the disease that is identifiable even in middle adulthood and in the absence of cognitive or behavioral symptoms. Although the number of known AD risk genes is growing rapidly, "up to 50% of the heritability of AD remains unexplained."[28] Rather than individual genes having a strong impact on susceptibility, it is more probable that the combination of multiple genes and environmental factors determines the risk of developing AD.[28]

Sex

Some early investigations showed a greater risk of AD for women than for men, such as the European Studies of Dementia (EURODEM) Incidence Research Study (adjusted relative risk, 1.54; 95% CI, 1.21-1.96) and a Swedish cohort study, where the association was particularly notable for those older than 90 years. However, it is important to consider the earlier mortality and greater morbidity rates in men than in women. Studies that considered age-specific incidence, such as the Monongahela Valley Independent Elders Survey (MoVIES) study, the Rochester study, the Framingham study, the Baltimore Longitudinal Study of Aging, the East Boston Study, and the Adult Changes in Thought (ACT) cohort study, found no difference between women and men in the incidence of dementia or AD.[32]

In the Study of Osteoporotic Fractures, cognitive function (Mini-Mental State Examination [MMSE]) was assessed in 9,704 women over 6, 8, 10, and 15 years (mean age, 72 y at baseline and 85 y at follow-up).[33] Nine percent of the women maintained optimal cognitive function (slope ≥0), 58% experienced minor decline (slope <0 but > lowest tertile), and 33% experienced major decline (slope ≤lowest tertile). Adjusted for confounding factors (age, education, baseline cognitive function, and study site), the factors that were most predictive of maintaining optimal cognitive function as opposed to minor cognitive decline included lack of comorbid medical conditions (diabetes mellitus, hypertension), presence of healthy behaviors (nonsmoking, moderate alcohol consumption), lack of difficulty with instrumental activities of daily living, and lack of poor social network.[33]

Hormone therapy

Hundreds of in vitro and animal studies have shown estrogen to have beneficial effects on neurotrophism and neuronal functioning. For example, estrogen is known to promote cholinergic neuronal growth and survival and, further, the metabolism of APP. Early observational studies suggested that women treated with hormone therapy (HT) had a reduced risk of AD compared with those who were not. However, the effect of estrogen on cognitive functioning is less consistent across observational/epidemiological studies and clinical trials of HT (see Janicki and Schupf[32] for a review). In observational studies, there may be confounding variables that influence the choice of women to use HT, such as a higher education level and better access to health care. In addition, the inconsistency of the research findings to date may be caused by the timing of HT, with benefits observed for previous use and/or when initiated early in menopause but with no benefit of current use in postmenopausal women unless initiated more than 10 years before cognitive assessment (or before the approximate age of 63 y).[34]

Importantly, clinical trials of HT have generally shown a neutral effect of estrogen-only treatment and a negative effect of estrogen-progestogen treatment on verbal memory. For example, the Women's Health Initiative Memory study found that postmenopausal women 65 years or older assigned to HT (combined estrogen and progestin) had impaired general cognitive function relative to those assigned to a placebo.[35] Moreover, the study showed that HT resulted in a twofold increase in the diagnosis of dementia relative to a placebo.[36] Because HT is also associated with increased risk for stroke, it was assumed that the declines in cognition and increased risk of dementia associated with this intervention were caused by an increase in subclinical cerebrovascular lesions. However, Coker et al[37] recently reported that neither the number of brain vascular lesions nor their volumes were substantially increased among women assigned to HT. However, this same group of researchers also reported that frontal cortex and hippocampal volumes were generally smaller in women prescribed HT relative to those given placebo.[38]

Thus, it appears that the potential of HT to reduce risk of AD or to improve cognition relies on the type of treatment (with estrogen-only treatment being preferable to combined estrogen-progestogen) and initiating treatment within a "critical window"—early perimenopause or just after the onset of menopause.[32]

Education and occupation

In 1994, Stern and colleagues[39] reported on nearly 600 individuals of whom 106 developed AD during their study. A higher level of educational and occupational attainment was associated with a reduced risk of AD (2.02; 95% CI, 1.33-3.06). Several other studies have also found a reduced risk of cognitive decline and/or dementia associated with greater amounts of educational attainment, complexity of work, and cognitive activity that is broadly defined (see Reichman et al[40] for a review). Interestingly, some research has revealed that although higher educational and occupational attainment may confer a reserve that delays the onset of clinical symptoms, once dementia develops, these same factors may be associated with a faster rate of decline.[39] Although it is plausible that

achieving higher educational attainment and pursuing more complex occupations provide cognitive stimulation that may confer benefits to cognitive functioning in later life, it is important to note that there are potential confounds associated with such variables, such as socioeconomic status.

Bilingualism

Another factor that is emerging as a potent moderator of cognitive aging is bilingualism. Bilingualism requires executive control to coordinate the selection of the appropriate language to use in a particular context and monitoring of the situation to control switching between languages. Some evidence suggests that bilinguals have slower rates of cognitive decline than monolinguals do.[41] Incredibly, lifelong bilingualism appears to delay the onset of dementia by approximately 4 years.[42] Schweizer et al[43] compared a group of bilingual AD patients with a group of monolingual AD patients who were matched on level of cognitive function. The bilinguals showed more atrophy in the medial temporal lobes yet equivalent memory and executive functioning as monolingual controls. In addition, bilinguals have both enhanced white matter integrity in the corpus callosum extending to the superior and inferior longitudinal fascicule and anterior to posterior functional connectivity.[44] This pattern suggests a link between bilingualism and brain reserve (see below) whereby enhanced frontal connectivity can compensate for age-related volumetric reductions in medial temporal lobes.

Critically, whereas other variables that have been suggested to promote brain reserve (eg, diet, education, occupation) have some degree of self-selection and an association with socioeconomic status, bilingualism is not necessarily associated with these confounds. In the great majority of cases, people become bilingual because they or their parents move to another country, so they must learn a second language to survive—it is not simply because they are bright or are "good at languages."[42]

Summary of risk factors

The great hope for the "baby boom" and subsequent generations as they age is that lifestyle interventions may prove to protect against cognitive decline associated with AD in later life. Based on observational and epidemiological studies, the most promising targets for the prevention of dementia are cognitive, physical, and social activity, as well as diet.[44] Perhaps, not surprisingly, interest among today's consumer public in learning how to prevent cognitive loss and how to strengthen such abilities in mid and later life appears to be steadily growing. It has given rise to what is now termed the brain fitness movement.

Brain Fitness Movement

The interest in finding methods to "keep our brains sharp" by maintaining or enhancing cognitive performance has led to the emergence of a new global commercial industry. Although numerous cognitive training and related "products," such as nutritional supplements, are being marketed and sold to consumers to promote brain fitness, with a few exceptions, most of these methods have scant scientific evidence to support their effectiveness.[40]

Despite the relative paucity of proven techniques to strengthen cognitive function that translates into better daily function or the prevention of dementia, the biological capacities of neurogenesis and neuroplasticity and the related concepts of brain or cognitive reserve provide a firm rationale for serious efforts to continue in this area.[40] Neurogenesis and neuroplasticity refer to the brain's ability to generate new cells and reorganize its physical structure (eg, neuronal networks) and function in response to environmental experience.[46] For example, animals living in "enriched environments" with greater cognitive stimulation display an increase in brain synaptic density and numbers of synapses, enlarged dendritic length, increased dendritic branching, and the creation (neurogenesis) and maturation of new neurons and connections.[47]

The concept of reserve refers to a threshold model of vulnerability to the cumulative effects of aging. That is, the ability to deal with pathological burden within the brain when it arises depends on the initial integrity of the central nervous system and the potential to use existing neural pathways and/or to recruit new pathways that are not typically used to accomplish a task.[48]

Cognitive training

Observational studies have shown that engaging in cognitive stimulating activities related to education and occupation is associated with superior memory and cognitive function and a reduced risk of dementia in later life; however, the results of cognitive interventions in healthy aging have largely been mixed.[40,49]

Two meta-analyses have been conducted on randomized controlled trials of cognitive training interventions in healthy older adults (one on 10 studies[50] and one on 7 studies[47]). The cognitive training interventions have varied widely, consisting of piano lessons, memory or reasoning strategy instructions, or practice at discriminating auditory tones, to name just a few. It is difficult to extract generalities from the limited number of studies that have been conducted, particularly given the vast differences in design characteristics (in total time spent training, outcome measures, longitudinal follow-up, type of control group, and sample size). Nonetheless, Papp et al[50] reported a small but significant overall mean weighted effect size of 0.16 favoring cognitive training over controls; Valenzuela and Sachdev[47] reported a larger effect size—a weighted mean difference score of 1.07. The authors of both articles noted that the effect sizes of individual studies were largest when the outcome measures were closely related to the type of training (ie, near transfer).

Some studies have examined the effectiveness of cognitive training on improving cognitive function in individuals with mild severity AD and vascular dementia. In an early review of six randomized clinical trials comparing cognitive training interventions with control conditions, none demonstrated statistically significant effects of cognitive training in any

domain.[51] The authors of this review concluded that their findings did not provide "strong support" for the use of cognitive training interventions for patients with early-stage AD or vascular dementia; however, the number of well-controlled studies and the numbers of participants were limited at the time of their analysis.

In a more recent review, Sitzer and colleagues[52] conducted a meta-analysis on controlled trials of cognitive training in individuals with AD. The authors reported a significant effect (Cohen $d = 0.47$) for cognitive training strategies in general but significant difference across specific domains ranging from 2.16 for verbal and visual learning to −0.38 for visuospatial functioning. These results suggest that cognitive training does demonstrate some potential promise in the treatment of AD. However, as with the cognitive training studies on healthy older adults, most studies report small sample sizes and use of neuropsychological test measures instead of performance-based measures of daily functioning to determine the effectiveness of the training intervention. In addition, the studies have used a wide range of treatment strategies that varied in duration, which makes it difficult to draw definitive conclusions about their overall effectiveness.

As previously discussed, it is quite important to distinguish between different types of cognitive training interventions (compensatory or strategy-based training and restorative or process-based training) and between the effectiveness of such trainings on different outcome measures (near transfer to tasks similar to the trained tasks and far transfer to everyday cognitive functioning). However, although the effectiveness of cognitive training interventions in AD remains equivocal, it is important to note that there is no evidence of any negative side effects of participating in cognitive training interventions.

Social engagement

In addition to benefiting one's psychological well-being, greater social engagement seems to also be associated with a reduced risk of dementia. Those with a larger social network had reduced incident dementia relative to a control sample in at least one observational study.[53] Although no clinical trials have investigated the potential benefits of social engagement for the prevention of cognitive decline or development of dementia, some intriguing research has been conducted on the benefits of volunteering activities on cognitive functioning and mental health in seniors. For example, the Experience Corps program consists of older volunteers working for a minimum of 15 hours per week within a school for grades K-3.[54] The work involves special areas of need within the school: literacy tutoring, management of behaviors in the children, and library use. In an 8-month follow-up study, Carlson and coworkers[55] found that active volunteer participants with impaired baseline executive functions showed the greatest degree of improvement in executive and memory functioning, whereas the similarly impaired controls declined in executive function ability ($P < 0.05$). Carlson and colleagues[55] subsequently assessed the benefits of Experience Corps in "at risk" volunteers (ie, African American women with low level of education, low income, and low MMSE score at baseline). Not only were cognitive gains found in executive inhibitory processes, but also intervention-specific increases in brain activity were observed in the prefrontal and anterior cingulate cortex at 6-month follow-up using functional MRI.

Health factors

As discussed earlier, the combination of factors that pose a risk for cardiovascular disease and type 2 diabetes—the so-called metabolic syndrome—also elevates one's risk for MCI and the development of vascular dementia and/or AD. High body mass index, atherosclerosis, hyperlipidemia, hypertension, cerebrovascular pathology, and cardiac disorders all increase the risk of developing cognitive impairment that may result in vascular dementia and/or AD. For example, older adults (mean age, 74 y) with the metabolic syndrome (n = 1,016) were more likely to develop cognitive impairment (indexed by a drop in at least 5 points on the MMSE) over 5 years than were those without the metabolic syndrome (n = 1,616).[56] Current smokers were more likely than former smokers or nonsmokers to exhibit cognitive decline (MMSE) over at least 1 year (relative risk, 1.41; 95% CI, 1.16-1.71).[57] Individuals with type 2 diabetes were more likely than nondiabetic individuals to show cognitive decline (MMSE; odds ratio, 1.2; 95% CI, 1.05-1.4) over 2 to 6 years.[58] In concert with these findings, a great deal of research has been increasingly focused on the potential for modifications in diet and exercise to protect against vascular risk factors associated with cognitive decline and dementia.

Diet

Several observational studies have shown that a diet rich in nuts, fish, fruits, and vegetables—the so-called Mediterranean diet—is associated with a reduced risk of dementia and AD.[59,60] For example, Gu et al[61] categorized the reported food consumption of 2,148 older adults based on the composition of specific nutrients in their diet (ie, saturated fatty acids, monounsaturated fatty acids, omega-3 and omega-6 polyunsaturated fatty acids [PUFAs], folate, and vitamins E and B_{12}). The authors assessed the association between nutrient intake from whole dietary patterns and risk of developing AD after approximately 4 years. The dietary pattern that was significantly associated with reduced AD risk was a diet rich in omega-3 and omega-6 PUFAs, vitamin E, and folate and low in saturated fatty acids and vitamin B_{12}. The protective dietary pattern was positively correlated with intake of dark and green leafy vegetables, salad dressing, nuts, fish, tomatoes, poultry, cruciferous vegetables, and fruits and negatively associated with intake of high-fat dairy, red meat, organ meat, and butter. Importantly, the association between this dietary pattern and AD risk remained even after controlling for factors such as age, education, ethnicity, sex, smoking, alcohol consumption, use of nutrient supplements, and APOE status. Moreover, a healthy diet (consisting of a similar dietary pattern) at midlife has been associated with a decreased risk of dementia/AD in late life.[62]

Unsurprisingly, there has been increasing consumer interest in the consumption of dietary supplements containing

antioxidants and/or PUFAs. However, most randomized controlled studies comparing nutrient supplementation with placebo have not consistently found an association between use of supplements such as vitamin E and omega-3 fatty acids and cognitive outcomes.[45] Plassman et al[63] reviewed observational and randomized controlled trials on nutrient supplementation and concluded that there was little evidence to suggest that taking dietary supplements protects against cognitive decline. Current research on supplementation is focusing on the possible benefits of statins and homocysteine-lowering supplements on cognitive functioning.[16,64-66] However, many researchers are beginning to acknowledge the importance of considering one's whole dietary pattern because of potential interactions or synergistic effects among different components of a diet.

Encouragingly, diet interventions have fared better than supplement interventions. For example, a 4-week high-fat, high-glycemic index diet versus a low-fat, low–glycemic index diet had dramatic effects on AD biomarkers including CSF levels of Aβ42, APOE (which is important for Aβ clearance), and F2-isoprostanes (which are indicative of neuronal injury). The high-fat diet moved CSF Aβ42 levels in a direction consistent with amplified AD-related pathology, whereas the low-fat diet moved levels in the opposite direction; the low-fat diet increased levels of APOE and reduced levels of F2-isoprostanes, whereas the high-fat diet increased F2-isoprostane concentrations. The low-fat diet also increased delayed visual recall.[67] Although the small, restricted sample of this study limits the generalizability of these findings, it hints at the possibility of even short-term dietary interventions to prevent or reverse some aspects of the pathophysiological process and/or cognitive outcomes of AD.

Physical exercise

Observational studies have generally shown that greater amounts of physical activity, broadly defined, over the course of one's lifetime are associated with a reduced risk of dementia.[68] Encouragingly, the positive effects of exercise training interventions in later life have also revealed benefits to memory and cognitive function.[49] For example, Lautenschlager et al[69] conducted a randomized controlled trial on 138 adults older than 50 years with memory complaints. Participants were randomly assigned to either a 6-month exercise program or education classes and standard care. Whereas those in the exercise group had improved scores on the Alzheimer's Disease Assessment Scale–Cognition, those in the control group had declining scores, an advantage that was maintained at the 18-month follow-up. In a study conducted by Erickson et al,[70] the participants, 120 older adults without dementia, were randomly assigned to either an aerobic exercise training group (mean age, 67.7 y) that engaged in approximately 30 minutes of walking, three times per week, for 1 year or a stretching control group (mean age, 65.5 y) that engaged in the same number of sessions.[70] Strikingly, exercise training increased hippocampal volumes and memory scores; in contrast, hippocampal volumes and memory scores declined over the 1-year study period in the control group.

Some research has suggested that the beneficial effects of exercise may be particularly robust for women. In a 6-month randomized control trial, Klusmann and colleagues[71] assessed the effects of mental and physical activity on cognitive performance in older women 70 to 93 years of age. Study participants were randomly assigned to an exercise group, a computer course group, or a control group. At follow-up, women in the computer group and the exercise group showed improvements in episodic memory and maintenance in working memory compared with the control group, which showed a decline in cognitive performance. In another study, those who participated in 45 to 60 minutes of aerobic exercise three to four times a week over 6 months demonstrated improved executive functioning relative to a stretching and balance training control group; the findings were notable particularly for women in the exercise group.[72]

Some research has suggested that there may be synergistic effects of physical exercise and other factors such as diet and HT. For example, the researchers of the aforementioned diet intervention who showed the impact of high- versus low-fat diet on CSF Aβ42 levels in healthy older adults and individuals with MCI subsequently revealed that the effects were moderated by participant's level of physical activity. For healthy adults, high amounts of physical activity minimized the negative effect of a high-fat diet on CSF Aβ42 levels, whereas for individuals with MCI, high physical activity had enhanced the effects of the low-fat diet on Aβ42 levels.[73] Some studies have even combined physical exercise interventions with other interventions with the hope that physical exercise might potentiate the effects of other factors. For example, Scarmeas et al[74] have shown additive effects of physical exercise and diet interventions. Erickson and colleagues[70] examined the effects of both HT and level of physical fitness in postmenopausal women and found significant interaction effects. Regardless of whether the elderly women had been treated with HT, physically fitter women demonstrated enhanced cognitive performance and increased measures of brain volume. In addition, shorter term HT (<10 y) was associated with greater gray matter volumes in the prefrontal and temporal cortex and enhanced executive control performance relative to longer term HT (>16 y). However, higher levels of aerobic fitness negated the relatively negative effects of long-term HT.

Although these studies focused on individuals without dementia, exercise interventions in patients with AD have revealed benefits as well. Rolland and colleagues[75] conducted a randomized controlled trial of an exercise program with 134 nursing home residents with AD. Residents either received standard care or participated in 1 hour of strength, balance, flexibility training, or walking twice a week for 12 months. Those in the intervention group had a slower rate of decline in activities of daily living than did those who received routine nursing and medical care. Heyn and colleagues[76] conducted a meta-analysis of 12 randomized controlled trials that examined the effects of a physical exercise intervention on the cognitive function of individuals with dementia. Most studies showed a medium to large effect size (mean effect size,

0.57). Incredibly, many of the programs consisting of at least 30 minutes of aerobic exercise (typically walking) per session, for at least three sessions per week and over at least 6 months, significantly reversed some of the cognitive impairments of these individuals with dementia.

Summary of risk for and prevention of AD

It is now understood that AD is likely to be multidetermined through interactions between heritable causal and susceptibility genes, environmental exposures, midlife health status, and lifestyle choices. In addition, mounting scientific evidence suggests that the neuropathological processes characteristic of AD can be detected several years before the onset of clinical signs and symptoms. Although most available brain fitness methods and products have scant scientific evidence to support their effectiveness, ongoing research advances do indeed support the potential for memory and other intellectual functions to be strengthened and maintained through cognitive training, social engagement, dietary choices, and physical exercise. Particularly promising effects have been observed from aerobic exercise interventions. However, despite some hopeful results, given the methodological limitations of so many of the studies published to date in the brain fitness literature, we cannot yet conclude that there are available interventions that can reliably reduce our risk for dementia or AD as we age.

CONCLUSIONS

It has been a little more than a century since Alzheimer first described the clinical and pathological features of the dementia affecting his now legendary middle-aged patient Auguste D. Since that time, we have come to understand that the disorder subsequently named for him is the preeminent cause of dementia. AD in our age is ranked among the most serious public health challenges facing an aging world population. Long past Alzheimer's time, the pathogenesis of the disease is today significantly better understood but still frustratingly complex and vexing. However, despite the challenges ahead, new and exciting approaches for earlier diagnosis and intervention are emerging. With our improved appreciation for the capacity of the older brain to be potentially strengthened through methods that exploit the innate capacities of neurogenesis and neuroplasticity, middle-aged and older adults may now experience a new sense of hope that we can keep our brains as well as our bodies healthier longer; at least this is what we today wish for. Future generations must be left to determine whether our present-day aspirations for the fruits of the brain fitness movement will ultimately prove to be a breakthrough moment in our species' ability to stave off decline and endure or be seen as yet another period of well-intentioned but narcissistic human folly.

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