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Butyrylcholinesterase genotype and gender influence Alzheimer's disease phenotype

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Abstract Retrospective data are presented to support a spectrum of early Alzheimer's disease (AD) along a continuum defined by gender and genotype. The putative neurodegenerative mechanisms driving distinct phenotypes at each end of the spectrum are glial hypoactivity associated with early failure of synaptic cholinergic neurotransmission and glial overactivation associated with loss of neural network connectivity due to accelerated age-related breakdown of myelin. In early AD, male butyrylcholinesterase K-variant carriers with one or two apolipoprotein ε4 alleles have prominent medial temporal atrophy, synaptic failure, cognitive decline, and accumulation of aggregated beta-amyloid peptide. Increasing synaptic acetylcholine in damaged but still functional cholinergic synapses improves cognitive symptoms, whereas increasing the ability of glia to support synapses and to clear beta-amyloid peptide might be disease-modifying. Conversely, chronic glial overactivation can also drive degenerative processes and in butyrylcholinesterase K-variant negative females generalized glial overactivation may be the main driver from mild cognitive impairment to AD. Females are more likely than males to have accelerated age-related myelin breakdown, more widespread white matter loss, loss of neural network connectivity, whole brain atrophy, and functional decline. Increasing extracellular acetylcholine levels blocks glial activation, reduces myelin loss and damage to neural network connectivity, and is disease-modifying. Between extremes characterized by gender, genotype, and age, pathophysiology may be mixed and this spectrum may explain much of the heterogeneity of amnestic mild cognitive impairment. Preservation of the functional integrity of the neural network may be an important component of strengthening cognitive reserve and significantly delaying the onset and progression of dementia, particularly in females. Prospective confirmation of these hypotheses is required. Implications for future research and therapeutic opportunities are discussed.
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1. Introduction

The pathologic features of Alzheimer's disease (AD), which include extracellular beta-amyloid (Aβ) peptide containing plaques, intracellular neurofibrillary tangles, synaptic and neuronal degeneration, altered glial morphology, and impaired energy metabolism, have been difficult to link in a convincing framework. Although AD is classically considered a disease of gray matter, it is increasingly appreciated that there is significant disruption of white matter [1]. Aging- and disease-related myelin losses are being suggested to underlie the etiology and progression of AD [1]. Myelin is the major component of white matter and the key structural element in functional neural networks. Because the processes involved in higher cognitive functions result from interconnected neural circuits, it is being increasingly suggested that many age- and disease-related impairments arise from degenerative processes that affect

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respective neural networks [2], often encompassing remote cortical areas. The extensive myelination of the human brain, the continual metabolic investment in its maintenance and repair, and its eventual age-related breakdown are important distinctions from the brains of nonhuman primates and other mammalian species that seem less susceptible to the development of AD pathology [1]. The bilateral spread of AD pathology recapitulates the myelination pattern in reverse, with later-myelinating temporal and frontal regions—containing the most structurally vulnerable myelin—developing lesions first [1,3].

The information presented in this review concerns interindividual variations in the brain's immune environment that result in different phenotypes of AD. Particular baseline characteristics may affect the likelihood of developing AD, the pathophysiological and phenotypic expression of the disease, and its rate of progression. For example, amnestic mild cognitive impairment (MCI) seems to be equally common in males and females, but there is increased likelihood of progression to AD among females [4]. It is increasingly appreciated that male and female gender may differentially affect neurodegenerative processes, response to treatment, and that gender and genotype may interact [5]. Furthermore, individuals carrying the apolipoprotein E (*APOE*) epsilon4 (ε4) allele, and particularly those with both *APOE* ε4 and butyrylcholinesterase K-variant (BuChE-K) alleles, have the fastest cognitive decline among subjects with amnestic MCI and mild AD and the slowest decline in more advanced stages of the illness [6–9]. Differential response to treatment by genotype, gender, and age in amnestic MCI, mild AD, and moderate AD also suggests that these factors may influence underlying AD pathophysiology [5,9–13].

The neurotransmitter functions of "neuronal" or "synaptic" acetylcholine (ACh) are responsible for transmission in both central and peripheral cholinergic synapses. In the central nervous system (CNS), cholinergic neurotransmission plays a crucial role in cortical activity, controlling cerebral blood flow and the sleep–wake cycle, as well as modulating cognitive performance and learning processes. In the autonomic nervous system (ANS), ACh is responsible for the ganglionic transmission of the entire system and postganglionic transmission of the parasympathetic arm [14]. Loss of efficient cholinergic synaptic neurotransmission contributes to acceleration of pathologic processes by decreasing cortical neuroplastic responses, both directly and through altered amyloid precursor protein (APP) metabolism [15]. In addition, cholinergic deafferentation of arteries within the brain results in cerebral amyloid angiopathy (CAA) [16]. Importantly, ACh is not restricted to neurons and synapses. Extracellular ACh acts as a local anti-inflammatory signaling molecule that blocks proinflammatory responses in regions distal from synaptic sites [17]. For example, ACh released from cholinergic neuron end terminals of the efferent vagus nerve inhibits acute inflammation in the periphery and in the cerebral microvasculature [18,19].

The enzymatic functions of both acetylcholinesterase (AChE) and BuChE include hydrolysis of ACh [15,20]. However, both AChE and BuChE are more appropriately considered as a combinatorial series of variant proteins that allow these enzymes to participate in various biological processes [15,21]. Thus, AChE and BuChE have numerous enzymatic and nonenzymatic roles that are modified on the basis of interactions and context (e.g., cell or subcellular localization, tissue type, health or disease status) [22,23]. In addition to particular populations of neurons, BuChE is localized in glia, myelin, and endothelial cells, and continues to increase in concentration into adulthood, especially in the deep cortex and white matter [24]. Developmentally late-myelinating association regions, such as the entorhinal cortex, that contain more BuChE are more susceptible to age-related loss of white matter integrity and myelin and also to developing proteinopathies [25]. Extracellular ACh may have a role in the maintenance of myelin (Fig. 1) [26]. In addition to increasing neurotransmission in ascending cholinergic pathways in the brain [15,20], sustained inhibition of AChE and BuChE enzymatic activities are anti-inflammatory (Fig. 1). Women are more likely to experience age-related breakdown of myelin [27,28].

This review examines the roles of gender and BuChE genotype in the phenotypic expression of AD and their interaction with risk factors for the development of AD, such as aging. Specifically, the roles of BuChE, gender, apoE, methionine–homocysteine cycle deficits, and extracellular ACh in AD pathophysiology and immune homeostasis are reviewed. Published and unpublished data on gender, genotype, and age from longer-term controlled studies with rivastigmine—an inhibitor of BuChE and AChE—in amnestic MCI and AD are reviewed. A model is proposed of a spectrum of innate immune activation in early AD along a continuum defined by gender and genotype that profoundly affects the phenotype of the disease and its response to treatment. A deeper understanding of this phenotype continuum and of pharmacologic effects will enable more appropriate use of current "cholinesterase inhibitor" therapies and promote successful future development of treatments to delay the onset, or modify the progression, of AD.

2. BuChE in health and disease

In the periphery, BuChE is synthesized in parenchymal liver cells and adipose tissue [29] and is secreted into the bloodstream where it has a half-life of several days [30]. BuChE is also found in cholinergic synapses of the ANS and in endothelial cells. In the CNS, BuChE is predominantly associated with neuroglial cells including oligodendrocytes, astrocytes, and microglia [22]. BuChE-positive neurons and glia are primarily distributed in deep cortical layers and in the underlying white matter. BuChE levels and polymorphisms may influence AD pathology through various enzymatic and nonenzymatic effects.

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