Stroke Literature Synopsis (Clinical)

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Cerebral small vessel disease (cSVD) is the most common pathology underlying vascular cognitive impairment, is a frequent cause of stroke and is the leading cause of functional decline in the elderly. Despite its prevalence, our understanding of cSVD remains limited compared to other vascular diseases. Thankfully the landscape is changing and important new studies in cSVD are recently available, or on the horizon. For this month's synopsis, we have selected three papers themed around clinical and research aspects of cSVD.

Given the link between cSVD features that are visible on brain imaging, and risk of future stroke and dementia, it seems likely that neuroimaging markers of cSVD should predict functional and cognitive outcomes. A study by Georgakis and the DEMDAS collaboration addressed this question (**Georgakis MK, et al.Cerebral small vessel disease burden and cognitive and functional outcomes after stroke. *Alzheimer's & Dementia.2022*.doi: 10.1002/alz.12744**). In this prospective multicenter cohort of 666 ischemic and hemorrhagic stroke survivors, the authors described aggregate cSVD burden using a global cSVD score based on presence of four neuroimaging markers (lacune count, white matter hyperintensity, cerebral microbleeds, enlarged perivascular space). The authors then explored association between the global cSVD measure, and more detailed individual assessments of the component cSVD markers, with cognitive and functional outcomes up to 12 months post-stroke.

As expected, the global cSVD score was associated with poor cognitive and functional outcomes. However, the global score did not add prognostic value to commonly used baseline predictors of outcome. Conversely, including more granular information on individual cSVD markers assessed across their severity did improve the calibration and discrimination of predictive models. These results highlight the trade-off between simplicity of assessment and accuracy of prediction. Simply awarding one point for the presence of each cSVD feature without considering the severity of individual lesion types did not offer sufficient detail to improve prediction.

Given the association between cSVD burden and poor outcomes, can we intervene to prevent cognitive and functional decline? For a vascular condition such as cSVD, antithrombotic medications seem a plausible treatment. A recent Cochrane systematic review summarized the available evidence (**Kwan J, et al.Antithrombotic therapy to prevent cognitive decline in people with small vessel disease on neuroimaging but without dementia.*Cochrane Database of Systematic Reviews.2022* doi:10.1002/14651858.CD012269.pub2**). The authors included randomized controlled trials (RCT) of individuals with neuroimaging evidence of at least mild cSVD where antithrombotic therapy was administered for a minimum of 24 weeks and compared to either placebo or treatment as usual, or where different antithrombotic regimens were compared. Only three RCTs met the selection criteria. Across these trials, there was no convincing

evidence to suggest clinically relevant cognitive or functional benefit but there was a potential safety signal, with an increased bleeding risk for certain antithrombotic strategies.

This review is important but not definitive as the included trials were insufficiently powered to answer the question of interest. The review also highlights other issues for future cSVD trials. For example, can we use more sophisticated risk stratification beyond a binary presence/absence of cSVD change on neuroimaging and how should we measure success of a cSVD intervention? In this review, no trials assessed important aspects of the cSVD phenotype, such as apathy and mood disturbances. Given that the clinical manifestations of cSVD are multifactorial and not limited to cognitive decline, how can we uncover the clinical features of greatest relevance to cSVD patients and clinicians?

Efforts to answer some of these questions have already been made. The Framework for Clinical Trials in Cerebral Small Vessel Disease (FINESSE) is from an international expert collective who have provided guidance and recommendations around clinical trial design in cSVD (**Markus HS, et al.Framework for Clinical Trials in Cerebral Small Vessel Disease. *JAMA neurology*.2022.doi:10.1001/jamaneurol.2022.2262**). These recommendations were developed in response to the growing body of evidence that disease mechanisms and functional consequences of cSVD differ from other stroke etiologies and so, trial designs may also need to differ. A key consideration is the need to account for heterogeneity in cSVD populations, whereby people living with cSVD tend to be present with differing symptoms and be diagnosed by different health services (i.e., stroke or geriatric services, memory or cognitive neurology clinics, etc.). Related to that is the importance of assessing cSVD disease stage, including whether there is history of neurological complications. The benefit of this guidance can be appreciated by applying the framework to the example of antithrombotics as an intervention. The net clinical benefit of antithrombotic therapy might differ across individuals with and without history of intracranial hemorrhage (ICH), and early administration of treatment when the disease process may be modifiable is likely to confer greater benefit than administration in advanced cSVD.

Guidance around assessing outcomes in cSVD trials is also offered. Cognitive testing is recommended, and these tests should be brief, suitable for remote assessment, but sensitive enough to detect clinically meaningful (including subtle) changes over the duration of a trial. In addition to incident disease-based end points (i.e., stroke and dementia), functional ability, neuropsychiatric symptoms, behavioral changes, and quality of life should all be considered.

Further work is needed before we translate our increasing understanding of cSVD into effective treatments. In the meantime, having a solid framework for trial design will increase the chances of research discriminating effective from non-effective treatments.