EDITORIAL OPEN ACCESS

Genetic risk for Alzheimer disease affects the brain throughout the lifespan

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Neuronal cell death and loss of synapses are hallmarks of the pathology of Alzheimer disease (AD). The incidence of AD increases with age, and both regional and global brain atrophies have been identified as pathological correlates. Thus, AD can, in many respects, be regarded as a paradigmatic neurodegenerative disorder. However, disrupted function of the presenilin genes, the most common cause of early-onset familial AD (FAD), can also affect brain development, including early processes of neuronal migration and morphogenesis.[1]

Evidence for reduced brain volume has been observed in middle-aged patients with FAD[2] and even in infants carrying the apolipoprotein E (APOE) ε4 allele,[3] the main common variant associated with late-onset AD (LOAD). Earlier neuropathologic work had identified neurofibrillary changes characteristic of AD in young adults, leading to the speculation that the brain changes associated with AD may precede the clinical syndrome by up to 50 years.[4] Converging evidence thus suggests that AD develops through a protracted process of neuropathologic changes that warrants a lifespan perspective.

The identification of additional common risk factors for LOAD and the development of polygenic risk scores summarizing their cumulative effects has further boosted research into the biological mechanisms of AD genetic risk. In this issue of *Neurology® Genetics*, Walhovd et al.[5] investigated the association between AD polygenic risk (including but not confined to the APOE ε4 variant) and hippocampal volume in 1,181 cognitively healthy people (some of whom contributed multiple scans over a time period of several years) with a wide age range (4–95 years). They confirmed the reduction in hippocampal volume found earlier in a sample of young adults[6] and, importantly, demonstrated that it was fairly consistent across age groups. The absence of strong interaction effects with age would suggest that AD polygenic risk mainly leads to an earlier onset of brain ageing (and loss of cognitive reserve) rather than an accelerated ageing process, although more longitudinal data would be needed to confirm this interpretation. What is also interesting about these findings is that, as the authors rightly point out, they are at odds with an antagonistic pleiotropy account of ageing, which posits that genetic variants that are detrimental in later life have a positive effect on fitness earlier in life to remain in the gene pool of a species. At least regarding the brain phenotype of hippocampal volume, there was no evidence of a beneficial effect of AD-related genes earlier in life.

What, then, are the clinical implications of the identification of brain correlates of genetic AD risk across the lifespan? One of the key approaches in the development and evaluation of new treatments is based on the early identification of prospective patients before the onset of clinically manifest symptoms. The biomarkers developed so far have limited clinical utility for AD prediction[7] and thus new multimodal approaches, incorporating both genetic risk scores and parameters of neural structure and function, should be welcome. The lifespan focus of the study by Walhovd et al. is particularly useful in this respect. Modifiable risk factors for AD build up over years,[8] and recent epidemiologic studies have highlighted the importance of

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dementia prevention in early life, for example, through the enhancement of cognitive reserve.[7] Although we are still far away from any use of hippocampal volume as a clinical proxy for cognitive reserve, the study by Walhovd et al. makes a compelling case for further longitudinal research into links between AD risk and brain structure.

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Disclosure

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