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Characterizing the Preclinical Stages of Alzheimer's Disease and the Prospect of Presymptomatic Intervention

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Abstract

Studies of asymptomatic carriers of genes that are known to predispose to Alzheimer's disease (AD) have facilitated the characterization of preclinical AD. The most prevalent genetic risk factor is the e4 allele of apolipoprotein E (APOE). Neuropathological studies of young deceased e4 carriers have shown modest but abnormal amounts of neocortical amyloid and medial temporal neurofibrillary tangles that is also reflected in cerebrospinal fluid (CSF) biomarkers, abeta-amyloid and phosphotau in particular. MRI studies have shown progressive hippocampal and gray matter atrophy with the advent of mild cognitive impairment (MCI), and fluorodeoxyglucose PET scans show reduced cerebral metabolism in posterior cingulate and related AD regions evident even in 30 year olds. Cerebral amyloidosis disclosed by more recent amyloid ligand PET studies in asymptomatic 60 year olds increases in parallel with e4 gene dose. Longitudinal neuropsychological studies have revealed accelerated memory decline in e4 carriers beginning around age 55–60 years whose severity again parallels e4 gene dose. The clinico-pathological correlation of declining memory and AD-like neuropathological change defines preclinical AD and has set the stage for the accelerated evaluation of presymptomatic AD treatments. In this article, we briefly consider some of the earliest detectable changes associated with the predisposition to AD, and some of the prevention trial strategies that have been proposed to help find treatments to reduce the risk, postpone the onset of, or completely prevent AD symptoms as soon as possible.

Keywords

preclinical; APOE; normal aging; prevention

There is growing interest in the preclinical detection, tracking and scientific study of Alzheimer's disease (AD) and the evaluation of prevention treatments. This interest is reflected in part by the development of research criteria for preclinical AD [1] and by the development of strategies to accelerate the evaluation of preclinical (or presymptomatic) AD treatments [2, 3].

Since 1993, we have been using brain imaging methods, neuropsychological tests, and clinical ratings to detect and track the changes associated with the predisposition to AD prior to the onset of symptoms in cognitively normal people with two copies, one copy and no

copies of the apolipoprotein E (APOE) e4 allele, reflecting three levels of genetic risk for AD. We have also used this cohort to help evaluate genetic and non-genetic risk factors for AD, and to provide a foundation for the accelerated evaluation of presymptomatic AD treatments.

In this article we review some of the progress made in the characterization of preclinical AD, its distinction from normal aging, and its characterization based upon a range of laboratory, imaging, and cognitive biomarkers.

Rationale for Focusing on Preclinical Stage Alzheimer's Disease

The pathobiological onset of Alzheimer's disease (AD) is clinically silent. It takes years before patients begin manifesting memory impairment that exceeds that of their age-peers, a prognostically worrisome stage termed Mild Cognitive Impairment (MCI) and several more years before their cognitive skills decline to a functionally disabling degree heralding the clinical onset of dementia [4–6]. Fibrillar amyloid deposition, one of the two defining neuropathological features of AD, is nearly maximal by the MCI stage, while neurofibrillary tangle formation continues to advance, more or less in parallel with cerebral atrophy and progressive dementia severity [7, 8]. There remains no established way of slowing the disease, and based on preliminary findings [9], many have expressed the concern that existing anti-amyloid approaches in patients with frank dementia have been “too little too late” to maximize their potential beneficial effects.

Optimizing disease modification strategies requires intervention against appropriate therapeutic targets that may vary with disease stage. Except for a small number of well designed prevention trials utilizing agents based largely on epidemiological data [10–12], experimental paradigms to date have targeted patients with established cognitive deficits. The earliest symptomatic stage patients enrolled have been those with MCI [13] while the vast majority have enrolled patients with frank dementia when fibrillar amyloid pathology is essentially maximal. Current therapeutic failures, therefore, might reflect intervention that is either too late, or else targets that are less relevant to disease initiation and early progression [14]. For therapy to succeed, and particularly anti-amyloid therapies, intervention prior to or early in the amyloid cascade when patients are still asymptomatic, may be necessary. (While we have emphasized the need to accelerate the evaluation of preclinical AD treatments, we do not wish to suggest that we abandon the development of better treatments for symptomatic patients, some of which may involve targeting both early and later stages of the postulated pathogenic cascade, such as a combination of amyloid and tau-modifying agents [15]).

Treating asymptomatic individuals because they might one day develop AD is conceptually and operationally challenging. It first requires a better understanding of what distinguishes preclinical AD from normal aging, and second, over what timeframe symptoms of AD are most likely to emerge (there may even be some preclinical therapies that are most effective before the earliest biological changes of AD). It is well known that the risk of AD increases with age, and this has been the driving force behind most experimental designs, but since the early 1990's genetic insights have improved our understanding of disease risk, and might therefore provide a better foundation upon which to design preclinical AD trials [2, 3]. There is also a growing interest in using preclinical AD biomarkers to define individuals at increased risk for symptomatic conversion for preclinical trials, even though more information may be needed about their subsequent clinical course.

Distinguishing Preclinical Stage Alzheimer's Disease From Normal Aging

Genetic Factors

To date about 200 known autosomal dominant mutations affecting the genes for amyloid precursor protein (APP), presenilin-1 (PS1), and presenilin-2 (PS2) affecting roughly 500 kindreds are known to cause early onset familial AD (EOFAD), but collectively account for less than 1% of all cases [16]. Similarly, cerebral amyloidosis occurs in all patients with trisomy 21 (that includes the APP gene) so that patients with Down's syndrome develop progressive dementia in addition to their developmental cognitive impairment. The final common pathway underlying all three of these mutations is overproduction and deposition of cerebral abeta-amyloid. Far more prevalent, but less directly causal is the e4 allele of the gene for apolipoprotein E (APOE) that accounts for as much as half of all late onset familial and "sporadic" cases of AD [17, 18]. The global prevalence of e4 varies from as much as 40% among small populations of highly indigenous people to as low as 5% in some Mediterranean and Asian countries [19–21]. North America and Europe overall are on the higher end, with roughly 20–25% of the population having at least one copy of the e4 allele and 2% being e4 homozygotes [22]. APOE e4's exact mechanism of action is unknown, but it reduces abeta clearance [23], has known associations with abeta amyloid both intracellularly at the translocase of the outer mitochondrial membrane pore [24, 25], and extracellularly within the perivascular spaces [26] and parenchymally where the e4 isoform promotes abeta aggregation [27]. Further, lowering plasma levels of apolipoprotein E reduces cerebral abeta burden in vivo [28].

With the advent of genome-wide association studies (and next generation sequencing studies), we can expect to see a growing number of AD susceptibility genes, with more modest effects than the APOE e4 allele. To date, there are at least 10 confirmed susceptibility genes [29–35] (and www.alzgene.org), which are less likely to be useful in predicting a person's clinical course, but may help to clarify disease mechanisms and suggest new treatment strategies.

Neuropathology

Neuropathological studies of normal aging and AD have shown overlap between the two. Neurofibrillary tangle (NFT) formation begins in the entorhinal cortex, is nearly universal over age 65 years, and is generally considered part of normal aging. Extension of NFTs into neocortical regions, however, is never considered part of normal aging and only occurs to a significant extent in those who develop AD or another tauopathy [7, 36]. Amyloid deposition, in contrast, begins in neocortical regions, and while it is a hallmark feature of AD at least 40% of individuals dying after age 65 years without signs of dementia have neocortical amyloid plaques at autopsy suggesting it may be a part of either normal or "pathological" aging [7, 8, 37].

It has been known for decades that many nondemented elderly patients have incidental AD-like neuropathology in their brains discovered at autopsy [38, 39]. More recently it has become possible to correlate such incidental pathology with APOE genotype. In a large Finnish series, Kok et al showed that 40% of e4 carriers dying in the 50's had some neocortical amyloid, and 40% had some neurofibrillary tangle pathology [40]. Though mental status was not reported, it is reasonable to assume that the vast majority of these individuals were nondemented at the time of their deaths simply on the basis of their young age. In an elderly cohort, Caselli et al found that neocortical amyloid load corrected with APOE genotype in the brain overall, in all subregions examined, and in cerebral vasculature [41]. Further, non-neuritic plaques accounted for the difference. There was no significant difference in neuritic plaques or NFT's. That "benign" amyloid pathology correlated with

APOE genotype raises the question of whether even benign forms of amyloid are an early stage of a continuous AD spectrum, an inference further supported by imaging data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort that showed *e2* carriers had less atrophy than *e3/3* homozygotes [42]. These data suggest that changes of normal aging merge smoothly into those of AD without any discontinuity or clear dividing line.

Imaging

Brain imaging and cerebrospinal fluid (CSF) biomarkers continue to help in the preclinical detection, tracking, and scientific study of AD. While the range of informative imaging measurements continues to grow [43], the best established measurements for the preclinical detection and tracking of AD include structural magnetic resonance imaging (MRI) measurements of regional and whole brain tissue shrinkage, fluorodeoxyglucose positron emission tomography (FDG PET) measurements of decline in the regional cerebral metabolic rate for glucose (CMRgl), and PET measurements of fibrillar amyloid- β (A β) burden.

For instance, reductions in hippocampal and entorhinal cortex volumes become apparent in the early stages of memory decline and may anticipate progression to MCI and Alzheimer's dementia [44–48]. Other MRI studies have found reductions in regional brain volume, cortical thickness and gray matter and accelerated rates of brain tissue loss in cognitively normal people who are at higher genetic risk for AD or who show subsequent evidence of cognitive decline [49–54]. FDG PET studies have demonstrated characteristic and progressive CMRgl reductions, most commonly in posterior cingulate (figure 1), precuneus, parietal, temporal and frontal regions) in people with one or two copies of the *APOE e4* allele, in Down syndrome patients and mutation carriers at risk for autosomal dominant early-onset AD, and in those with higher rates of subsequent cognitive decline [55–67]. PET studies using Pittsburgh Compound B (PiB) and other radioligands have found significant fibrillar A β deposition in about 30% of cognitively normal adults over the age of 70, perhaps 10–15 years before clinical onset, and that the magnitude and spatial extent of fibrillar A β is associated with older age and the genetic risk for late-onset AD [68–75; figure 2]. These studies have found preferential deposition in the striatum in carriers of some but not all early-onset AD-causing mutations AD [67, 76]. They may ultimately determine the extent to which fibrillar A β , alone or in combination with other measurements, predicts subsequent clinical decline.

Other imaging techniques have contributed to the preclinical study of AD. For instance, functional MRI studies have suggested altered patterns of regional activation and deactivation during memory encoding or other cognitive tasks in APOE *e4* carriers and early-onset AD-causing mutation carriers [77, 78]. Functional connectivity MRI studies have suggested dysfunction of the default mode network in the clinical and preclinical stages of AD [79–81].

What are the earliest brain changes associated with the predisposition to AD? As previously noted, PET studies suggest the onset of significant fibrillar A β burden about 10–15 years before the clinical onset of AD and that it may reach a virtual plateau by the time most patients have MCI. It has been suggested that fibrillar A β deposition is associated with non-progressive reductions in CSF A β_{42} levels and that it anticipates downstream brain imaging and CSF changes [82], including progressive MRI measurements of brain shrinkage, progressive PET measurements or rCMRgl decline, nonprogressive elevations in CSF total tau and phospho-tau levels and, eventually, cognitive decline [1, 83]. Several imaging studies have suggested even earlier functional and structural brain changes, as reflected in young adults, adolescents and children carrying the *APOE e4 allele* [61; figure 1]. Other studies have shown relationships between the spatial distribution of fibrillar A β in the later

preclinical and clinical stages of AD and the spatial distribution of several functional brain measurements in normal young adults. For instance, researchers have reported some of the earliest fibrillar A β in the vicinity of the posterior cingulate cortex and precuneus [72], one of the most metabolically active regions of the brain. Other researchers have recognized the close relationship between the spatial distributions of fibrillar A β and functional connectivity MRI measurements in the default mode network (the network of brain regions that are most active in the resting state, when people are not engaged in the performance of specific tasks [84], indeed, they have demonstrated an even more striking relationship between the spatial distributions of fibrillar A β and the spatial distribution of aerobic glycolysis (the extent to which rCMRgl exceeds the regional metabolic rate for oxygen (CMRO₂ in the brain) in young adults [85, 86]. This information has led some of us to consider the role of synaptic and perisynaptic processes in the earliest predisposition to AD [87], though the biological changes associated with fibrillar A β accumulation play a relatively early role in the progressive preclinical stages of AD.

Cerebrospinal Fluid Biomarkers

Cerebrospinal fluid (CSF) studies have found characteristic abnormalities in the latter preclinical and clinical stages of AD, including reductions in CSF A β ₁₋₄₂ levels, alone or in combination with elevated total-tau or phospho-tau levels [82]. Reductions in CSF A β ₁₋₄₂ levels have been proposed to reflect accumulation of this peptide in diffuse and neuritic plaques and, based on anecdotal evidence, to precede PET measurements of fibrillar A β burden. For spinal fluid tests, the ability of a positive test to correctly predict that an individual has AD is 94%. The ability of a negative test to correctly determine that someone does not have AD approaches 100%. However, it is also possible to have a result that falls into an “indeterminate range [88].” In asymptomatic individuals, CSF levels of abeta begin to fall, suggesting the onset of AD, in the early 50’s in e4 carriers [70]. It is not known how long from the time of a positive test, an asymptomatic person will start developing symptoms, or the rate of progression of symptoms in a symptomatic person, but correlations between different biomarker tests, such as concordance of MRI-based measures of hippocampal atrophy and CSF levels abeta amyloid and phosphotau can be used to predict earlier symptomatic onset relative to those in who the biomarker tests provide disparate results [89].

While brain imaging, CSF and other biomarkers are not clinically indicated to predict a cognitively normal person’s risk for the clinical onset of AD, they promise to further characterize the trajectory of different biological changes associated with the predisposition to AD, and they promise to help define the preclinical stages of this disorder.

Neuropsychology

Because AD is slowly progressive, and because some aspects of AD such as neocortical amyloid deposition have been shown to be well advanced by the time patients present with MCI, it has been logical to assume that subtle cognitive or other behavioral changes may be detectable that precede MCI, thus constituting presymptomatic or preclinical AD. This is important for two reasons. First, it is not always clear whether small traces of AD-like neuropathology actually constitute an early stage of the disease but if they are accompanied by cognitive decline then we have fulfilled a clinical-pathological correlation diagnostic criterion. AD is a problem because it impairs cognition, and so this is its most defining feature. If it did not impair cognition, the neuropathological changes would simply be a curiosity. Second, if we can identify and characterize preclinical AD, we may be able to intervene therapeutically to delay or prevent clinically significant cognitive loss. Therapeutic targets may differ according to disease stage, and knowing when AD begins biologically may disclose a very different array of targets than when it has progressed beyond the

symptomatic threshold. Whether that biological onset is discovered neuropsychologically or otherwise matters less, but until we have defined AD onset and a way to track its preclinical progression, a multidimensional approach seems the safest strategy.

Identifying the neuropsychological onset of AD is easily confounded by the wide range of individual abilities, some of which fall below psychometric norms, especially if assessed only once. Longitudinal assessment offers the advantage of using change rather than absolute scores, but may also be confounded by the inclusion of symptomatic or imminently symptomatic individuals. That such individuals show an inexorable decline is not new information, and so even a few can skew the results of such an assessment. Most studies to date have utilized cohorts of elderly individuals with lower age limits of 65 and mean ages in the 70's and sometimes higher and so are at considerable risk of including such individuals. Community based samples additionally include, necessarily, individuals who have a variety of illnesses including stroke, former head injury, polypharmacy, and so forth so while they indeed are representative of the population, they are not appropriate for discovering subtle AD-based presymptomatic neuropsychological decline. Capitalizing on the known effect of APOE genotype on AD risk and age of onset, we found accelerated memory decline with an e4 gene-dose trend beginning around age 55–60 years (figure 3, [90]). Although executive skills appeared largely unaffected at this time save for mild differences in mental arithmetic performance, there was greater evidence of executive skill decline at the time of symptomatic conversion to MCI [91]. Among individuals with cerebrovascular risk factors (any combination of hypertension, diabetes mellitus, hypercholesterolemia, and history of cigarette smoking), presymptomatic memory decline was further accelerated in the e4 homozygote subgroup, but not in the e4 heterozygote or noncarrier subgroups (figure 4, [92]). APOE e4 homozygotes appear more vulnerable to a variety of other stresses including fatigue [93] and anxiety [94, 95].

In addition to identifying the onset of cognitive decline, there is interest in developing a battery or test that might distinguish individuals with preclinical AD from those without. It has been known for many years that psychometric tests such as the Wechsler Adult Intelligence Scale require greater correction for advancing age even by age 30, and a recent study from France has further quantified such an effect in men and women showing that decline accelerates between our 40's and our 60's [96]. Parra and colleagues have developed a memory "binding" task in which different features of a stimulus (shape and color) must be recalled. Asymptomatic PS1 mutation carriers perform normally on traditional memory tests, but perform less well than asymptomatic noncarriers on this memory binding task [97]. In our own work, however, although we have found that APOE e4 carriers have accelerated memory decline relative to noncarriers beginning between age 55–60 as noted above, we have not found that baseline comparisons of memory performance on any measure differ at this stage, even at a group level. It will be of interest therefore to test novel paradigms such as the Parra binding paradigm (or any of several new computer based tasks [98, 99] in similar APOE cohorts to see whether this might prove to be a more sensitive task.

It is reasonable to assume that at some time in the progression of preclinical stage AD toward MCI memory performance will decline to a point where baseline comparisons finally differ, but this raises the question of whether such a point would still constitute preclinical stage AD rather than early stage MCI. An alternative approach to a baseline test showing such a difference would be some form of cognitive "stress test" in which affected individuals differ only under the conditions of the stress, but not otherwise. We have previously shown that APOE e4 carriers, and particularly homozygotes have reduced ability to withstand fatigue [93] and anxiety [94, 95]. Capitalizing on this observation, Stonnington et al were able to show that when administered lorazepam, e4 carriers performed less well than noncarriers on a memory measure [100].

Defining Preclinical AD: Groups and Individuals

Putting these multiple lines of evidence together, neuropathological and imaging studies of cognitively normal individuals reveal traces of AD-like change that correlate with APOE genotype. Longitudinal neuropsychological studies have shown that these anatomical and physiological changes are accompanied by the most defining clinical feature of AD, that is cognitive and particularly memory decline. This clinicopathological correlation defines preclinical AD. Regarding the sequence of change, one of the earliest markers to date are FDG-PET patterns in young adults that reveal reduced posterior cingulate glucose metabolism [61]. (The pattern is topographically similar to FDG-PET patterns of AD itself but less severe.) Laser capture studies of posterior cingulate neurons in similarly aged APOE e4 carriers have shown mitochondrial defects in the absence of any traces of amyloid pathology [101]. Whether these findings should be considered an early stage of AD itself remains open to further study, but as such, could be construed as the earliest change of AD. Neuropathological studies and CSF biomarkers suggest that by our early 50's, amyloid pathology is beginning to accrue in APOE e4 carriers, and it is during our 50's that longitudinal neuropsychological studies have shown "normal age-related" memory decline begins to accelerate in e4 carriers. Structural imaging measures are not far behind, and a new model of AD pathophysiology begins to emerge based upon the study of young APOE e4 carriers that differs from current models based upon older adults.

Although this may help point the way forward in the designing prevention trials, it does not yet lead us to a clinical intervention. The defining features of presymptomatic or preclinical AD are based on group comparisons, while clinicians must diagnose and treat individuals. Possibly the combination of risk (APOE) and biomarker (CSF, amyloid imaging, other imaging modalities) studies, coupled with longitudinal neuropsychological assessment will further refine diagnosis and make possible the earlier identification of AD in at least some, but careful sensitivity and specificity studies will be needed before this can move from the research protocol to clinical practice.

Launching a New Era in AD Prevention Research

In our preclinical AD studies, starting in cognitively normal APOE e4 homozygotes, heterozygotes and non-carriers, and more recently extended to the study of PS1 mutation carriers from the world's largest early-onset AD kindred in conjunction with our colleagues from the Banner Alzheimer's Institute and the University of Antioquia, we have had an over-riding interest in the accelerated evaluation of preclinical (or presymptomatic) AD treatments—those treatments intended to reduce the risk or completely prevent the clinical onset of AD symptoms. We and our colleagues have argued that now is the time to launch a new era in AD prevention research, to provide the scientific means (i.e., biomarker endpoints) and financial incentives (the accelerated regulatory approval pathway) needed to evaluate the range of promising preclinical AD treatments, and find ones that work as quickly as possible.

We previously used imaging techniques to track the FDG PET and structural MRI changes associated with the predisposition to AD in late-middle-aged APOE e4 carriers, and we raised the possibility of conducting 24-month presymptomatic AD trials in these at-risk individuals without having to study thousands of people or wait many years using clinical endpoints. We soon recognized the importance of demonstrating that a treatment's effects on AD biomarker endpoints are reasonably likely to predict a clinical benefit, a necessary step before regulatory agencies are likely to offer to approve a treatment based solely on these reasonably likely surrogate endpoints under the agencies' accelerated approval provisions.

We and our colleagues have proposed an “Alzheimer’s Prevention Initiative (API)” to evaluate promising amyloid-modifying treatments in presymptomatic AD trials sooner than otherwise possible in cognitively normal persons who, based on their age and genetic background, are at the highest imminent risk of AD symptoms: 60–80 year-old APOE e4 carriers and, in our first trial early-onset AD mutation carriers [102] within 15 years of their kindred’s estimated age at clinical onset. (Leaders of the first trial are Drs. Pierre Tariot, Francisco Lopera and Eric Reiman.) We have proposed using each of the best established brain imaging and CSF biomarkers, as well as sensitive clinical endpoints (which we continue to develop) in 2–5 year trials. If, after 2 years, the treatment does not budge any of the biomarker or clinical endpoints in the right direction, we would declare futility and hopefully give our participants access to the next promising investigational treatment. If, instead, the endpoints seem to move in the right direction, we would continue to the study to assess the effects on our clinical (composite cognitive) endpoint. The API is intended to evaluate amyloid modifying treatments sooner than otherwise possible in those individuals at the highest imminent risk of AD symptoms, to help provide the evidence needed to evaluate the range of promising presymptomatic AD treatments using biomarker endpoints, to provide a better test of the amyloid hypothesis by testing these treatments at a preclinical stage in which they are more likely to exert a beneficial effect, and give at-risk individuals access to some of the most promising investigational treatments [103].

We are pleased to note that we are not alone in the effort to accelerate the evaluation of presymptomatic AD treatments (2,3,104,105). While there is no guarantee that any of the promising AD-modifying treatments now in development will reduce the risk of AD, there is only one way to find out.

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Figure 1. Reduced posterior cingulate glucose metabolism disclosed by fluorodeoxyglucose positron emission tomography in patients with probable Alzheimer's disease (left) and similar but less robust changes in cognitively normal young adult APOE ε3/ε4 heterozygotes (right).

Figure 2.

Progressively increasing cerebral amyloid burden disclosed by Pittsburgh Imaging Compound B (PiB) positron emission tomography with increasing *APOE* *e4* gene dose in asymptomatic individuals age 50–69 years old, and in patients with probable Alzheimer’s disease.

Figure 3. Mean longitudinal trajectories of the auditory verbal learning test long term memory score by APOE genotype based on a mixed model (see ref 90). There is increasing acceleration of declining memory performance beginning at age 55–60 with increasing e4 gene dose.

AVLT Longitudinal

Risk Factor: CV Risk (HT,DB,Smk,Chol; Any Epoch)

Figure 4.

Mean longitudinal trajectories of the auditory verbal learning test long term memory score by cerebrovascular risk factor status in APOE e4 homozygotes based on a mixed model (see ref 91). APOE e4 homozygotes show no test-retest effect from the earliest age in this model (40's) and have an accelerated pattern of decline relative to e4 homozygotes without any cerebrovascular risk factors.