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Stroke Literature Synopsis (Clinical)

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Stroke is essentially a disease of the brain, but physicians and researchers have not always given the cognitive aspects of stroke disease the same attention that they give to physical sequela. In this Synopsis we discuss three papers that directly or indirectly investigate vascular cognitive health.

The most feared disorder of cognitive health is dementia. With limited therapeutic options, the scientific, clinical, and lay communities have all been desperately looking for new drug treatments. Van Dyck and colleagues conducted an 18-month, multi-centre, double-blind, phase 3, placebo-controlled trial of the IgG1 monoclonal antibody Lecanemab on a population of 1795 participants with mild cognitive impairment or mild Alzheimer's Disease (AD) dementia (**van Dyck C.J. et al. Lecanemab in Early Alzheimer's Disease. NEJM.2023. doi:10.1056/NEJMoa2212948**). The drug was certainly effective at altering the amyloid protein associated with AD. In a PET imaging substudy, decreased amyloid burden was seen at 18 months in the intervention arm. In terms of clinical effect, significantly improved cognitive scores were seen with Lecanemab compared with placebo for various cognitive assessments. The primary endpoint was severity of dementia as measured by change in Clinical Dementia Rating Sum of Boxes at 18 months. Here again a statistical difference was seen in favour of Lecanemab (difference:-0.45; 95%CI:-0.67 to -0.23).

These results are promising, but the benefits come with potential adverse effects that are particularly relevant to the stroke physician. The main safety concerns are around amyloid-related imaging abnormalities (ARIA). Macrohaemorrhage was seen in n=5 taking Lecanemab (placebo n=1), microhaemorrhage in n=126 (placebo n=68), and superficial siderosis in n=50 (placebo n=21) participants, respectively. The longer-term effects remain unknown, but close clinical and imaging monitoring of those taking the drug is required, particularly given two deaths associated with haemorrhage during the trial's extension and a case report of fatal bleeding following administration of thrombolysis for ischaemic stroke.

Given the lack of an effective disease modifying treatment in dementia, are these cerebral bleeding risks outweighed by the cognitive benefits? Although the cognitive changes with treatment are statistically significant, it is less clear that these results translate to a meaningful benefit. The between group difference falls short of what we would usually consider a minimum difference of clinical importance. We also lack information on how Lecanemab affects other factors such as quality of life, and caregiver burden that are arguably more important to people living with dementia than biological disease-modification markers. The current costs of the drug and associated imaging are prohibitive, leading to potential issues around equality of access. So, while a new potential AD treatment is a cause for optimism, clearly, there are still a multitude of concerns to be addressed.

The existence of pure vascular dementia, without AD or other neurodegenerative pathologies, has been a point of research contention for at least the past two decades. This is due in large part to the well described impact of AD-related pathologies on cognitive impairment, and the development of vascular dementia terminology to encompass additional vascular contribution. A study by Oveisgharan and colleagues looked to determine the prevalence of post-mortem vascular pathologies in a population with clinical cognitive impairment during life (**Oveisgharan, S. et al. Frequency and Underlying Pathology of Pure Vascular Cognitive Impairment. JAMA Neurol.2022. doi:10.1001/jamaneurol.2022.3472**).

In the cohorts studied (n=1767, enrolled in either the Religious Orders Study or the Rush Memory and Aging Project) subjects were assessed for presence of macroinfarcts, microinfarcts, atherosclerosis, arteriolosclerosis, cerebral amyloid angiopathy, indices of AD, hippocampal

sclerosis, and Lewy bodies. Of the total group studied, 369 (20.9%) did not show evidence of significant AD or other neurodegenerative pathology i.e., they exhibited 'pure' vascular cognitive impairment. Of the vascular lesions assessed, macroinfarcts, particularly in frontal white matter, were the lesions most associated with cognitive decline. This work offers useful data and proves that pure vascular cognitive impairment not only exists but is relatively common in people with cognitive decline. These data have implications for future research and current practice. A pure vascular pathology may have more success with vascular-focused treatments than those with mixed dementia. While we await specific vascular cognitive interventions, these data also highlight the potential longer term cognitive benefits of primary and secondary stroke prevention.

This cohort was also used to investigate an area that is infrequently researched, yet of increasing social concern – older adult scams. Kapasi and colleagues examined the relationship between scam susceptibility and various cerebrovascular pathologies in a sub-cohort of 408 participants with both clinical and post-mortem phenotyping (**Kapasi A. et al. Association of Stroke and Cerebrovascular Pathologies With Scam Susceptibility in Older Adults. *JAMA Neurol.* 2022.**

doi:10.1001/jamaneurol.2022.3711). The team characterised cerebrovascular brain health, and then assessed associations with responses to statements designed to determine vulnerability to fraud. Psycho-social factors such as wellbeing, neuroticism, life purpose and depression were also assessed, along with a battery of 19 neuropsychological tests.

Greater scam susceptibility was seen in those with cerebral macroinfarcts, a finding robust to adjustment for vascular risk burden and cognition. Why this association exists is unclear, but what is clear is that scam susceptibility involves complex decision-making and is reliant on the integration of many neural networks. We may well see more research in the field of cognition and scam susceptibility, given the increase in both prevalence of dementia and sophisticated scam techniques. The paper provides a prescient warning to those living with cerebrovascular diseases around the need to be mindful for scams.

Taken together, these three studies highlight the complex relationship between vascular pathology and cognition. Despite exciting progress in imaging and treatment there is still much to be elucidated around vascular brain health.