alzheimer's research&therapy

VIEWPOINT

Phenotypic differences between apolipoprotein E genetic subgroups: research and clinical implications

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Abstract

With the recent interest in Alzheimer's disease course modification and earlier, even preclinical, intervention, questions have arisen regarding the potentially confounding impact of apolipoprotein E (APOE) genotype on study design, therapeutic outcomes, and even clinical practice. APOE e4 carriers have a faster rate of cognitive decline both preclinically and during the mild cognitive impairment (MCI) stage, and a higher burden of cerebrovascular amyloid that may be the basis for the observed gene-dose-related increased frequency of immunomodulatory therapy-induced meningoencephalitis and cerebral microhemorrhages. To date, this has impacted study design in some research trials but not clinical practice.

The discovery in 1993 that apolipoprotein E (APOE) genotype influenced the relative risk and age of onset of Alzheimer's disease (AD) represented a paradigm shift that continues to advance our understanding of AD pathogenesis. APOE e4 accounts for at least half of all AD cases, and while phenotypic differences between APOE genetic subgroups are relatively modest, they nonetheless raise important practical questions for both researchers and clinicians. For trialists, how might APOE genotype influence therapeutic as well as adverse outcomes? For clinicians, at what point should APOE genotype influence patient management? To put these questions into perspective, let us recall some of the phenotypic differences between APOE-related AD subgroups.

Clinical differences between APOE subgroups

Clinically, the effect of APOE genotype on age of onset has been reconfirmed many times since the original report from Roses' group [1]. APOE e4 increases the likelihood of conversion to dementia in patients with MCI by over fourfold [2]. The age of AD onset declines with increasing e4 dose and increases with increasing e2 dose. Preclinical memory decline accelerates in APOE e4 carriers prior to age 60 in a gene-dose pattern [3]. Van der Flier and colleagues [4] reviewed an extensive literature and proposed that e4 carriers have a more typical amnestic syndrome with greater hippocampal atrophy and an older age of onset while non-e4-related AD was characterized by variant syndromes (dysexecutive, aphasic, apraxic, and visual) with less hippocampal atrophy and a younger age of onset. In our Arizona APOE cohort, a longitudinal study of cognitive aging started in 1994 [3], we have had 34 incident AD cases (unpublished data), including seven e4 noncarriers (one of whom developed visual variant AD), and 27 carriers (seven of whom developed a variant AD syndrome). Additionally, four e4 carriers have developed a clinical synucleinopathy, including one with levodopa-responsive Parkinson's disease. We therefore see little evidence of the distinction described by van der Flier and colleagues, though admittedly our series of incident cases to date is relatively small.

Neuropathological differences between APOE subgroups

Neuropathologically, there is over a 97% chance that an e4 carrier dying with dementia will have AD at autopsy [5]. It has been thought that e4 has a greater effect on amyloid than tau-based pathology, supported by the relative under-representation of e4 (and over-representation of e2) among patients with neurofibrillary tangle-predominant AD, a subgroup that tends to be in the older age range, but a more recent study of the oldest subjects showed that e2 carrier status was associated with greater amyloid as well as tau pathology, and the effect on amyloid was greater than that on tau [6]. More clearly established is that APOE e4 carriers have a higher burden of congophilic amyloid angiopathy (CAA) and CAA-related intracerebral hemorrhage [7]. Murray and colleagues [8] reviewed the neuropathological findings in 889 cases of AD, 472 of which had APOE genotype information, and proposed three subtypes, including

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hippocampal sparing (concordant with van der Flier and colleagues' non-e4 AD description), accounting for 11% of cases, typical AD, accounting for 75% of cases, and limbic-predominant, accounting for 14% of cases. APOE genotype failed to distinguish these groups, with e4 carrier frequencies of 50%, 59%, and 62%, respectively. However, when they stratified these subtypes by age of onset as less than or greater than 65 years, a high proportion of limbic-predominant cases were e4+ (71% of 45 late onset limbic predominant AD cases were e4+). A non-AD clinical diagnosis was more common in the hippocampal sparing group but this did not relate to e4 carrier status (in contrast to van der Flier and colleagues' hypothesis).

Treatment responses in APOE subgroups

Another important consideration regards treatment response. An Alzheimer's Disease Cooperative Study group reported that, among a cohort of 516 patients with amnestic MCI, e4 carriers progressed more rapidly than noncarriers and called attention to the importance of balancing APOE genotype in clinical trial treatment arms [9]. Several studies have sought differential responsiveness to symptomatic therapy, with Poirer and colleagues [10] reporting in 1995 that e4 carriers responded less well than noncarriers to cholinomimetic therapy, and subsequent work suggested that gender may further influence this relationship, but not all studies have replicated these differences.

In recent disease modification trials, APOE effects have been more pronounced. In the AN1792 active vaccination trial 6% of patients developed an autoimmune meningoencephalitis characterized radiologically by patchy vasogenic edema [11]. Although there was only minimal evidence of clinical efficacy, there was convincing neuropathological evidence of amyloid plaque clearing [12], but also a striking increase in cerebrovascular amyloid and associated microhemorrhages [13]. Bapineuzumab, a humanized monoclonal antibody, has caused similar vasogenic changes that are three times and seven times more prevalent in e4 heterozygotes and homozygotes, respectively, compared with e4 noncarriers [14], but amyloid-ligand positron emission tomography evidence of treatment efficacy seems to be no different between APOE subgroups [15]. These findings have prompted changes to ongoing trials so that e4 carriers now receive only the lowest doses of bapineuzumab.

Conclusion

Returning to our first question, there is strong evidence that APOE genotype influences the accuracy of diagnosis, age of symptomatic onset, and rate of disease progression both preclinically (relevant for prevention strategies) and during the MCI stage. Whether or not they are related to APOE genotype, clinical variants need to be handled separately because outcome measures designed for typical patients will be less sensitive to variant syndromes. Perhaps most importantly, APOE e4 carriers are at greater risk of immunotherapy-induced meningoencephalitis and microhemorrhages, and this has already prompted changes in study design. As for clinical practice, currently, the principles underlying dementia treatment are governed by managing symptoms and the drugs used are selected regardless of APOE genotype. Whether or not they might work less well in e4 carriers remains a question, but seems less relevant since there are no better options to offer yet. As we enter the era of personalized medicine, and with the further development of new treatments, that could certainly change, but until APOE or any other genomic signature influences choice of optimal therapy, treatment will remain tailored to symptoms.

Abbreviations

AD, Alzheimer's disease; APOE, apolipoprotein E; CAA, congophilic amyloid angiopathy; MCI, mild cognitive impairment.

Competing interests

The author declares that he has no competing interests.

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