The role of systemic inflammation in cerebral small vessel disease.

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ABSTRACT

Cerebral small vessel disease (SVD) is a distinct microvascular disorder that can lead to lacunar stroke, an important stroke subtype that accounts for a quarter of all ischaemic strokes. SVD is associated with imaging biomarkers such as white matter hyperintensities (WMH). The cause of SVD is largely unknown, although inflammation and blood-brain barrier failure via endothelial dysfunction have been implicated. Elevated plasma biomarkers of inflammation are associated with coronary heart disease and large vessel stroke but the role of inflammation in SVD is less well understood. Our hypothesis is that inflammation plays a role in SVD and we sought to examine this by reviewing the literature for evidence of this, and by conducting a brain imaging study of patients with a known inflammatory disease and reviewing the images for evidence of inflammation and SVD, and comparing findings with controls groups.

Section A: This thesis begins with a systematic review and meta-analysis of 13 plasma biomarkers of four physiological processes (coagulation, fibrinolysis, endothelial dysfunction and inflammation) in lacunar stroke versus non-lacunar stroke (to control for having any stroke) and non-stroke (to compare to the general population). We sought to know if there were differences in these biomarkers between lacunar stroke and other stroke subtypes and non-stroke controls as a way of generating hypotheses for the disease mechanisms that might lead to lacunar stroke. Findings revealed differences in several biomarkers between lacunar stroke and healthy controls but only fibrinogen, D-dimer, von Willebrand factor and interleukin-6 were different (all significantly lower in lacunar stroke) between lacunar stroke and other stroke subtypes. There was heterogeneity between studies, including variations in the definition of lacunar stroke and most studies measured the biomarkers in the acute phase post stroke, which is potentially confounding. To further examine plasma biomarkers of inflammation and endothelial dysfunction in SVD, we used data from a prior study of mild stroke conducted at

the Brain Research Imaging Centre, University of Edinburgh, UK. Lacunar stroke patients were compared to cortical stroke patients. The lacunar group had lower levels of tissue plasminogen activator independent of age, sex and vascular risk factors but we found no difference in the other plasma biomarkers.

Section B: Non-resolving systemic inflammation is a feature of inflammatory autoimmune rheumatic diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). These patients are at increased risk of stroke but much knowledge relates to stroke in general; less is known about associations with stroke subtypes including SVD, or when in life stroke risk is greatest. Consequently, we sought to better understand the influence of inflammatory rheumatic diseases on stroke and SVD. The review and meta-analysis of cerebrovascular disease in rheumatic diseases showed an excess risk of stroke in RA, SLE, ankylosing spondylitis, gout and psoriasis over the general population. Meta-analyses of stroke subtypes (ischaemic and haemorrhagic) in RA and SLE showed an excess risk of stroke over the general population. Stroke risk across rheumatic diseases was highest in those aged <50 years and reduced with ageing. We then requested data from NHS Lothian covering 15 years so that we could assess stroke, including stroke subtypes, among patients diagnosed with various arthropathies. We linked 6,613 rheumatology patients' records with stroke admission records, grouped the various rheumatic diseases into the two main types of arthritis, inflammatory and non-inflammatory, and also compared the strokes in these rheumatology patients to general population data. There was no difference in stroke prevalence between inflammatory and degenerative (non-inflammatory) arthropathies, although the strokes occurred up to two decades earlier than in the general population.

Section C: Lastly, we conducted a prospective MRI neuroimaging study of patients with SLE and reviewed and meta-analysed diffusion tensor imaging (DTI) (an imaging technique used to assess sub-visible white matter microstructure damage) in SLE to place our findings into

context. The research question here was to ascertain if patients with a known inflammatory disease had brain imaging evidence of SVD, and to compare findings to controls. We compared imaging markers of SVD and DTI between SLE patients and age-matched healthy controls and sought associations between the imaging biomarkers and plasma biomarkers of inflammation and endothelial dysfunction, measures of fatigue and cognition, and scores of rheumatic disease activity. Fifty-one patients were recruited. There was higher mean diffusivity in all white matter tracts versus controls indicating a diffuse increase in brain water mobility in SLE. Meta-analysis confirmed higher mean diffusivity in SLE patients versus controls. Fatigue in SLE was significantly higher than a normal reference range and was associated with depression, anxiety, higher body mass index, lower mean diffusivity and some blood markers of inflammation and endothelial dysfunction. The most fatigued were youngest which explained the association with lower mean diffusivity. Damage to the brain's white matter microstructure may be accelerated in SLE as the age-related declines in the general population are normally seen much later in life. The aging pattern is consistent with inflammation-related microvascular-mediated brain damage where the inflammation is systemic in origin.

Summary: This thesis has demonstrated an increase in SVD burden in the inflammatory rheumatic disease SLE and increased stroke risk at younger ages in other inflammatory rheumatic diseases. Thus, systemic inflammation as seen in inflammatory rheumatic diseases could have effects of the brain directly, including influencing stroke risk which is clinically noteworthy and would benefit from further testing in appropriately designed studies such as an inception cohort that follows inflammatory rheumatic patients from diagnosis, with regular brain imaging to track brain changes and correlates with inflammatory flares and impact on cognition.