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Featured Article

Blood-brain barrier failure as a core mechanism in cerebral small vessel disease and dementia: evidence from a cohort study

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Abstract

Introduction: Small vessel disease (SVD) is a common contributor to dementia. Subtle blood-brain barrier (BBB) leakage may be important in SVD-induced brain damage.
Methods: We assessed imaging, clinical variables, and cognition in patients with mild (i.e., nondisabling) ischemic lacunar or cortical stroke. We analyzed BBB leakage, interstitial fluid, and white matter integrity using multimodal tissue-specific spatial analysis around white matter hyperintensities (WMH). We assessed predictors of 1 year cognition, recurrent stroke, and dependency.
Results: In 201 patients, median age 67 (range 34–97), BBB leakage, and interstitial fluid were higher in WMH than normal-appearing white matter; leakage in normal-appearing white matter increased with proximity to WMH ($P < .0001$), with WMH severity ($P = .033$), age ($P = .03$), and hypertension ($P < .0001$). BBB leakage in WMH predicted declining cognition at 1 year.
Discussion: BBB leakage increases in normal-appearing white matter with WMH and predicts worsening cognition. Interventions to reduce BBB leakage may prevent SVD-associated dementia.
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Keywords: Blood brain barrier; Small vessel disease; Stroke; White matter hyperintensities; Dementia

1. Introduction

Worldwide, 36 million people are estimated to be living with dementia [1]. Cerebral small vessel disease (SVD) causes about 40% of these dementias, alone or in mixed pathologies [2]. SVD also causes a fifth of the 15 million strokes that occur per year worldwide [1]. These three-million SVD (or lacunar) strokes are not severe; so, most lacunar stroke patients survive physically independent, but 36% have mild cognitive impairment or dementia [3]. The frequent cognitive impairment may reflect the association of lacunar stroke with other SVD features [4]. These features (white matter hyperintensities [WMH], lacunes, and microbleeds) are typically regarded as clinically "silent" but substantially increase the risk of dementia and stroke individually [5–7] and combined predict cognitive impairment [8].

Alzheimer's disease (AD) and stroke are typically managed and researched separately, but there is substantial evidence of overlap in pathogenesis, for example, dementia expression in life closely reflects the burden of microvascular disease more than of typical AD pathology (amyloid β plaques and neurofibrillary tangles) at postmortem [9–11]. WMH are common in AD [12]. Management of vascular risk factors [13], lifestyle interventions [14], and stroke prevention [15] could help prevent dementia. However, direct application of vascular prevention strategies that are effective in preventing large artery atherothromboembolic stroke may be ineffective or hazardous if given long term to patients with SVD or AD. Thus, blood pressure reduction and dual antiplatelet drugs failed to prevent cognitive decline or recurrent stroke [16], dual versus single

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antiplatelet drugs were hazardous after lacunar stroke [17], and antiplatelet drugs increased risk of cerebral hemorrhage in AD [18], reflecting our incomplete understanding of mechanisms underlying SVD and AD [19,20], and that a different approach is needed [21].

A potential contributor to, or initiator of, the microvascular damage common to both SVD and AD is cerebral microvessel endothelial (or blood-brain barrier [BBB]) failure [2,22,23]. This could explain the perivascular cell and protein infiltrates, perivascular edema, and secondary axonal and neuronal damage seen pathologically in sporadic SVD [24,25]. It could also provide a route for entry of amyloid β and inflammatory cells into the brain in AD [26,27]. Human studies, mostly using cerebrospinal fluid (CSF)/plasma albumin ratio, show that BBB leakage increases subtly with advancing age and is worse in dementia (including AD) than in age-matched controls [28]. The BBB is also more leaky in white and deep gray matter in diabetes-associated mild cognitive impairment [29], in white matter and CSF in lacunar than atherothromboembolic stroke [30], and in white matter in patients with leukoaraiosis [31], vascular [32], and Alzheimer's dementias [33,34]. Recently BBB leakiness was noted to increase in the hippocampus (but not other tissues) with mild cognitive impairment [35].

These studies of BBB function in vivo in patients to date have been small (all $n < 50$ except 1 [30]) sampled small volumes of brain [35] or used permeability models that ignore aging effects on blood volume and vascular surface area [36,37] that limit the measurement of permeability accurately. Thus, there is no comprehensive, whole-brain, tissue-specific, in vivo assessment of BBB leakiness in human SVD and none with concurrent independent measures of brain interstitial fluid or tissue damage, making it unclear if BBB leakage is real, pathogenic, or an epiphenomenon in SVD. If pathogenic, then we hypothesized that the leak should worsen with worsening SVD burden, be spatially related to major markers of SVD such as WMH, and be accompanied by increased interstitial fluid. BBB leakage should increase with age, in small vessel (i.e., lacunar) versus atherothromboembolic (i.e., cortical or large artery) ischemic stroke [30] and in hypertension (a major SVD risk factor [38]), and predicts worsening of SVD-associated clinical or imaging features.

We prospectively studied a large cohort of patients with lacunar stroke (a model for vascular effects on neurodegeneration that identifies patients at high risk of cognitive impairment [3]) and cortical ischemic stroke (a control group with similar vascular risk factors [39] and medications), with a range of WMH, followed up at 1 year. We examined the magnitude and spatial distribution of BBB leak and tissue integrity in relation to WMH as a major marker of SVD, using three-dimensional (3D), whole-brain, dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI), diffusion-tensor imaging, T1 mapping, and spatially detailed, tissue-specific analysis.

2. Methods

2.1. Recruitment and eligibility

We recruited patients prospectively who presented with a lacunar or mild cortical ischemic stroke classified clinically using the risk-factor-free Oxfordshire Community Stroke Project classification [40]. We included patients aged ≥18 years, able to consent, within 4 weeks of mild ischemic stroke (i.e., National Institutes of Stroke Scale score [NIHSS] ≤5, unlikely to cause physical dependency), with an MR diffusion-weighted imaging (DWI) infarct compatible with the index stroke symptoms (Fig. 1), or

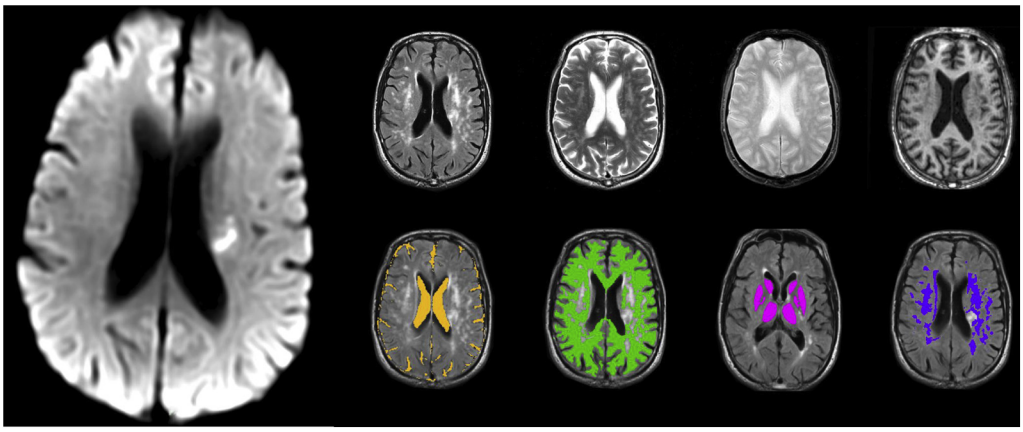

Fig. 1. Magnetic resonance brain imaging sequences and processed images. Left, diffusion-weighted image shows recent small deep infarct in the left centrum semiovale (white area) as the index infarct. Top row, left to right, fluid-attenuated inversion recovery and T2-, T2*-, and T1-weighted axial brain images at the same level as in the large diffusion-weighted image on the left. Bottom row, left to right, colors indicated masking obtained by semiautomated image processing to identify cerebrospinal fluid (yellow), normal-appearing white matter (green), deep gray matter (pink), and white matter hyperintensities (purple); note the index infarct was masked by hand.

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