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Review

Apolipoprotein E and Sex Bias in Cerebrovascular Aging of Men and Mice

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Alzheimer disease (AD) research has mainly focused on neurodegenerative processes associated with the classic neuropathologic markers of senile plaques and neurofibrillary tangles. Additionally, cerebrovascular contributions to dementia are increasingly recognized, particularly from cerebral small vessel disease (SVD). Remarkably, in AD brains, the apolipoprotein E (ApoE) ε4 allele shows male excess for cerebral microbleeds (CMBs), a marker of SVD, which is opposite to the female excess of plaques and tangles. Mouse transgenic models add further complexities to sex–ApoE ε4 allele interactions, with female excess of both CMBs and brain amyloid. We conclude that brain aging and AD pathogenesis cannot be understood in humans without addressing major gaps in the extent of sex differences in cerebrovascular pathology.

Trends

Older men have a higher risk of cerebral microbleeds (CMBs), augmented by the ApoE4 allele. By contrast, EFAD mice show the opposite sex effect, with a threefold to tenfold female excess of CMBs, which dwarfed possible effects of ApoE alleles.

Cerebral small vessel disease is increasingly implicated in cognitive impairment of aging, particularly in conjunction with Alzheimer disease.

Reactive oxygen species (ROS) are mechanistically associated with CMBs in several mouse models. In humans, the limited data also support mechanistic links of ROS to CMBs.

Most amyloid plaques in EFAD mice include a CMB; similar vasocentric plaques are seen in humans with the Flemish AD variant.

Sex and Apolipoprotein E Alleles

Our biological sex engenders important trade-offs: men have shorter life spans than women, yet while women live longer, they incur more risk of Alzheimer disease (AD) throughout life. Worse yet, the **apolipoprotein E (ApoE)** ε4 allele (see Glossary) risk factor for AD has a definitive female bias. This greater female vulnerability to AD was recognized in two benchmark postmortem studies [1,2]. Both studies showed a female excess of AD pathology (neuritic plaques and neurofibrillary tangles), which was greatest in ε4 carriers. Correspondingly, levels of cognitive deficits per unit of brain amyloid show a fivefold excess in women [1].

In contrast to a female bias in the classical AD markers, cerebrovascular pathologies, particularly cerebral microbleeds (CMBs), showed a threefold male excess in three independent clinical AD cohorts–the Amsterdam Dementia Cohort [3], the Alzheimer Disease Neuroimaging Initiative (ADNI) [4], and the Karolinska Imaging Dementia Study (KIDS) [4,5].

CMBs are associated, by imaging and postmortem studies, with amyloid-β (Aβ)-containing vessels [**cerebral amyloid angiopathy (CAA)**], again with ε4 bias [6], as well as with **hypertensive arteriopathy**. Hypertension also shows a male bias (relative to premenopausal women) [7].

Moreover, we recently reported an ApoE ε4 male bias and interaction, for CMBs, in the ADNI and KIDS cohorts (see Figure 1C) [4]. This is the first indication that cerebrovascular pathology may have a different sex–ApoE allele bias than the aforementioned female bias in AD mechanisms that are considered 'neuron based' because of the neuronal production of Aβ. Furthermore, there may be species differences in ApoE ε4–sex interactions: By 7 months of age, EFAD transgenic mice carrying human ApoE alleles with familial AD (FAD) genes have a female excess of CMB and CAA, opposite to the aforementioned pattern observed in

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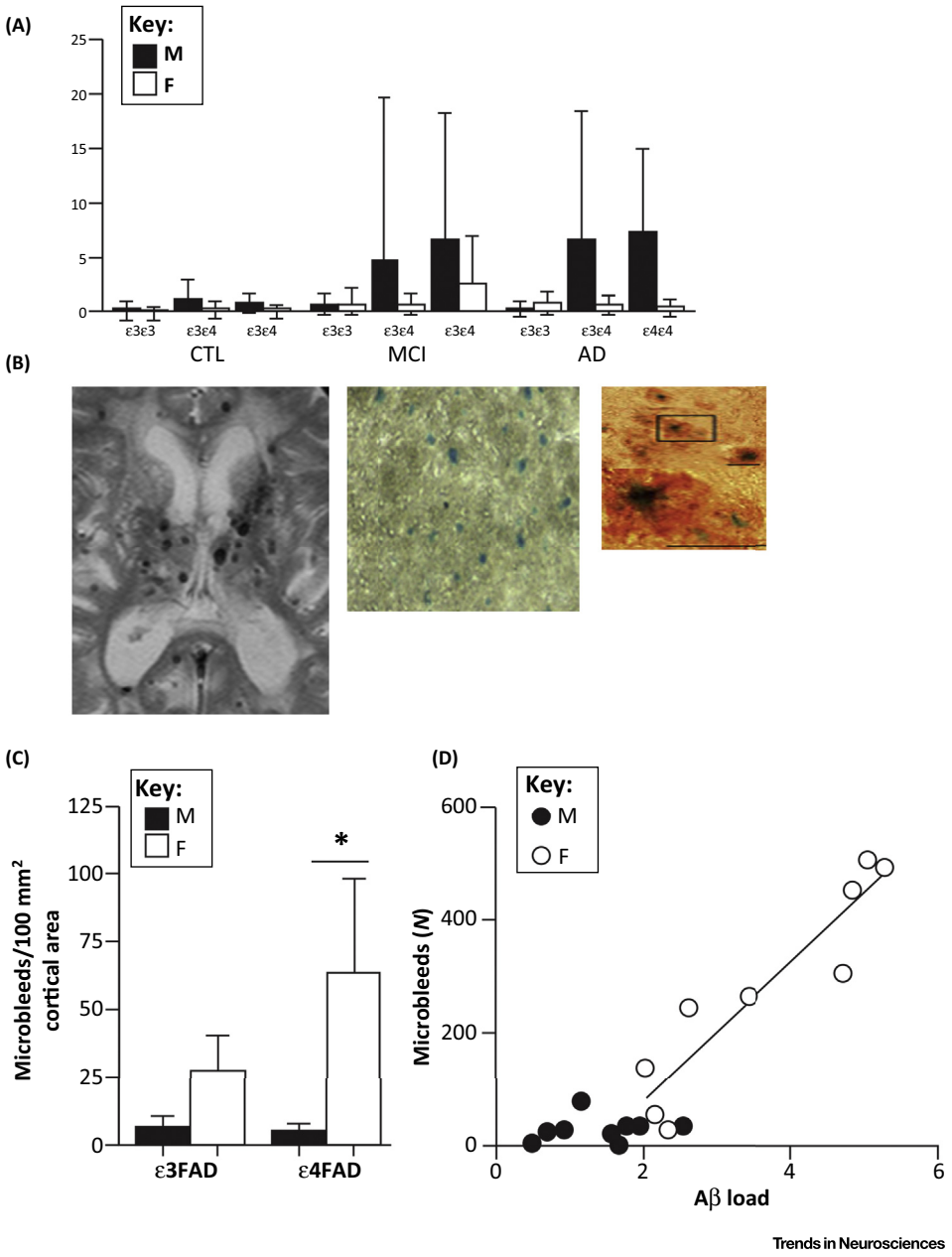

Figure 1. Cerebral Microbleeds. Figures are redrawn from [8] except B Panel 1. (A) Human microbleed frequencies analyzed by apoE *ε4* alleles in cohorts in two large memory clinics: Alzheimer Disease Neuroimaging Initiative and Karolinska Imaging Dementia Study. Error bars denote the standard error of the mean. Male AD and MCI patients show a statistically significant excess of CMBs over female patients ($P < 0.05$); the male CMB excess is further exacerbated by *ε4* ($P < 0.05$), as tested by the Mann–Whitney *U* test. AD, Alzheimer disease (*ε3/ε3, n* = M42/F33; *ε3/ε4, n* = M46/F60; *ε4/ε4, n* = M25/F36); CMBs, cerebral microbleeds; CTL, controls (*ε3/ε3, n*= M84/F98; *ε3/ε4*, *n* = M43/F66; *ε4/ε4, n* = M5/F6); F, female; M, male; MCI, mild cognitive impairment (*ε3/ε3, n* = M144/F133; *ε3/ε4, n* = M120/F88; *ε4/ε4, n* = M37/F33). (B) CMB images: Panel 1, male AD patient, with multiple CMBs on a T2*-weighted magnetic resonance image; Panel 2, female EFAD mouse showing whole field stained for hemosiderin by Prussian blue; and Panel 3 (enlarged), individual microbleeds Prussian blue and co-immunostained for Aβ (orange). The majority (67%) of hemosiderin puncta resided within Aβ deposits. (C) EFAD mice: CMB frequencies show female excess with additive effect of *ε4*. *$P < 0.05$. (D) EFAD mice: the number of CMBs regressed against the Aβ load in the cerebral cortex of individual mice showed linear increase above a threshold level of 1.7 Aβ units; this relationship holds for females, but not for males. Both apoE alleles were included. Aβ, amyloid-β.

Glossary

Apolipoprotein E (ApoE): ApoE was first recognized in blood cholesterol transport where it is secreted by the liver [78]. Of the three apoE alleles, ε4 was associated with elevated blood cholesterol levels [79], with a widely varying frequency between human populations (Box 4). In the brain, ApoE is secreted by astrocytes as a transporter of lipids to neurons [19]. Because the major lipoproteins ApoA1 and ApoB are at minimal levels in brain, ApoE in conjunction with a ApoJ, has a prime role in synaptic membrane remodeling [8].

Cerebral amyloid angiopathy or congophilic amyloid angiopathy: small cerebral vessels with amyloid deposits that stain with Congo red dye. The amyloid causes vascular fragility and often results in microbleeds in the cerebral lobes.

Cerebral small vessel disease: pathology of brain microscopic vessels smaller than 2 mm diameter, including arterioles, capillaries, and venules. Because these vessels are below the resolution of current brain imaging, surrogate markers of the disease (Box 1) are used. The two most common etiologies of small vessel disease are hypertensive arteriopathy and cerebral amyloid angiopathy. Small vessel disease prevalence increases strongly at later ages and may be fivefold to tenfold more prevalent than large-vessel stroke [15,17]. At advanced ages, multiple cerebrovascular pathologies are increasingly common.

EFAD mice: transgenic mice with familial Alzheimer disease mutations crossed with mice carrying human ApoE alleles by targeted gene replacement (gene knock in).

Hypertensive arteriopathy: hypertensive damage to vessels causing arteriosclerotic changes and vascular fragility and microbleeds, particularly in the basal ganglia.