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Midlife predictors of Alzheimer's disease

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Abstract

Factors contributing to increased risk for Alzheimer's disease (AD) include age, sex, genes, and family history of AD. Several risk factors for AD are endogenous; however accumulating evidence implicates modifiable risk factors in the pathogenesis of AD. Although the continued task of identifying new genes will be critical to learning more about the disease, several research findings suggest that potentially alterable environmental factors influence genetic contributions, providing targets for disease prevention and treatment. Here, we review midlife risk factors for AD, and address the potential for therapeutic intervention in midlife.

Keywords

Alzheimer's disease; dementia; midlife; genes; family history; estrogen; vascular risk; education; MRI

1. Introduction

Alzheimer's disease (AD) is an irreversible neurodegenerative disorder characterized by progressive loss of memory and other cognitive function. In the moderate stage of AD, patients show personality changes, loss of behavioral skills, and at the disease end stage, loss of motor skills and death. An estimated 35.6 million people worldwide will be living with dementia in 2010. This number is estimated to nearly double every 20 years, to 65.7 million in 2030, and 115.4 million in 2050 [1], with AD comprising between 50-70% of these dementia cases [1-3]. Presently, there is no cure or effective treatment for AD, although several promising therapies are under investigation. In order to develop preventative therapies, it will be necessary to identify the contributors to disease, and test the efficacy of interventions early in the disease process prior to the destructive neurodegeneration that is characteristic of AD. To that end, several predictors of AD—both endogenous and modifiable—are already identified, and several more candidates are presently under study. Here, we describe both potential and established risk factors for AD, and discuss the significance of research findings in the context of disease prevention.

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2. Neuropathology of AD

It is generally accepted that AD neuropathology accumulates slowly before the clinical diagnosis of probable AD. A definitive diagnosis of AD is only made post mortem, whereupon the brain is characterized by two main pathological features: neurofibrillary tangles (NFTs), and amyloid plaques. Additionally, AD involves a significant loss of neurons which may be particularly discriminative in diagnosing AD in the oldest old [4], although presently neuronal loss is not considered part of the diagnostic criteria. Neurofibrillary pathology is secondary to the abnormal metabolism (hyperphosphorylation) of tau protein. Tau protein is highly concentrated in brain cells and appears to promote cell stability by linking microtubules that form the “skeleton” of neurons, oligodendrocytes, and astrocytes. Tau also has a critical function in anterograde axonal transport. In AD, hyperphosphorylation of tau appears to underlie the transformation of the protein from a soluble cytoskeletal element to an insoluble form of tau that gradually forms aggregates inside the neuronal cell body, NFTs. The second pathological feature of AD is the formation of neuritic amyloid plaques, deposits consisting of A β -peptide resulting from the enzymatic cleavage of Amyloid Precursor Protein (APP), and surrounded by neurofibrillary pathology and microglia [5]. Both NFTs and neuritic plaques are presumed contributors to neuronal death in AD.

Several investigations have focused on characterizing brain alteration present in the stage prior to AD diagnosis: the “preclinical” stage, also called “asymptomatic AD”. Post mortem investigations of non-demented individuals indicate that approximately 40% of people 65 years of age and older may harbor AD neuropathology [6]. In addition, AD associated pathology in the absence of dementia has been found at surprisingly young ages. In an evaluation of 2,661 brains obtained from individuals aged 25-95, Braak and Braak [7] found plaques and tangles in individuals in the lowest age group (below 30 years of age). By age 41-50 years, at least some extent of amyloid pathology was present in close to 10% of individuals, and by 51-60 years, the percentage was over 15%. By age 41-50 years, some extent of tau pathology was present in over 40% and by age 51-60 years, some extent of tau pathology was present in over 60%. The majority of these cases would not have satisfied criteria for AD diagnosis and the possibility that NFTs and plaques are a feature of benign aging can not be excluded, however, Braak and Braak observed that pathology, once initiated, appears to be an ongoing process [7].

3. Genetic Risk

Apolipoprotein E (APOE) is the most well-known genetic risk factor for late onset AD. The APOE gene, located on chromosome 19, has three major alleles, ϵ 2, ϵ 3, and ϵ 4, with six possible genotypes (ϵ 2/ ϵ 2, ϵ 2/ ϵ 3, ϵ 2/ ϵ 4, ϵ 3/ ϵ 3, ϵ 3/ ϵ 4, ϵ 4/ ϵ 4). The ϵ 2 allele shows a moderately protective effect against AD, and ϵ 4 confers an increased risk. The ϵ 4 allele frequency is approximately 15% in the general population but approximately 40% in patients with AD. APOE ϵ 4 does not determine who will develop AD, but it is associated with earlier development of AD, and being homozygous for ϵ 4 (ϵ 4/ ϵ 4 genotype) confers the highest risk [8,9]. A regulator of cholesterol, APOE ϵ 4 is associated with both a higher absorption of cholesterol in intestine, and higher plasma cholesterol levels; a characteristic that may have once contributed to APOE ϵ 4's purported beneficial effect on survival in conditions of low food supply [10]. APOE ϵ 4's modern association with vascular disease, diabetes, and dementia, suggests that together with present environmental variables, its contribution is at least partially harmful.

Although APOE ϵ 4 has been linked to health disorders across the lifespan, it is primarily associated with diseases of aging, and its negative effect is most likely realized at middle-age. APOE ϵ 4 homozygotes begin to show cognitive decline in their 50s [11], while heterozygotes decline in their 60s, and cognitive decline in noncarriers is delayed until their 70s [11]. Brain

imaging using F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) indicates that preclinical brain abnormalities are present in cognitively normal APOE $\epsilon 4$ carriers aged 50-65 years. These individuals showed a pattern of decreased glucose metabolism that largely overlaps with the pattern found in AD, including decreased metabolism in medial temporal lobes, lateral parietal lobes, and posterior cingulate [12]. Both PET and magnetic resonance studies indicate that cognitively normal APOE $\epsilon 4$ carriers also show differences in brain structure compared to non-carriers, [13,14] differences in functional activation during cognitive tasks [15], decreased brain perfusion [16], increased amyloid burden [17], and differences in brain white matter compared to non-carriers [18,19].

APOE $\epsilon 4$ is the most widely studied gene associated with late onset AD and has been linked with a number of brain changes, however, its failure to account for the majority of late onset AD cases combined with the high heritability of the disease signifies that one (or likely more) genes remain to be identified. Autosomal-dominant AD is caused by a mutation in one of three specific genes (*PSEN1*, *PSEN2*, or *APP*), but accounts for only 5-10 percent of all AD cases. Several candidate genes for late onset AD have been identified using genome-wide association studies that investigate genetic variation across the entire human genome in order to test for relationships with the presence or absence of a particular disease. Of the single nucleotide polymorphisms (SNPs) associated with AD risk, three promising candidates include a variant of *CLU*, encoding clusterin, on chromosome 8; a variant of *CR1*, encoding the complement component (3b/4b) receptor 1, on chromosome 1 [20]; and variants near a gene encoding the PICALM protein [21]; [see Bertram & Tanzi for a review of other topical genes including *ACE*, *GAB2*, *MAPT*, and *SORL1* [22]]. Despite these advances, present gene candidates do not show the odds ratio of disease association that is found with APOE, and much of the heritability of AD remains unexplained.

4. Family History

Offspring of parents with AD have six time greater risk for developing the disease compared to those without a family history of AD [23-25]. Not surprisingly, APOE $\epsilon 4$ is overrepresented in individuals with family history; however, it appears that family history embodies a risk (either genetic, environmental, or both) that exerts an effect above and beyond $\epsilon 4$. The presence of family history together with APOE $\epsilon 4$ increases cumulative lifetime risk for AD. For first degree relatives of AD patients, possessing a 3/3 genotype is associated with a life time risk for AD of 29.2%. The life time risk increases to 46.1% for first degree relatives with a 3/4 genotype, and further increases to 61.4% for those with a 4/4 genotype [26].

Due to their increased risk, adult children of AD patients are a rich cohort for understanding predictors of AD. At present, established cohorts include the Adult Children Study at Washington University, MO, [27], and the Wisconsin Registry for Alzheimer's Prevention (WRAP) [28]. WRAP is an NIH-funded statewide registry of over 1300 adults (ages 40-65 years), 900 of whom are offspring of AD patients. Family history positive (FH+) participants have parents with autopsy or medical record confirmed AD, and controls in WRAP have non-demented parents, with mothers who survived to at least age 75, and fathers to at least age 70. The FH+ group is currently close to 1000 participants and the control group is over 300 participants. Baseline visits occurred between 2001 and 2006, with 4 year follow-up visits between 2006 and 2010 (ongoing), and subsequent follow up every 2 years as a third wave of testing began in 2008. This project and others confirm that family history of AD embodies a risk factor independent of APOE $\epsilon 4$, and it is expected that the features defined in FH+ participants may serve as potential prognosticators of incipient AD. Cognitively normal adults with positive family history show altered neuropsychological function [28,29], altered functional brain imaging patterns [30-36], differences in brain white matter microstructure

[37], altered resting brain perfusion [36], and lower rate of cerebral metabolism of glucose [38,39] compared to non-risk individuals.

5. Sex

The incidence of AD in women is 1.5–3 times higher than the incidence in men [40]. Women's increased risk for AD coincides with menopause [41,42], implicating estrogen deficiency as the primary sex-related risk factor for AD. Estrogen reduces the formation of β -amyloid [43, 44] and protect against its toxic effects [45] *in vitro*. Additionally, several studies in animal models of AD support a protective effect of estrogen against AD pathology [46-50], although some results are negative [51-53] and additional work is needed.

Epidemiological studies of hormone therapy suggest a protective effect of estrogen, including results of the Cache County study [54], the Baltimore Longitudinal study of Aging [55] and others [56,57]. Notwithstanding these encouraging results, an ancillary study of the Women's Health Initiative Study—a large, randomized, controlled, blinded trial—the WHI Memory Study (WHIMS) found adverse effects of hormone therapy whereby participants in the treatment group showed an increase in the incidence of dementia and cognitive decline [58].

WHI changed clinical practice and decreased the prevalence of hormone therapy use [59-64], primarily due to the finding that estrogen increases the risk of cardiovascular disease [65]; however, methodological limitations continue to be of concern and WHI's generalizability to all cases of hormone therapy has been questioned [66-69]. In particular, it is possible that the results of the trial are limited to the type of estrogen administered in WHI, conjugated equine estrogen (CEE). CEE binds to estrone receptors and does not replace the form of estrogen that shows a larger decline at menopause: estradiol. Additionally, the age of WHI participants (mean age 63 years) was well over the mean onset age of climacteric. With regard to the cognitive findings of WHIMS, estrogen administered at older ages may facilitate increased brain damage as opposed to providing a protective effect [70]. Approximately 70% of WHI participants were between the age of 60 and 79 years [68], an age range where brain cell damage induced by oxidation and inflammation is likely already present [71]. Animal models suggest that neuroinflammation interacts with estrogen. Estrogen administration before lipopolysaccharide (LPS) induced inflammation is protective, while administration post-LPS is detrimental [72]. These findings and others underscore the need for examining timing of hormone therapy. Two clinical trials are presently underway to consider differential effects of early and late hormone therapy: the Kronos Early Estrogen Prevention Study (KEEPS) (Harman et al. 2005), and the Early versus Late Intervention Trial with Estrogen (ELITE)[73]. The outcomes of these trials will be important for guiding future research initiatives.

6. Vascular Risk

Vascular risk factors are linked with an increased risk of AD [74-79]. The extent to which vascular mechanisms serve as instigators of AD or are concomitant but separate facets of disease, remains to be clarified. Since vascular risk factors in midlife predict later development of AD, suggests that vascular mechanisms (at least in part) may play a role in AD pathogenesis.

Midlife hypertension has a stronger association with dementia than late-life blood pressure levels [80,81]. Elevated serum cholesterol levels in midlife also increase the risk of developing AD decades later [74,82-84]. Obesity (BMI ≥ 30) at midlife is associated with over a three fold increased risk for AD, while being overweight (BMI ≥ 25) is associated with a two fold increased risk for AD [85]; this association holds even when other cardiovascular risk factors and diabetes co-morbidities are controlled. Similarly, the Cardiovascular Health Study, a population-based, longitudinal study of coronary heart disease and stroke, found that a high BMI at age 50 was associated with a higher risk of dementia [86], while at older age BMI no

longer appears to offer protection—individuals in CHS who were 65 or older did not show a relationship between BMI and dementia.

Using data from the population-based Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) study ($n = 1409$), Kivipelto and colleagues confirmed that increased vascular risk at midlife predicted dementia 20 years later [87]. Kivipelto et al. constructed a baseline risk score composed of body mass index, systolic blood pressure, diastolic blood pressure, total cholesterol, current smoking status, and level of physical activity. The risk of dementia for those with the highest baseline risk score was 16.4%, compared to only 1% for those with the lowest risk score. Of the factors comprising the overall risk score, hypertension, hypercholesterolaemia, and obesity were the most predictive of dementia.

Risk of AD is also elevated in the presence of diabetes, in particular type 2 diabetes and hyperinsulinemia [88,89]. The onset of type 2 diabetes is most common in middle age and risk for AD is elevated when diabetes occurs in middle age compared to old age; diabetes before the age of 65 corresponds to a 125 percent increased risk for AD [90]. Several findings link hyperinsulinemia (increased levels of circulating insulin associated with insulin resistance) to AD. Insulin competes with A β for insulin degrading enzyme (IDE) by crossing the blood brain barrier from periphery to CNS. IDE is the principal regulator of A β levels in neurons and glial cells and IDE knockout mice have hyperinsulinemia, glucose intolerance, and increased cerebral accumulation of A β [91]. Peripheral hyperinsulinemia can also increase AD risk by impeding the production of brain insulin, reducing amyloid clearance [91].

Like hypertension, hypercholesterolemia, and obesity, diabetes has a genetic component [92], but its known association with diet, and its increasing prevalence in industrialized countries suggests modulation by environment. Even modest changes such as weight loss of 5% to 10% can reduce the risk of conversion from impaired glucose tolerance to diabetes [93] which in turn may decrease risk for AD.

7. Environmental & Lifestyle Factors

Several studies support a relationship between lifestyle and decreased risk for AD, with protective candidates including diverse factors such as healthy diet [94], moderate alcohol consumption [95,96] and social activity or support [97,98]. Education is also considered protective against AD [99,100]. Studies of identical twins from the Swedish Twin Registry with dissimilar levels of basic education indicate that the more educated twin—found to be more likely to be engaged in mentally stimulating activities—shows a delay in dementia onset compared to their co-twin [101]. The protective effect of education may be attributable to cognitive reserve (or brain reserve), where increased stimulation (via learning) results in brain changes that allow people to cope more effectively with brain damage. Although education is not associated with reduced neuropathology [102,103], experience based brain changes may include increased synaptic density, neurogenesis, or improvements in the efficiency and flexibility of brain networks which in turn provide a buffer against normal or pathological age-related decline [104]. The observed protective effect of education may also be due to the fact that individuals with a higher education elude dementia diagnosis, perhaps due to superior test-taking skills. Further work is needed to determine if the beneficial effect of education generalizes outside of a clinical setting.

While educational achievement and other lifestyle factors may be shaped in early life, data indicate that activities even at midlife are important for predicting later AD. The Alzheimer's Disease Case-Control Study at Case Western Reserve University used a retrospective design to assess cognitive activity in early and middle adulthood. Of importance for determining group membership (AD vs. control), was the intensity of intellectual activity in middle adulthood, not early adulthood. Furthermore, an increase from early to middle adulthood in the percentage

of intensity of intellectual activities was associated with a statistically significant decrease in the probability of membership in the case vs. the control group even when controlling for covariates, again underscoring the importance of midlife intellectual activity [105].

Like mental activity, physical activity has also been linked to improved cognition and AD prevention [106,107]; and similar to intellectual activity, midlife level of physical activity is predictive of dementia. A study of 1449 people surveyed about physical activity at mid-life and re-assessed approximately 20 years later indicated that participating in leisure-time physical activity at least twice a week was associated with lower odds of dementia later in life compared to a sedentary lifestyle [108]. Similarly, analyses of twins from the Swedish Twin Registry (2870 controls compared to 176 AD cases) indicate that mid-life physical activity is higher in controls compared to AD cases [109]. It is possible that mid-life differences are already indicative of preclinical disease, however, examples of intervention—such as in physical activity—suggest that cognitive outcomes are modifiable [107,110].

8. Treatments

At the time of a clinical AD diagnosis, neurodegeneration is well underway and significant brain damage has already occurred. Clinical treatment of AD is primarily governed by drugs that target AD-related deficiency in acetylcholine through the use of cholinesterase inhibitors or drugs that inhibit the breakdown of acetylcholine, such as donepezil, rivastigmine and galantamine [111]. Other drugs such as memantine and possibly lithium regulate glutamate activity which is known to be abnormal in the AD brain [112,113]. While these treatments may offer temporary protection against cognitive decline, they do not reduce neuronal loss.

Novel AD therapies target specific components of the disease and continue to undergo development. Immunotherapy treatments (vaccines that promote A β clearance from the brain) include active immunization with A β and passive immunization with anti-A β antibodies. This treatment increases amyloid clearance, however, a phase II clinical trial involving active immunization of mild to moderate AD patients was halted after 5% of patients developed meningoencephalitis [114]. Brain-derived neurotrophic factor (BDNF) is associated with reversal of synapse loss, normalization of aberrant gene expression, improvement in cell signaling and restoration of learning and memory in animal models. A small trial in humans showed deceleration of AD progression in patients who were injected with cells that increased nerve growth factor levels in forebrain. Follow-up PET scans showed a significant increase in glucose uptake in most cortical regions and cerebellum. However, complications arising from the procedure caused brain injury in two of the patients and death in one [115]. Therapies that target the inflammatory and oxidative components of AD are supported by epidemiological studies, however when tested in clinical trials, the majority have shown disappointing results in the treatment of AD or MCI (e.g. NSAIDs, Vitamin E, Gingko Biloba, and Ginseng) [116-120] or the results of clinical trials are not yet available (Curcumin)[121].

Although treatments continue to undergo development, none have proven capable of halting neuronal death or reversing the neurodegenerative changes that have already occurred by the time AD is diagnosed. Even mild cognitive impairment—a transition for some patients between normal aging and AD—shares a similar neuropathological profile to AD [122], suggesting that “true” preventative trials need to be initiated prior to cognitive decline, at least by midlife and possibly earlier. Preventative therapies that target the underlying pathological mechanisms in AD, including the formation of amyloid plaques, tau pathology, inflammation, estrogen deficiency, and vascular etiologies, if implemented prior to cognitive decline, may reveal the more promising effects that have been suggested by epidemiological studies.

9. Conclusion

The high heritability of AD and its association with risk genes for co-morbid disease underscore the genetic component of the disease, and reinforce the need for additional genome wide association studies. Other endogenous factors that predispose to developing AD include family history of AD, and female sex. Equally important however, are studies that suggest these variables are not sufficient in determining the disease. Twin studies underscore that even in individuals that are genetically identical, epigenetic forces are in effect that predispose certain individuals to disease while others are protected [123]. Factors that appear non-modifiable may have their influence attenuated by intervention. If initiated early, it is possible that aging related hormonal changes may be tempered by hormone therapy; hypertension, hypercholesterolaemia, obesity, and diabetes (all of which have genetic contributions) may be modified by diet, exercise, or pharmaceutical intervention; and even the effect of APOE, the most established genetic risk factor for late onset AD, appears to be modified by several factors including nutritional factors like B12 [124], alcohol consumption [125], exercise [126], estrogen [127,128], antihypertensive treatment [129], and education [130].

The projected incidence of AD in the coming years can be dramatically reduced if disease development could be delayed by only a few years [131]. Studies focusing on midlife are essential to understanding the potential for prevention of AD. Furthermore, positive results of midlife studies provide an incentive for advocating simple preventions at earlier life stages when prevention is more likely to be beneficial. Future work must not only aim to provide clinicians with the tools they need to predict and detect AD, but also to provide patients at risk with reasonable and hopeful options for disease prevention.

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