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EDITORIAL

"When sex influences the brain: implications for Alzheimer disease"

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Issues of sex and gender are currently at the center of discussions of social and political expectations in many countries. While there is little that the discipline of neuropathology can contribute to those conversations, there are aspects of the biological impact of sex which intersect with disease mechanisms. There are well-established differences in the hormonal environment across our life spans. In various disease settings, probably most prominently for cardiovascular disease risk and symptomatology, there has been a range of work examining distinct patterns of clinical presentation, differences in detection of disease in clinical settings, and recommendations for varying types of management [3]. As a result of these observations and other data, several years ago, the US National Institutes of Health explicitly required all research applications to be assessed the extent to that they "account for the possible role of sex as a biological variable in vertebrate animal and human studies" as part of the review criteria [1]. Thus, there has been increasing recognition in the scientific community of the extent to which disease mechanisms and manifestations can be influenced by sex.

When considering the impact of sex through the action of gonadal hormones on the brain, it is necessary to consider distinct phases of brain development and maturation. These begin with intra-uterine development, as reflected in the regulation of the Wolffian and Mullerian duct system which occur at the time of phases of neurogenesis. Following puberty and during adolescence, hormonal milieus are different at a time when significant components of brain maturation are still occurring. There are specific unique changes associated with pregnancy and the post-parturition period which occur in some but not all women. And finally, in later life, there is commonly a loss of hormones which were previously present (although this can be altered pharmacologically) and this typically begins around the ages when individuals may be in the pre-clinical stages of neurodegenerative diseases. Although the peripheral and systemic effects of these rises and falls in levels of the distinct hormones are well recognized, the expression of varying types of estrogen and androgen receptors across neuronal populations raises the possibility that the system hormonal environment has the potential to influence developmental as well as disease processes within the central nervous system.

Into this arena of the interplay of sex and disease, a series of groups are now reporting in this issue of *Acta Neuropathologica* studies which demonstrate differences in aspects of Alzheimer disease (AD) between men and women [2, 4, 8]. While each takes a different approach and examined distinct populations, each also demonstrated differences between the groups which raise interesting biological and clinical questions. Beginning with genetic studies, the paper from Deming et al. [2], the investigators used a range of biological parameters including CSF biomarkers (Aβ42, total tau) and neuropathologic measures amyloid burden and tangle density to determine sex-specific associations with genetic loci from GWAS studies, including both previously identified "hits" as well as novel loci. The essential finding from the studies is that there are distinct loci which demonstrate association with aspects of the neuropathologic phenotype of AD in one sex but not the other. These results demonstrated that some of the previously identified GWAS loci had the association with an aspect of disease phenotype driven by one sex; for the CSF biomarkers of Aβ42 and total tau, the associations were strong in women but absent in men. By extending these genetic studies into tissue, the authors were able to identify likely specific gene products in the association regions that correlated with the distinct risk of neuropathologic lesion burden. Among the interesting associations was the finding that the expression of a protease inhibitor (Serpin Family B Member 1; SERPINB1) could be related to the burden of amyloid in prefrontal cortex—and the authors highlight relationships between this protease inhibitor, neutrophil trafficking, and response and gonadal hormone levels.

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This connection between genetic loci and the immune system fits with many other lines of recently emerging evidence for a contribution of the immune response to Alzheimer disease (AD) remains to be determined. This interaction could be particularly complex, as there are aspects of AD pathogenesis for which the immune system can be beneficial (degradation of Aβ by microglia) as well as deleterious. In keeping with the potential contribution of the immune system to AD initiation and progression, as well as the relationship between neuropathologic lesion burden and clinical deficits, it is appropriate to also recall that autoimmune disorders, both those which affect the central nervous system exclusively (such as multiple sclerosis) as well as systemic disorders which may involve the brain (such as systemic lupus erythematosis) demonstrate sex-based differences in incidence rates [6, 7]. Whether the underlying bases of this difference in inflammatory disease risk based on sex might contribute to differences in AD biomarkers and histologic findings needs further exploration.

In the second of the studies in this issue, Liesinger et al. [4] examined the neuropathologic findings and clinical histories from series of cases collected through Florida Autopsied Multi-Ethnic cohort and focused on those who met diagnostic criteria for AD based on high Thal and Braak stages [5]. When comparing between sexes, although the incidence of AD in their cohort showed no differences by sex, men had earlier onset of disease, fewer neurofibrillary tangles when matched for age and less typical patterns of presentation. The last of these features can perhaps be explained by the greater incidence of hippocampal-sparing pattern of lesion distribution in men than in women. The authors also highlight a difference in the frequency of AD between genders as a function of age at death (as that was when neuropathologic assessment was made); interpretation of this data is complex, as end-of-life considerations by individuals and families can influence timing of death and are driven by multiple personal and social factors rather than just biological ones. It is unknown how genetic information discussed above might interact with the findings in this report.

The final paper of the trio by Oveisgharan et al. [8] examines sex differences in the neuropathologic findings in brains from the well-characterized ROS-MAP cohorts (although the extent to which women from religious orders are representative of the broader female population in terms of various patterns of gonadal hormone variation is an open question). In this combined cohort, there is again an excessive burden of the neuropathologic findings of AD, particularly tangle burden, in women compared to men when corrected for other appropriate variables. In addition, there was a greater burden of arteriolar sclerosis-associated injury in women—and the contribution of multiple forms of cerebrovascular disease to the manifestation of cognitive impairment has been well established through multiple studies.

Together, these three papers suggest important biological differences in the patterns of neuropathologic lesions observed between men and women as well as hint at distinct biological mechanisms which may contribute in one sex of the other. The interaction between genetic risk loci and the gonadal hormone history of the brain may also provide unique insights which open doors for new therapeutic approaches.

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