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Abstract

Microvascular and Blood–Brain Barrier Dysfunction in COL4A1-Related cSVD Can Be Identified by MR DSC Perfusion Imaging †

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Introduction: Pathogenic variants in COL4A1 compromise basement membrane integrity, leading to cerebral small vessel disease (cSVD) characterized by white matter hyperintensities (WMHs), microbleeds, and ischemic or hemorrhagic strokes [1–3]. Despite the clinical impact, no imaging biomarkers currently exist to assess disease severity or predict stroke risk in COL4A1-related cSVD. In this study, we evaluated microvascular flow heterogeneity and blood–brain barrier (BBB) permeability using dynamic susceptibility contrast (DSC) MR perfusion imaging [4].

Methods: We retrospectively analyzed five Dynamic Susceptibility Contrast Magnetic Resonance (DSC MR) perfusion imaging studies from four patients with symptomatic COL4A1 mutations (p.G212A, p.G1248R, p.G1242D). Three patients (one with p.G212A and two with p.G1248R) had a single imaging study, while one patient with p.G1242D underwent imaging at two distinct timepoints. The mean age of the COL4A1 cohort was 33.42 years (range: 6.2–47.6 years). For comparison, we included ten age-matched control patients (mean age: 53.6 years; range: 28–74 years) who underwent DSC MR perfusion imaging and showed no evidence of cerebrovascular abnormalities. DSC data were processed using Cercare® software perfusion toolbox v1.0 to extract capillary transit time heterogeneity (CTH), apparent leakage constant (Kapp), oxygen extraction capacity (OEC), and cerebral metabolic rate of oxygen ($CMRO_2$ max). Brain regions were segmented into WMH, normal-appearing white matter (NAWM), and gray matter (GM) using a 3D Slicer 5.4.0. Statistical analyses included unpaired *t*-tests and one-way ANOVA.

Results: Compared to the controls, COL4A1 patients exhibited significantly increased BBB permeability (Kapp) across all brain regions ($p < 0.0001$). CTH was elevated in WMH ($p = 0.0014$) and NAWM ($p = 0.0036$) but reduced in GM ($p = 0.0217$). Within COL4A1 patients, WMH regions showed higher CTH, greater OEC, and lower $CMRO_2$ max compared to NAWM, indicating more severe microvascular dysfunction.

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Conclusions: These results demonstrate that DSC-MRI perfusion imaging sensitively detects global and regional microvascular abnormalities in COL4A1-related cSVD. Elevated Kapp and altered CTH may serve as promising imaging biomarkers for risk stratification, disease monitoring, and therapeutic evaluation in this population.

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