Clinical impact of MRI-evident, deep vs periventricular T2 abnormalities on cognitive impairment in cerebrovascular disease and other leukopathologies

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Background: Subcortical white matter hyperintensities (WMH) are considered to be the result of both subcortical arteriosclerotic disease related to cardiovascular disease (CVD) risk factors, multiple sclerosis and other leuko-encephalopies/dystrophies and/or transependymal exudate/subependymal injury associated with CVD risk factors or other neurologic disorders such as normal pressure hydrocephalus (NPH). Traditional semiquantitative rating scales and quantitative T2 WMH volumetric measurements, routinely used in clinical translational research paradigms, do not distinguish between such lesions on the basis of subcortical localization creating a confound in establishing causality and or effects of interventions on CVD risks and or NPH. Understanding the differential effects of deep (d-WMH) and periventricular (pv-WMH) lesions on cognitive outcomes is essential for targeted clinical trial design for CVD, MS, and NPH among many other neurologic diseases demonstrating increased T2 WMH on MRI.

Methods: A cross-sectional analysis of clinical and quantitative MRI data on 114 subjects with normal cognitive function (n=52) and mild cognitive impairment (n=62) exhibiting a spectrum of T2 WMH was performed. Quantitative d-WMH and pv-WMH volumes were calculated using a previously described method including acombination of SPM8 http://www.fil.ion.ucl.ac.uk/spm/ and MIPAV version 7.1.1 morphology; http://mipav.cit.nih.gov.ezproxy.uky.edu/ techniques. A P-value of 0.01 was chosen as the threshold to define WMH (2.33 × SD) relative to the WM voxel mean in each individual image. d-WMH and pv-WMH volumes were examined in relation to cognitive test scores using linear regression models adjusted for age, gender, and education.

Results: Increased d-WMH volumes were associated with decreased performance on the Trail Making Test A & B (p= 0.001 and p= 0.003, respectively), Wechsler Adult Intelligence Scale Digit- Symbol Test (p= 0.043), and long-delayed free recall on the California Verbal Learning Test (p= 0.008). In contrast, increased pv-WMH volumes were associated with poor performance on only the Trail Making Test A (p= 0.012) and Digit Span Forward Length (p= 0.038).

Conclusion: These data suggest distinct, yet ovelapping, profiles of cognitive performance decline are associated preferentially with d-WMH and pv-WMH. These data have implications for both clinical trial outcome measure development and clinical bedside evaluation of interventions designed to slow, halt or reverse the causative disease process in disorders such as CVD, MS, NPH, and other leukopathologies. Further work examining cortical loobe involvement of d-WMH and pv-WMH may further refine our understanding of the cognitive sequalae of WM injury in neurologic disease e