REVIEW ARTICLE

ApolipoproteinE and Alzheimer's Disease: a Genetic, Molecular and Neuroimaging Review

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ABSTRACT: Alzheimer's disease (AD) is the most common cause of dementia in the elderly and an increasingly significant health concern in our aging population. In the past 10 years, our understanding of this disease has increased dramatically. While the discovery of three rare genetic mutations that can cause AD has provided much information about the causes and progression of the disease, a great deal of attention has been focused on apolipoprotien (ApoE) because of its involvement in the more common, later onset form of AD. Due to the rapid pace of recent advances, it has not been easy for health care professionals, researchers and the general public to keep abreast of these developments. This paper reviews recent research in ApoE and late-onset AD, emphasizing molecular neuropathological, genetic and neuroimaging findings and highlighting current controversies that remain to be addressed.

RÉSUMÉ: Apolipoprotéine E et maladie d'Alzheimer : revue des aspects génétiques, moléculaires et neuroradiologiques. La maladie d'Alzheimer (MA) est la cause la plus fréquente de démence chez les gens âgés et elle est une préoccupation de plus en plus importante en ce qui concerne la santé dans notre population vieillissante. Au cours des 10 dernières années, notre compréhension de cette maladie a augmenté considerablement. Bien que la découverte de trois mutations rares pouvant causer la MA a fourni beaucoup d'attention à cause de son implication dans la forme plus commune de la MA, la MA à début plus tardif. À cause du rythme rapide des progrès, il n'a pas été facile pour les professionnels de la santé, les chercheurs et le public en général de se tenir à date sur ces développements. Cet article revoit les recherches récentes sur la MA à début tardif et l'ApoE, en mettant l'emphase sur les observations moléculaires, neuropathologiques, génétiques et neuroradiologiques et souligne les controverses actuelles qui ne sont pas encore résolues.

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Alzheimer's disease (AD), first described in 1907 by Alois Alzheimer, is characterized by a progressive loss of cognitive abilities, usually beginning with difficulties in episodic memory and soon encompassing language, visuospatial and executive dysfunction.[1] Classic pathologic features include neurofibrillary tangles, amyloid plaques, and neuronal and synaptic loss.[2] AD is the most common cause of dementia in the elderly, affecting more than 5% of all people age 65 and over and about 25% of those aged 85 and older.[3,4] In 1991, the Canadian Study of Health and Aging estimated that over 160,000 Canadians met criteria for AD.[3] If current trends continue, by the year 2031 the number of cases of AD will triple, while the population will increase by only a factor of 1.4.[3] The direct and indirect annual costs of dementia in Canada are estimated to be over four billion dollars.[5] In addition to advancing age, risk factors for developing AD include a family history of dementia,[6] substandard education,[6] a history of head injury,[6] and, recent evidence suggests, a history of smoking.[7] Lower risk has been reported with a history of arthritis,[6] use of NSAIDs (non-steroidal anti-inflammatory drugs)[8] and use of estrogen replacement in postmenopausal women.[9,10]

Recent research into the etiology and pathology of AD has made important progress. Diverse approaches are rapidly converging to improve understanding of the disease process and methods of detection and possibly prevention. Three genes have been identified, β-amyloid precursor protein (β-APP) and two pre-senilin proteins (PS-1 and PS-2), that cause early-onset AD (before age 65), whereas apolipoproteinE (ApoE) epsilon 4 has been identified as a susceptibility gene for later onset disease. For the first time, certain individuals at risk for developing AD are being identified and treatments are being considered to slow the course of AD. Because of the rapid pace of recent advances, it has not been easy for health care professionals, researchers and the general public to keep abreast of these developments. This paper highlights recent progress in the areas of genetics, molecular biology and neuroimaging, focusing on ApoE and later-onset AD.

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The Neuropathology of AD

The major neuropathological hallmarks of AD are extracellular deposits of "senile" amyloid plaques, intraneuronal neurofibrillary tangles, synapse loss and the death of neurons.[11] Plaques and tangles are, by definition, required for the definitive diagnosis of AD;[2] however they are only detectable with tissue examination. Discussions are still ongoing concerning the best pathological criteria for diagnosis of AD.[2,12-14]

Plaques

Plaques are complex extracellular deposits in the neuropil. They contain β-amyloid (Aβ), a peptide that is 39-43 amino acids long, produced in normal cells by proteolytic cleavage of the β-amyloid precursor protein (β-APP, or APP). APP is a Type I transmembrane protein expressed in a variety of different cell types; however, its specific function is unclear. In normal metabolism of APP, the long, extracellular N-terminal domain is cleaved to form a soluble protein. There are two major identified pathways of APP cleavage: the α-secretase pathway (non-amyloid producing) and the β/γ-secretase pathway which produces amyloid. The γ-secretase can generate either a 40 (Aβ-40) or 42 (Aβ-42) amino acid peptide. The Aβ-42 fibrils are insoluble and interact to form β-pleated sheets which form the key component of the plaques found in the brains of people with AD. While Aβ-42 fibrils are present in normal aging, the proportion and amount of these fibrils are increased in AD.[15]

There are two types of plaques, neuritic and diffuse plaques. Neuritic plaques contain masses of Aβ associated with abnormal axons and dendrites (neurites), as well as activated microglia and reactive macroglia.[16] Most amyloid plaques, however, are not neuritic but rather are diffuse plaques which lack abnormal neurites and microglia. Diffuse amyloid plaques contain mostly Aβ-42 (whereas neuritic plaques contain both Aβ-40 and Aβ-42), as well as unprocessed APP, ApoE, α-1-antichymotrypsin, IgG, complement proteins, amyloid P and glycosaminoglycans in a complex bundle.[16,17] The complete composition and mechanism of assembly of plaques, as well as their role in AD pathogenesis, has yet to be elucidated. It has been shown that plaque deposition can be affected in multiple ways, leading to speculation that there are many different mechanisms leading to a final common pathology. For example, the Alzheimer's associated changes that occur in people with Down's Syndrome (DS) lead to excessive Aβ in the brain and relatively few, but dense, plaques.[18,19] Conversely, carriers of APP mutations or ApoE ε4 show multiple smaller deposits that may be related to greater formation of the amyloidogenic Aβ-42 fragment.[18]

Tangles

Just as Aβ is a major component of plaques, tau protein has been found to be a main protein component of neurofibrillary tangles (NFT). NFTs are bundles of long protein filaments in the cytoplasm of neurons. Tangles consist of pairs of helical filaments wound about each other. The filaments are mainly made of microtubule-associated protein tau. In normal cells, tau binds to and stabilizes microtubules, promoting their assembly by polymerizing tubulin. Tau is thus necessary for the growth and maintenance of axons and dendrites and for the transport of materials throughout the length of the cell. In AD, tangles form when tau proteins are abnormally hyper-phosphorylated causing them to self-assemble into the helical paired filaments that form NFTs. While NFTs are found throughout the brain, they are particularly concentrated in the input and output projections of the hippocampus to multiple cortical and subcortical structures associated with memory processing.[20,21] Senile plaques have a wider and more variable distribution. These distributional differences may relate to the finding that NFT counts correlate more strongly to cognitive function than do plaque counts,[17,21,22] although a recent study has raised the issue that plaque distribution may correlate with type of deficit rather than with severity.[23] Furthermore, disease duration and severity are both correlated directly with synapse loss and numbers of NFTs.[21,22] NFTs have been used to map the topography of AD and to stage its temporal evolution.[11,13,24-26]

Synapse loss and cell death

The final characteristic pathology of AD is synapse loss and cell death. Cellular damage in AD accumulates slowly, resulting in synapse loss and then cell loss, which leads to selective brain atrophy. Synapse loss is the most sensitive correlate with cognitive measures.[27,28] Autopsy and imaging studies have shown that the cell death seen in AD initially affects areas in the medial temporal limbic region, the parietotemporal association cortex and later, the frontal cortex.[24-26,29]

The synapse loss and neuronal death that occur in AD affect multiple neurotransmitter systems, but particularly targeted is the nucleus basalis of Meynert, the source of cholinergic innervation to the cortex, and the septal nucleus, which provides cholinergic innervation to the hippocampus.[30,31] Many potential therapies for AD aim to facilitate acetylcholine function. Several acetylcholinesterase inhibitors have recently become available including tacrine, donepezil, metrifonate, rivastigmine and galantamine.[32,33] Clinical trials with these compounds have shown symptomatic benefit for six months and up to two years,[34] though whether there is any effect on ultimate disease course has not been determined. Other treatment strategies aim to protect nerve cells. For example, estrogen promotes the growth and survival of cholinergic neurons and may also decrease cerebral amyloid deposition.[35] There is epidemiological evidence that estrogen use in postmenopausal women may delay the onset and ameliorate the severity of Alzheimer's disease.[9,36,37] Propentofylline, another drug under study for treatment of Alzheimer's and vascular dementia, limits the damage to nerve cells by inhibiting the activation of microglia and astrocytes and by reducing the effects of free radicals, glutamate and calcium in the extra-cellular environment. It has shown modest benefits over a one year interval[38] and may soon be available in Canada and Europe. The aim of emerging treatments will be to provide not only symptomatic relief, but also to slow or halt the neurodegenerative process in AD patients.

The significance of AD neuropathology

It is likely that, rather than being separate pathologies, the plaques, tangles, synapse and cell loss are part of a complex, interrelated process fundamental to the way in which the brain ages and copes with damage. They can all occur in the absence of apparent cognitive impairment; however, in AD, a variety of molecular pathologies cause abnormal amyloid deposition and tau hyper-phosphorylation.[39] Both amyloid plaque and neurofibrillary tangle density seem to be correlated with disease duration, but only tangle density and synapse loss, not plaque density, correlate highly with cognitive impairment.[17,21,22,40-42] The diversity

of symptoms and behaviors seen in AD partially reflects differences in the regional distribution of pathology. Evidence to date suggests that Aβ deposition is an early and necessary first process in AD pathology,[16] preceding the other brain changes and clinical symptoms perhaps by decades.[43]

The identification of a general timeline for the development of AD neuropathology has provided a great deal of incentive for the development of future treatments. Autopsy studies have revealed that it takes decades for the pathological process to unfold. AD related neurofibrillary changes, for example, may begin to accumulate 50 years before clinical onset.[43] Rather than attempting to reverse changes that have accumulated over several decades by the time clinical disease becomes apparent, a more successful treatment strategy would be to aim to slow the pathological process and delay the onset of AD.

Genetic Causes of AD (APP, PS-1 and PS-2)

The terminology of AD can be ambiguous. Clinically, Alzheimer's disease can be described as familial and sporadic, early-onset (generally before age 65) and late-onset (after 65), with early-onset predominantly seen in familial cases and late-onset in both familial and sporadic cases. While the exact frequency of familial, early-onset AD is unknown, it is extremely rare, likely comprising at most 1-2% of all AD cases.[44] Although evidence pointed toward genetic factors, it was not until investigation of a few families from around the world with extensive family histories of AD that a clear pattern of inheritance was identified for this rare, early-onset familial form of AD. Linkage analyses of these families led to the identification of three genes which, when mutated, cause AD.

The first AD gene identified through linkage analysis was on chromosome 21 and codes for β-APP. This chromosome was targeted because all individuals with Down's Syndrome have inherited an extra copy and will usually, by their fourth decade, develop the neuropathology of AD.[45] However, mutations in this gene were rarely reported, even in early-onset AD populations, and the search for additional genes continued. To date two other genes, presenilin-1 (PS-1) on chromosome 14 and presenilin-2 (PS-2) on chromosome 1, have been identified that cause AD when a mutated copy is inherited. All three genes (APP, PS-1 and PS-2), if mutated, result in elevated levels of Aβ[46] and in clinical expression of AD. PS-1 is estimated to account for almost 50% of early-onset AD cases, considerably more than either APP or PS-2.[47,48] There are a variety of PS-1 mutations, all of which seem to be highly penetrant;[49] that is, if a PS-1 mutation is inherited, AD will almost always develop. Mutations in β-APP and PS-1 are associated with early onset of AD (typically age 35-60) while PS-2 mutations result in an older (but still advanced) onset typically between ages 40-70.[48] Not all cases of early-onset familial AD are accounted for by APP, PS-1 and PS-2 mutations, so it is likely that other genes remain to be identified.

A recent thrust in both genetics and molecular biology research has been to understand the relationship between amyloid deposition and tau hyper-phosphorylation. One possible connection has begun to emerge via the presenilin genes. PS-1 and PS-2 mutations are both related to increased amyloid deposition.[46] Other reports have found that the PS-1 and PS-2 proteins are associated with neurofibrillary tangles in neuron cell bodies.[50] Thus, the same mutation appears to be affecting both amyloid and tau processing. Elucidation of the functions of the presenilin proteins and of the mechanisms by which they affect amyloid and tau proteins will be a major step toward understanding AD pathogenesis.

Apolipoprotein E: a genetic risk factor

Background

Familial, early-onset AD often shows a clear genetic inheritance but, as indicated, these cases constitute only 1-2% of AD patients. The remainder are late-onset familial or sporadic cases, with no clear genetic inheritance. However, recent studies have shown that a polymorphism of the Apolipoprotein E gene (ApoE) is associated with AD. ApoE is a critical modulator of cholesterol and phospholipid transport between cells.[51] In the rat brain, ApoE has been identified as a key factor in mobilizing and redistributing membrane components for synaptic plasticity in the central nervous system and for repair and growth after peripheral nervous system injury.[52] Apolipoprotein E is a polymorphic protein with three common alleles, ApoE epsilon 2 (ε2), ApoE epsilon 3 (ε3), and ApoE epsilon 4 (ε4). The ε3 allele is the most common; for example, in a Canadian population sample, the allele frequencies were reported to be 7.8% (ε2), 77.0% (ε3) and 15.2% (ε4);[52] in contrast, the ε4 allele frequency in AD patients is considerably greater, approximately 40%.[53] In both sporadic and familial late-onset AD, the risk is increased with ε4 in a dose-dependent manner. That is, the risk of AD increases, and the age at onset decreases, with the number of ε4 alleles.[53-57] On average, people with two copies of ε4 will develop AD at a younger age than those with only one, who in turn will develop it at a younger age than those with no ε4 allele.[58] Further, having a copy of ε2 (i.e. either 2/2, or 2/3) may be associated with a reduced likelihood of AD.[59-61] Compared to people with no copies of ε4, the risk of developing AD in a person with two ε4 alleles is from 8 to 30 times greater,[60,62] while those with one ε4 have an increased risk of about 3 times greater.[60,61,63-65] The increased risk with ε4 appears to be due to the fact that it accelerates the age of onset. In 1993 and 1994, a series of articles confirmed that the ApoE ε4 allele decreases the age of onset and increases the risk of developing AD.[53,62,66-70] This association has been confirmed worldwide,[61,65] although the allele frequency varies in different ethnic populations.

The biology of ApoE

Evidence suggests that ApoE may be involved in the key pathological changes of AD and that there may be isoform-specific biological differences in the functional roles of ε2, ε3 and ε4.

ApoE binds avidly to Aβ[71] and is localized in neurites where it may affect the biological expression of extracellular Aβ deposition.[72] Senile plaques contain ApoE even in the very early stages of formation, suggesting that ApoE accumulation precedes Aβ deposition.[73] There is also evidence that ApoE is involved in the deposition of amyloid into the beta-pleated-sheet form that occurs in plaques.[74] It has been shown that ApoE binds to Aβ in an isoform-specific manner.[17,75-77] Amyloid deposition may differ with ApoE genotype: ε2 shows the least deposition, ε4 the most, while ε3 is intermediate.[78-80] ApoE ε3 may also inhibit amyloid from polymerizing and depositing, while ε4 seems to be a less potent inhibitor,[81] perhaps because it is inefficient at forming soluble complexes with Aβ.[72,82] Due to their different binding properties, it has been suggested that the ε2 and ε3

isoforms but not ε4, may help to protect against the formation of amyloid aggregates, thus inhibiting or slowing the development of senile plaques.[83] This theory posits that ε4 may cause an accelerated pathology because of a reduced ability to suppress amyloid formation and deposition.

ApoE has also been shown to bind avidly to tau.[71] It is found in both neurites and neurons where it may affect tau metabolism and NFT formation.[84,85] There is also some evidence of ApoE isoform-specific differences in tau protein regulation.[17,77,86] *In vitro*, tau binds to ε3 better than to ε4.[87] Although the evidence is not yet convincing, some authors have suggested that the interactions of ApoE isoforms with tau may regulate intraneuronal tau metabolism and thus alter the rate of formation of paired helical filaments and neurofibrillary tangles.[87,88] Both ApoE and tau are detectable in cerebrospinal fluid (CSF) and their measures may prove to be useful in monitoring the progression of AD.[89-91]

Finally, there are preliminary indications that ApoE, through its role in lipid homeostasis in neurons, may be a key factor in compensatory synaptogenesis and synaptic remodeling after injury and in aging.[52,92] ε4 seems to inhibit axon outgrowth whereas ε3 may be a factor in extending it.[75,93] Experimental animals with the ε4 allele have reduced nerve regeneration and synaptogenesis following injury in the hippocampus.[52,94] Further, ApoE-deficient mice exhibit an impaired ability to recover from closed head injury[95] and have neurochemical derangements that seem to reflect the neurotransmitter systems affected in AD.[96] Taken together, these results suggest that ApoE may play an important role in neuronal repair following injury. Thus, ApoE may be important in synapse, neurite and cell loss in AD not only indirectly by affecting amyloid and tau metabolism, but also directly.

Overall, the presence of one ε4 allele is estimated to lead to an earlier onset of the histopathological process by about one decade, and a second ε4 allele causes further advancement.[11,46,97] ε4 may exert its effect as a risk factor by accelerating the characteristic pathologies of AD. Emerging indications of the biological role of ApoE in amyloid and tau metabolism and in response to injury and aging may begin to illuminate a mechanism by which it may be accelerating the onset of AD.

ApoE and Acetylcholine

The selective vulnerability of the cholinergic neurotransmitter system in AD may also relate to ApoE status. AD patients with one or two ε4 alleles have been found to have higher AChE activity and lower choline acetyltransferase (ChAT) activity than controls, resulting in reduced levels of acetylcholine.[51,94,98,99] Cholinergic deficits have been localized to the hippocampus,[51,52] the parietotemporal cortex[51,100] and the frontal cortex,[99] which are three prime targets of AD brain atrophy and dysfunction. Some investigators have argued that ApoE genotype may alter responsivity to cholinergic therapies, based on post hoc analysis of clinical trials with tacrine in which ε4 patients showed less cognitive improvement than ε2 or ε3 carriers.[51,101] However, biological measures of the cholinergic system have not found relationships with ApoE status. One recent finding indicated that temporal cortex cholinergic activities were reduced in AD regardless of ApoE genotype,[102] while another study found no difference in acetylcholinesterase activity or synaptic loss in relation to ApoE status.[103] Thus, the implications of ApoE status for responsiveness to cholinergic therapy remain unclear.

ApoE and brain cell responses to injury

ApoE ε4 has also been associated with other disorders highlighting its relevance to brain pathology in more general terms. ApoE genotype may affect neuropathology in Lewy Body Disease,[104] but it does not influence the development of AD lesions in Parkinson's disease.[105,106] ApoE status does not modify the risk of developing AD-associated psychiatric symptoms.[107] The frequency of ApoE ε4 is increased in patients with vascular dementia.[108] Further, ε4 increased the risk of dementia after stroke in a dose-dependent manner (two copies were seven times higher risk and one copy was two times higher risk than no copies)[60,109] and increased the risk of dementia over six times in those over 85 with white matter lesions.[110] The risk of developing AD with a history of head trauma was increased up to ten times in ε4 carriers compared to non-carriers.[111,112] However, some have argued that the effect of head injury is independent of ApoE status.[113] Finally, adults with Down's Syndrome who carry one or two ε4 alleles are five times more likely to develop dementia.[114]

Another environmental trigger that may work synergistically as a co-factor with ApoE in the development of AD pathology is herpes simplex virus (HSV-1). Some people carry latent viruses in brain cells that may occasionally reactivate, resulting in a subacute infection. There is recent evidence that ApoE status may alter degree of damage caused by these reactivations. The risk of developing AD is greater in people who carry both an ε4 allele and the HSV-1 virus than in those with only one of these factors.[115,116]

These various findings may indicate that ApoE ε4 may confer a "hypersensitivity" to brain injury and subsequent inflammatory responses. Insults to brain cells that might be innocuous in people with ε2 or ε3 may promote the eventual development of dementia in carriers of ε4.

Effects of ApoE status on Asymptomatic Elderly

The ε4 genotype is associated with functional deficits in activities of daily living in elderly people with normal neuropsychological profiles[117] and with a lower cognitive performance profile in otherwise normal older adult male twins.[118] An elevated frequency of ε4 alleles has also been shown in elderly people with memory impairments who do not meet criteria for dementia.[119] Older women carrying at least one copy of ε4 have been shown to have a higher risk (1.6 times) of cognitive decline over a six year period.[120] In a different large series of community dwelling participants, ε4 carrier status, vascular changes on MR and evidence of brain atrophy, were independent risk factors for cognitive decline.[121] Short term (i.e. episodic) memory deficits in older adults were also associated with ε4[122] and elderly subjects carrying the ε4 allele had poorer learning ability than those with 2/2 or 2/3 genotypes.[94] These "asymptomatic" cognitive findings in people who carry ApoE ε4 may help to identify those at increased risk for developing AD.

ApoE and neuroimaging

The topographical selectivity of AD neuropathology mentioned above has proved to be diagnostically useful. Plaques, tangles and synaptic and cell loss occur earlier and are more abundant in the medial temporal and other limbic regions and the temporal and parietal neocortex.[24-26,29,123] This pattern of microscopic change can be detected using structural and functional neuroimaging. Structural techniques such as magnetic resonance

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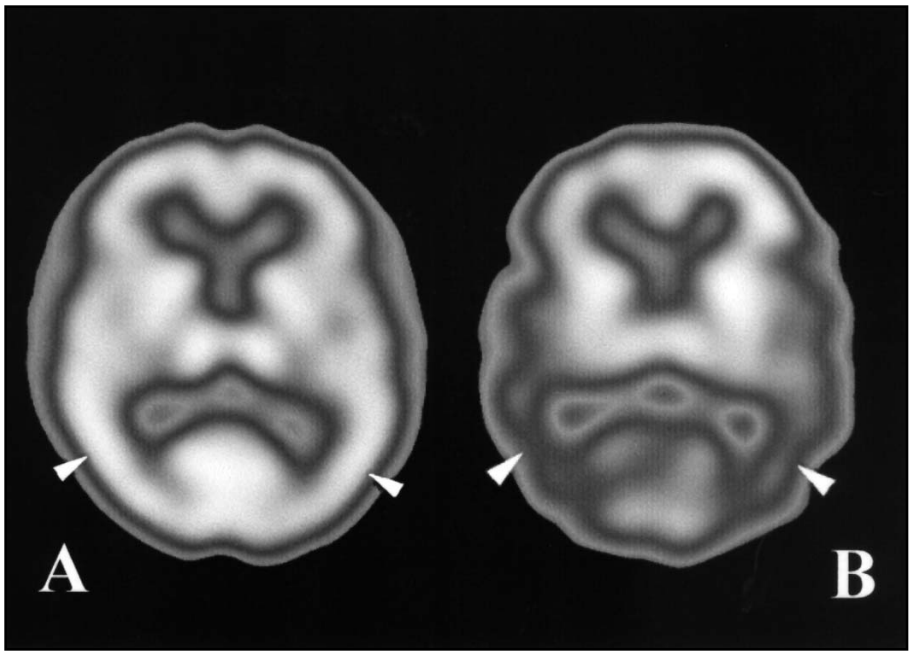

Figure 1: *Decreased blood flow in the parietotemporal region (arrows) helps to differentiate normal aging (A - an averaged SPECT image from 21 healthy elderly controls) from Alzheimer's disease (B - a 72-year-old female with moderate AD - Global Deterioration Scale (GDS)[190] = 4).*

imaging (MRI) and X-ray computed tomography scans (CT scans) are used to examine brain anatomy. Functional imaging techniques usually reveal information about blood flow or metabolism in various brain regions. For example, SPECT (single photon emission computed tomography) measures regional cerebral blood flow while PET (positron emission tomography) can measure either cerebral blood flow and/or glucose metabolism. Both PET and SPECT provide indirect measures of functional activity; more functionally active brain areas are metabolically more active and require more blood flow. PET and SPECT also have potential for imaging the distribution of neurotransmitter receptors.[124] Impairment of cerebral blood flow on SPECT and glucose metabolism on PET in certain predisposed brain regions is a common feature in patients with Alzheimer's disease.[125,126] The common pattern of decreased perfusion in the parietotemporal region (see Figure 1) correlates with both neuropsychological impairments[126-128] and neuropathology;[129] further, when used in the proper clinical context, SPECT perfusion deficits can help to distinguish Alzheimer's disease from other forms of dementia and may be useful as a component of preclinical prediction of AD.[130] In parallel with perfusion changes, patients with AD also commonly show selective atrophy on CT and MRI, most noticeably in medial temporal lobe structures (including the amygdalahippocampus complex - AHC) which are involved in memory processing (see Figure 2).[94,131-133] Regional atrophy measures correlate with the severity of dementia,[132] the neuropsychological impairments, the functional imaging deficits and the neuronal damage seen on autopsy.[40,134] The rate of this atrophy has been estimated to be 10 times greater per year in AD compared to normal aging[134,135] and some have suggested using brain atrophy seen on MRI to follow disease progression.[132]

When neuroimaging is combined with clinical assessment, it significantly increases diagnostic accuracy and specificity. For example, in an autopsy-confirmed series of 70 subjects, accuracy was as high as 97% compared to 80-90% with clinical criteria alone.[136] Thus, it is possible to diagnose probable AD with greater certainty than ever before, and measurement of changes in perfusion and atrophy could be used to help determine the effectiveness of emerging therapies.

Not surprisingly, neuroimaging studies have begun to investigate the effects of ApoE status on imaging parameters. In one series, patients homozygous for the ApoE ε4 alleles had more severe loss in hippocampal and amygdala volumes on MRI scans than AD patients without the ε4 allele.[94,128] Minor changes in hippocampal size on MRI can also be detected in non-demented elderly, particularly in those with an ε4/4 genotype.[94] However, a recent MR study showed that hippocampal volumes did not differ with ApoE genotype in either patients or normal controls; rather, hippocampal atrophy and ApoE genotype may be independently associated with AD.[137] In a PET study, patients had lower parietal metabolism than at-risk relatives carrying ApoE ε4[127] while those relatives in turn had lower parietal metabolism than relatives without ε4.[127,138] Another PET series showed that cognitively normal subjects who were homozygous for ε4 had significantly reduced glucose metabolism in the same areas as patients with probable Alzheimer's disease.[139] These findings suggest that there may be pathological changes occurring in at-risk individuals that are detectable on functional imaging before the clinical onset of AD. However, despite this evidence of ApoE associated pre-clinical changes, Corder et al. reported no differences on FDG-PET between AD patients with and without ε4.[140] Despite a recent small SPECT study that suggested differences on perfusion patterns longitudinally with ε4 status,[141] a recent larger preliminary study found no correlation between ApoE status and hypoperfusion patterns on SPECT in AD patients.[142] The preliminary imaging evidence therefore suggests that the presence of ApoE ε4 may predispose to the development of AD,

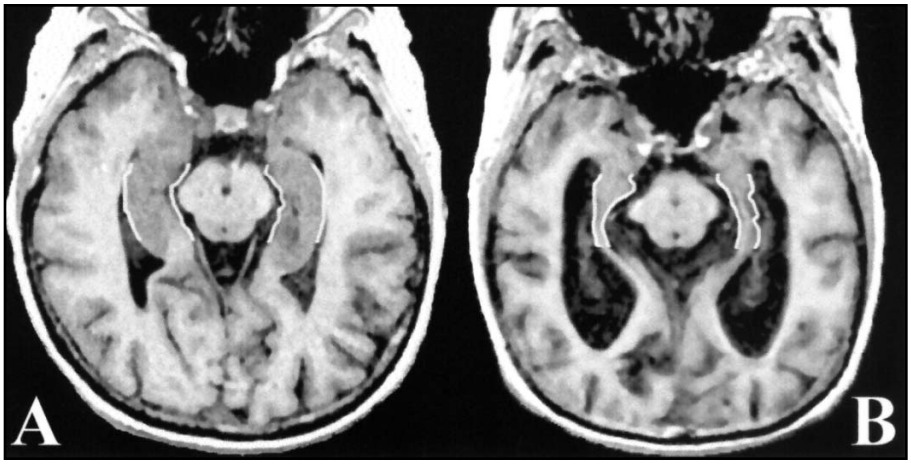

Figure 2: *Atrophy caused by Alzheimer's Disease processes can be visualized using structural imaging techniques such as T1-weighted MRI scans. Areas such as the medial temporal lobe (outlined in white) are not severely affected in normal aging (A - from a 74-year-old healthy female) and are especially affected in AD (B - from a 72-year-old female with moderate AD - GDS[190] = 4).*

without exerting detectable effects on the progression of the disease. Imaging information may prove to be most useful in identifying individuals who are at increased risk to develop the disease. This will be particularly important in the context of emerging treatments, especially if neuroprotective agents which slow the course of the disease become available.

Controversies in ApoE research

Despite the evidence that ApoE is involved as a risk factor in AD several controversies remain to be resolved.

1) Does ApoE status affect rate of decline in dementia?

While most reports agree that ε4 leads to reduced age at onset, its role in disease progression is less clear. ApoE status is associated with cognitive decline in community-dwelling women[120] and is a strong predictor of AD in individuals experiencing mild cognitive impairment.[143] Initial reports also indicated different rates of cognitive decline with ε4 genotypes in people with AD;[122,144,145] however, many subsequent findings have found no differences in the rate of cognitive or functional decline with ε4 once the disease has begun.[146-150]

Thus, many clinical and neuropsychological studies, such as the neuroimaging findings, imply that inheriting the ε4 allele may lead to an earlier age of onset and predispose to the development of the disease, without accelerating its progression once it is clinically manifest.[56,151-154] However, as addressed by Plassman and Breitner,[155] the rate of change in a disease as complex and variable as AD is difficult to evaluate precisely. Trajectories of decline will differ not only due to ApoE genotype, but also in relation to other, as yet unidentified genes, as well as other risk factors such as age,[154] environmental factors and individual differences in pre-morbid ability or "natural reserve".[155,156] Furthermore, most studies of progression and ApoE have examined clinical and neuropsychological measures which are correlated with, but a step removed from, the underlying biological changes. Continuing studies examining measures of biological progression, such as structural and functional neuroimaging over sufficiently long periods of time, must be explored further before it can be firmly concluded that ApoE status affects only age of onset but does not alter the rate of progression of AD.

2) Are there effects of sex?

Another controversy in ApoE research concerns sex differences. Almost twice as many females are affected with AD as males; this partly reflects the greater number of women in the older age groups but even age-corrected rates are elevated for women.[3,6] In late-onset familial AD, initial reports indicated an increased incidence of the ε4 allele in women[157] and it was speculated that this might explain some of the increased incidence of AD in women; however, recent publications do not support this finding. One study showed no difference in gender-specific allele frequencies between AD and control groups.[64] Another series found that susceptibility to AD differs between men and women regardless of ApoE status, but that AD appears to be more penetrant in women,[158] that is, more women with predisposing genotypes develop AD than do men with the same genotypes. Other studies have shown a reduced age of onset in women, but not men, who were ε4 carriers.[58] This suggests that the differences in ε4 frequency in women may be accounted for by an earlier onset and not by any difference in process. Still others argue that gender is not a factor at all.[159] This issue remains to be resolved in larger scale studies.

3) Are there ethnic differences?

Studies on ApoE have also examined various geographic and ethnic groups to investigate its role as a risk factor. The association with AD has been confirmed worldwide.[65,160-162] Within the United States, the ε4 allele frequency does not vary significantly between most ethnic groups.[58,65,160,163] However, the pattern of association between the ApoE alleles and AD shows differences in certain ethnic groups. For example, a lower incidence of AD, independent of ε4, has been found in Cherokee Indian populations.[164] Despite the demonstration of a higher incidence of AD in an African-American population,[67] many studies have demonstrated weaker associations between ε4 and AD in African-American populations compared to Caucasian populations.[65,165-167] Thus, in some ethnic groups there may be other important genetic factors that have yet to be identified.

4) What are the effects of ε2?

The role played by ε2 and ε3 is still under study. ε2 occurs with reduced frequency in late-onset AD patients.[66,71,127] There have been reports of a protective effect with the ε2 allele, both clinically[165,168,169] and neuropathologically.[170] A confusing finding is that ε2 may increase the risk of early-onset AD[171] while protecting against late-onset AD. At the moment the role of ε2 in early-onset AD remains controversial, in large part due to its rarity.

5) How can ApoE status be used clinically?

ApoE represents the first identified gene that is related to late-onset familial and sporadic AD. Thus, it has the potential to contribute greatly to both research and clinical developments. However, it must be emphasized that while ApoE genotype may indicate a degree of susceptibility, it is neither necessary nor sufficient to cause the disease.

Many subjects who are homozygous for ε4 never develop Alzheimer's disease, and approximately half the people who develop AD have no copies of ε4.[46,90] In a person without a family history of AD, the lifetime risk is about 15%. The lifetime risk for individuals with one copy of ε4 is 29% versus a 9% lifetime risk in those with no copies of ε4.[172] Thus, even with a copy of ApoE ε4, the lifetime risk of AD remains below 30%. One study estimated that if the ε4 allele did not exist, the incidence of AD would be reduced less than 14%.[173] In those without ε4, the risk is 9%, only 6% lower than the 15% risk for those in whom the ApoE status is not known; thus, there is a very low negative predictive value. In those with ε4, the risk is 29%, only 14% greater than in those who do not know their ApoE status; thus, there is also a relatively low positive predictive value. In a prospective study of elderly subjects with memory complaints, Tierney et al. showed that ApoE genotype did not add any further predictive value to neuropsychological tests of delayed memory and mental control.[149,174] Thus, the value of ApoE genotyping as an initial diagnostic tool has yet to be proved.

Some authors have promoted the use of ApoE in clarifying differential diagnoses in people with dementia, arguing that ε4 positive status in these patients can help rule in AD and rule out other causes of dementia.[175-178] Of particular importance are two recent large scale studies of the sensitivity, specificity, and predictive value of ApoE ε4 for the neuropathological diagnosis of AD. The first study, using the CERAD database, found that the sensitivity and specificity of the ε4 allele for AD were both 83%. The positive predictive value of ε4 was very high at 97%, while the negative predictive value was only 44%.[179] On this basis, Roses and others argue that when ApoE genotyping is used for patients already clinically diagnosed with AD, the specificity of the diagnosis is increased[180] and that ApoE genotype information is thus useful in bolstering diagnostic confidence.[179] The second study compared diagnoses from autopsy of over two thousand individuals with diagnoses obtained clinically or with ApoE genotyping. They too found that the addition of information about ApoE status significantly increased diagnostic specificity from 55% to 84%, although it decreased the sensitivity.[181] There are other diagnostic tests that have reported utility that is either comparable or superior to that reported for ApoE. For example, association of medial temporal lobe atrophy on CT and decreased parietotemporal uptake on SPECT was reported to have a specificity of 93% and a positive predictive value of 95%.[136,182] CSF tau levels were reported to distinguish AD from normal controls with 95% specificity and 91% sensitivity and may also be reliable as an index of progression.[90]

At the present time, the evidence suggests that ApoE genotyping, used in combination with clinical diagnostic criteria, may be useful in improving the specificity of a differential diagnosis of AD. In contrast, it must be emphasized that there is widespread agreement in the scientific literature and amongst professional bodies that the use of ApoE genotyping as a pre-symptomatic predictive test or as a stand-alone diagnostic test for AD is not supported.[60,181,183-186]

6) What lies beyond ApoE?

The search to find other genetic and environmental influences is continuing at an accelerated pace. The latest data on ApoE show that ε4 acts as a risk factor primarily among people who develop AD before age 70[153,165,187] and the majority of AD cases develop after this. Further, while ApoE may be involved in amyloid deposition and tau phosphorylation, it is likely only one of many factors.[188] Researchers have begun looking for other genes in families with a history of AD but without ε4. Recently, a region of chromosome 12 was identified which, by preliminary evidence, appears to be linked to late-onset Alzheimer's disease.[189] While researchers attempt to identify a gene in this region that may be involved in AD, other genetic associations are also under investigation. It seems likely that there will be other susceptibility genes identified in the next few years, each adding to our understanding of the disease process and potentially to our ability to treat it.

CONCLUSIONS

With the rapid outpouring of confusing, and occasionally contradictory, research findings, it is difficult to make sense of current developments. While there are three relatively rare genetic mutations identified that can cause AD, a great deal of attention has been focused on ApoE because of its involvement in the more common, later-onset form.

The mechanisms by which the ApoE polymorphisms affect AD are beginning to take shape and are generating many questions to be addressed by future research. At the molecular level, isoform-specific effects on both amyloid and tau processing have been suggested. ε4 seems to be leading to an earlier onset of both clinical and neuropathological symptoms by affecting amyloid plaque deposition, NFT formation, synapse growth and repair and ultimately, cell loss. Many other details of these biochemical pathways are not yet known and it seems likely that there may be multiple points at which these pathways can be affected, ultimately leading to the development of AD.

The effects of ApoE status on structural or functional neuroimaging measures by the time clinical symptoms are manifest requires further study. While there is no identified threshold at which accumulated damage causes cognitive and functional deficits, imaging studies may help elucidate pre-clinical changes and those that occur with established disease. In a more prognostic context, isoform-specific effects of ApoE have been noted at the level of cognition and behavior. The effects of ApoE status on both the development of AD and other diseases is consistent with a role for ApoE in the cellular response to aging and injury. The gender-specific risks of ApoE are unclear and while

consensus seems to be emerging that ApoE is most significant in onset of AD before age 70, age-specific risks must be confirmed and expanded. The role of ApoE status in disease progression after the onset of clinical symptoms seems to be minimal, although this also warrants further investigation.

With three identified genetic causes and one identified risk factor, there are a multitude of troubling ethical issues that surround discussions of AD, over and above the complex scientific ones. The appropriate use of genetic and other diagnostic information is by no means guaranteed. It must be emphasized that while ApoE is a risk factor for the development of AD it is neither necessary nor sufficient to cause it. While ApoE status may be helpful in assisting the differential diagnosis of dementia, it is not diagnostic and provides little useful information for healthy individuals concerned about their risks of AD.

Alzheimer's disease is a significant health problem, affecting millions of patients, families and friends around the world. Ongoing investigations have revealed much about the pathology of Alzheimer's disease. As the disease mechanisms are elucidated, potential treatments are being explored. Drugs aimed at enhancing acetylcholine transmission have already been subjected to clinical trials and are emerging for clinical use. New treatments will hopefully slow or halt the progression of the disease; reversal of existing damage still appears to be a distant goal. Emerging discoveries of pre-clinical changes in structural and functional neuroimaging, together with genetic factors, may soon be able to identify those at highest risk for AD long before clinical onset, thus allowing intervention before symptoms ever develop.

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