RESEARCH ARTICLE   **Open Access**

Increase of blood-brain barrier leakage is related to cognitive decline in vascular mild cognitive impairment

Man Li[1*], Yue Li[2], Long Zuo[1], Wenli Hu[2] and Tao Jiang[1]

Abstract

Background: Blood-brain barrier (BBB) breakdown, as an early biomarker for vascular mild cognitive impairment (vMCI), has only been validated by a few studies. The aim of this study was to investigate whether compromised BBB integrity is involved in vMCI patients, and detect the relationship between BBB breakdown and cognitive function. BBB leakage in vMCI was explored, and the relationship between BBB leakage and cognitive function was discussed in this study.

Methods: This is a cross-sectional study involving 26 vMCI patients and 21 sex- and age-matched healthy controls. Dynamic contrast-enhanced-magnetic resonance imaging was performed for all participants, to determine BBB leakage. Leakage volume, leakage rate, and fractional blood plasma volume (Vp) in the grey and white matter were evaluated. Neuropsychological tests were used to determine cognitive function. Leakage rate, leakage volume, and Vp in different brain locations, including deep grey matter, cortical grey matter, white matter hyperintensity, and normal-appearing white matter were compared between the two groups.

Results: Multivariable linear regression analyses revealed that in all regions of interest, the leakage rate was significantly higher in vMCI patients relative to controls. Leakage volume in normal-appearing white matter and white matter hyperintensity were significantly higher, while Vp in normal-appearing white matter, deep grey matter, and cortical grey matter were significantly lower in vMCI patients. Moreover, Montreal Cognitive Assessment scores decreased with the increase of leakage rate in white matter hyperintensity.

Conclusion: Increased BBB permeability was detected in vMCI patients and was related to cognitive decline, which suggested that BBB breakdown might be involved in cognitive dysfunction pathogenesis.

Keywords: Blood-brain barrier, Vascular mild cognitive impairment, Dynamic contrast-enhanced-magnetic resonance imaging, Cognitive function

Background

Vascular cognitive impairment (VCI) includes subjective cognitive decline, vascular mild cognitive impairment (vMCI), and dementia [1]. Vascular dementia is the second most common subtype of dementia, and comprises

about 14.5% of the total number of dementias [2]. VMCI is considered as an early stage of VCI, and it is most prevalent in elderly Chinese [3]. Its pathophysiology remains unclear, but various pathophysiological processes may affect its progress, including blood-brain barrier (BBB) defects, inflammation altered vascular reactivity, hypoperfusion, and innate immune processes [4–6].

It had been studied that BBB breakdown occurs in the early stage of cognitive dysfunction [7].

* Correspondence: pkumanli@163.com
[1]Radiology Department, Beijing Chao-Yang Hospital, Capital Medical University, No. 8, South Gongti Road, Chaoyang District, Beijing 100020, P.R. China
Full list of author information is available at the end of the article

Neuropathological, cerebrospinal fluid (CSF) biomarker, and non-quantitative neuroimaging studies have revealed the increase of BBB permeability in cognitively declining patients [8–10]. Some studies used dynamic contrast-enhanced-magnetic resonance imaging (DCE-MRI) to quantitatively evaluate BBB permeability in cerebral small vessel disease(cSVD) and stroke [7, 11, 12], showing that subtle BBB leakage was detected. Although increased BBB leakage in white matter was found in patients with VCI using DCE-MRI [13], there were scarce studies focusing on vMCI patients, and understanding of the relationship between cognitive function and BBB leakage was deficient. The aim of this study was to investigate whether BBB permeability change in different brain regions in vMCI patients. In addition, the matter whether the cognitive function was independently associated with BBB leakage change was tentatively examined.

Methods

Study participants

This is a cross-sectional study. Participants were recruited through Beijing Chao-Yang Hospital, Capital Medical University from May 2016 to June 2019. Twenty-six vMCI patients were enrolled, along with 21 sex- and age-matched healthy controls. All participants were subjected to neuropsychological evaluation and DCE-MRI to assess BBB permeability. Participants were recruited into the vMCI group if they met the following criteria: (1) complaints of cognitive function, activities of daily living may be normal or mildly impaired, (2) objective cognitive impairment in at least one cognitive domain, (3) MRI findings suggest that cognitive impairment is associated with vascular diseases [14, 15]. The MRI findings include:(1) > two lacunar infarcts outside the brainstem, (2) Single lacunes(> 5 mm)placed strategically in the striatum or the thalamus, (3)confluent deep WMH (Fazekas score = 2 or 3) or irregular periventricular WMH extending into deep white matter (Fazekas score = 3) combined with or without lacunes or microbleeds [14].Sex- and age-matched controls were recruited which presented for physical examination at the medical examination centre of Beijing Chao-Yang Hospital. Exclusion criteria included psychiatric disorders, alcohol/drug abuse, epilepsy, brain tumor, brain trauma, vascular malformation, cardiac and systemic disease, neurodegenerative disease, Parkinson disease, intracranial infection, and contraindications to MRI or intravenous gadolinium.

Ethics

Ethical clearance for this study was given by the institutional ethics committee of Beijing Chao-Yang Hospital, Capital Medical University. All participants provided signed informed consent before participating in the study.

Neuropsychological evaluation

All participants underwent a face-to-face neuropsychological test by two trained interviewers within 3 days before or after MRI examination. We calculated cognitive function using Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Digit Span Test (DST, including forward and backward), Trail-Making Test (TMT, including Part A and Part B), Symbol Digital Modalities Test (SDMT), Stroop color word Test (SCWT, including Part A, B and C), Clock Drawing Test (CDT, 4-point scale), and verbal fluency test (VFT). Overall cognitive function was assessed by MMSE and MoCA. Other cognitive domains included memory (delayed racall test in MoCA, DST), information processing speed (TMT-A), attention (SDMT), executive function (TMT B-A, SCWT C-B), spatial function (CDT), and language function (VFT) [14, 16].

Imaging protocol and analysis

MRI examinations were executed using a Siemens 3 T MR system(Siemens, Prisma, Munich, Germany), with a 64-channel array head coil. Structural MRI was first performed(See Supplementary Table 1, Additional file 1). DCE-MRI was then performed. The T1 DCE protocol was a fast sequence (repetition time/echo time [TR]/[TE]5.08/1.8 ms, flip angle 15°, slice number = 20 per volume, voxel size $1.2 \times 1.2 \times 3 \text{ mm}^3$, field of view [FOV]$23 \times 23 \text{ cm}^2$), this sequence included 60 volumes of continuous acquisition. Gadolinium (1.0 mmol/ml, at an injection volume of 0.1 mmol/kg body weight and an injection speed of 2.5 ml/s) was injected using a high-pressure injector after the acquisition of 4 volumes T1WI, flushing with 20 mL saline. Before dynamic imaging, baseline T1 mapping was performed using two flip angles (3°, 15°). T1 mapping [17] was done to convert the contrast-enhanced signal strength into concentration in the tissue.

DCE-MRI post-processing was carried out using Nordic ICE (Nordic Neuro Lab). Vascular input function was gained from the superior sagittal sinus [18]. Patlak model was applied to assess the subtle BBB leakage [19]. This approach obtained 3 parameters: area under the leakage curve (AUC), BBB leakage rate (K_{trans}), and V_p (Fig. 1). Regions of interest (ROIs) were manually outlined according to Axial T2 FLAIR sequence. ROIs included 4 areas: deep grey matter (DGM), cortical grey matter (CGM), white matter hyperintensity (WMH), and normal-appearing white matter (NAWM) (Fig. 2). The ROIs of control subjects were similar in size and location to those of patients. ROIs were 5 mm^2 in area. Medial temporal lobe atrophy (MTA) scale was used to
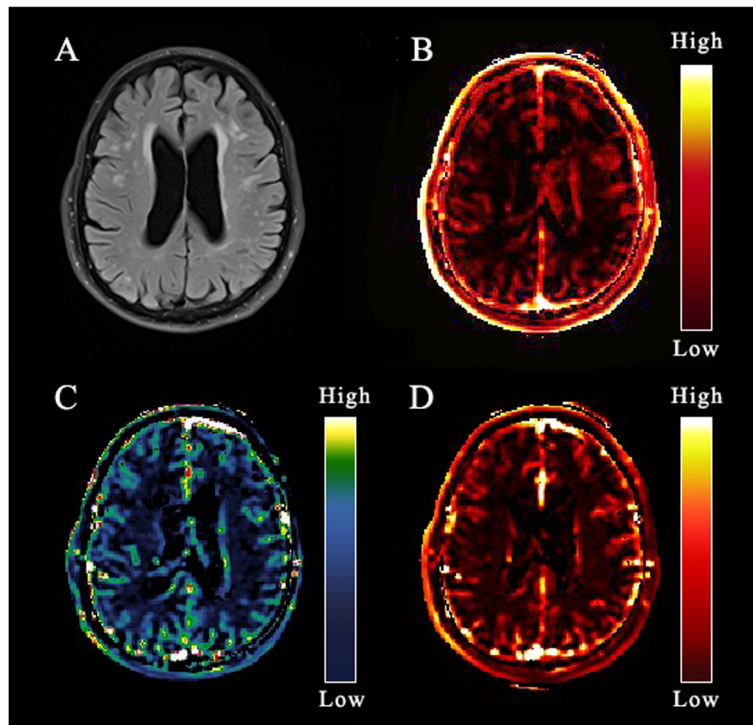
Fig. 1 An example map. **a** Axial fluid-attenuated inversion recovery (FLAIR) image of a79-year-old man; **b** BBB leak (K_{trans}) map; **c** Area under the leakage curve (AUC) map; **d** Fractional blood plasma volume (V_p) map
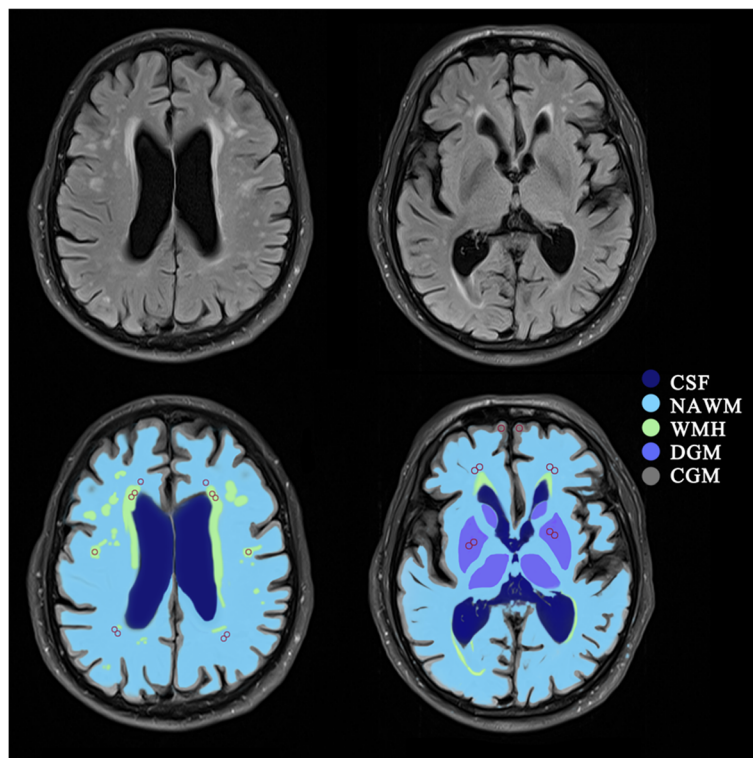
Fig. 2 Regions of interest (ROIs). Example of the template for sampling ROIs (red circles) in normal-appearing white matter (NAWM), white matter hyperintensities (WMH), cortical gray matter (CGM), and deep gray matter (DGM). CSF, cerebrospinal fluid

Li *et al. BMC Neurology*   (2021) 21:159

Page 4 of 8

measure the hippocampal atrophy on coronal T1-weighted MRI [20].

Statistical analysis

Independent sample *t*-test, Fisher's exact test, Mann-Whitney U test, and χ^2 test were used to compare the characteristics of participants and cognitive function in the vMCI vs control group. BBB leakage and V_p of all ROIs between the two groups were compared using univariable linear regression analysis, multivariable linear regression analysis was performed to correct sex, age, and vascular risk factors. The relationship between cognitive function and BBB leakage was assessed using Spearman correlation analysis. Next, associations of BBB leakage with cognitive function were investigated using univariable linear regression analyses; then, multivariable linear regression analyses were performed to correct vascular risk factors, sex, age, and education years. $P < 0.05$ indicated statistical significance.

Results

Participants characteristics

Fifty subjects participated in this study, of which, three were excluded due to MRI contraindication, image artifacts, or brain tumor. Of the remaining 47 participants, 26 had vMCI, and 21 were sex- and age-matched controls. Analysis of baseline characteristics revealed significant differences in hypertension between the two groups ($P < 0.001$; Table 1).

Table 1 Clinical characteristics of participants at baseline

	vMCI group N = 26	Control N = 21	P
Male, N (%)	12(46.2%)	8(38.1%)	0.583
Age, years	71.04 ± 8.99	66.67 ± 9.19	0.108
Education, years	11.58 ± 3.18	11.62 ± 3. 49	0.966
Vascular risk factors			
BMI, kg/m^2	26.02 ± 4.21	25.72 ± 2.42	0.774
Hypertension, N(%)	26(100.0%)	11(52.4%)	<0.001
Current Smoking, N(%)	4(15.4%)	3(14.3%)	0.623
T2DM, N(%)	4(15.4%)	3(14.3%)	0.623
Hyperlipidemia, N(%)	20(76.9%)	11(52.4%)	0.081
MTA scale			
Right(median (range))	0(0,1)	0(0,1)	0.085
Left(median (range))	0(0,1)	0(0,1)	0.085
MoCA	23.04 ± 2.32	28.00 ± 1.22	<0.001
MMSE	26.31 ± 1.12	29.24 ± 0.70	<0.001

Data are presented as mean ± SD, or counts (%)
Abbreviations: *N* number of persons, *vMCI* vascular mild cognitive impairment, *BMI* body mass index, *T2DM* type 2 diabetes mellitus, *MTA* medial temporal lobe atrophy, *MoCA* Montreal Cognitive Assessment, *MMSE* mini-mental state examination

Cognitive function

Analysis of cognitive functions revealed significant differences in MoCA, MMSE, information processing speed, attention executive function, spatial function, and language function between the two groups. The specific data are shown in Table 2.

Correlation between BBB leakage and vMCI

Quantitative analysis and comparison results between the two groups are shown in Table 3. Univariable and multivariable (corrected for vascular risk factors, sex, and age) linear regression analyses showed that participants in vMCI group had higher BBB leakage rate in all ROIs and higher BBB leakage volume in NAWM and WMH (Table 3).

Correlation between fractional blood plasma volume and vMCI

Univariable and multivariable (corrected for vascular risk factors, sex, and age) linear regression analyses found that the vMCI group had lower Vp in DGM, CGM, and NAWM (Table 3).

Table 2 Cognitive function in different domains of participants

	vMCI group N = 26	Control N = 21	P
Overall cognitive function			
MMSE	26.31 ± 1.12	29.24 ± 0.70	<0.001
MoCA	23.04 ± 2.32	28.00 ± 1.22	<0.001
Memory			
Delayed recall	4.62 ± 0.50	4.86 ± 0.36	0.059
DST-forward	7.85 ± 0.78	8.33 ± 0.97	0.063
DST-backward	3.77 ± 0.65	4.10 ± 0.70	0.106
Information processing speed			
TMT-A	59.23 ± 10.88	39.81 ± 9.11	<0.001
Attention			
SDMT	31.81 ± 4.45	39.57 ± 6.52	<0.001
Executive function			
TMT B-A	85.96 ± 31.97	56.71 ± 19.54	0.001
SCWT C-B	68.31 ± 24.81	49.81 ± 21.02	0.009
Spatial function			
Clock Drawing Test	3.31 ± 0.55	3.81 ± 0.40	0.001
Language function			
VFT	42.38 ± 10.09	51.43 ± 7.21	0.001

Data are presented as mean ± SD, or counts (%)
Abbreviations: *N* number of persons, *vMCI* mild vascular cognitive impairment, *MMSE* Mini-Mental State Examination, *MoCA* Montreal Cognitive Assessment, *DST* digit span test, *SDMT* symbol digital modalities test, *SCWT* stroop color word test, *CDT* clock drawing test, *VFT* verbal fluency test

Table 3 Leakage rate, area under the leakage curve, and fractional blood plasma volume in patients with vascular mild cognitive impairment (vMCI) and controls

	vMCI group	Control	Univariable [a]		Multivariable [b]	
			β	P	β	P
NAWM						
K_{trans} (10^{-4} min^{-1})	0.31 ± 0.14	0.20 ± 0.17	− 0.109	0.016	− 0.109	0.016
AUC	4.41 ± 1.04	3.52 ± 1.20	−0.886	0.008	− 0.888	0.006
Vp (10^{-2})	4.76 ± 1.97	7.51 ± 2.33	2.751	<0.001	2.751	<0.001
WMH						
K_{trans} (10^{-4} min^{-1})	0.56 ± 0.24	0.29 ± 0.18	−0.275	<0.001	−0.275	<0.001
AUC	6.02 ± 1.77	4.13 ± 1.25	−1.896	<0.001	−1.896	<0.001
Vp (10^{-2})	8.43 ± 4.39	10.49 ± 5.04	2.058	0.129	0.218	0.115
CGM						
K_{trans} (10^{-4} min^{-1})	1.57 ± 0.70	0.93 ± 0.56	−0.642	0.001	−0.642	0.001
AUC	17.90 ± 4.37	16.10 ± 5.76	−1.798	0.217	0.453	0.800
Vp (10^{-2})	20.92 ± 7.97	30.12 ± 9.73	9.192	0.001	9.170	<0.001
DGM						
K_{trans} (10^{-4} min^{-1})	0.99 ± 0.50	0.54 ± 0.35	−0.442	0.001	−0.442	0.001
AUC	11.44 ± 2.11	10.24 ± 3.43	−1.200	0.123	0.122	0.429
Vp (10^{-2})	15.36 ± 5.51	19.79 ± 7.10	4.434	0.017	4.445	0.009

Data are presented as mean ± SD

Abbreviations: *NAWM* normal-appearing white matter, *WMH* white matter hyperintensities, *CGM* cortex grey matter, *DGM* deep grey matter, K_{trans} leakage rate, *AUC* area under the leakage curve, V_p fractional blood plasma volume

Table 4 Association of leakage rate, area under the leakage curve, and fractional blood plasma volume with MoCA

	Spearman correlation		Univariable [a]		Multivariable [b]	
	r	P	β	P	β	P
NAWM						
K_{trans} (10^{-4} min^{-1})	−0.384	0.008	−6.260	0.026	−4.718	0.080
AUC	−0.316	0.030	−0.719	0.063	−0.246	0.590
V_p (10^{-2})	0.425	0.003	0.463	0.009	0.439	0.011
WMH						
K_{trans} (10^{-4} min^{-1})	−0.540	<0.001	−6.205	<0.001	−4.363	0.010
AUC	−0.551	<0.001	−0.780	0.002	−0.511	0.063
V_p (10^{-2})	0.122	0.412	0.048	0.631	−0.003	0.977
CGM						
K_{trans} (10^{-4} min^{-1})	−0.425	0.003	−1.214	0.061	−0.571	0.358
AUC	−0.264	0.073	−0.140	0.115	0.011	0.913
V_p (10^{-2})	0.443	0.002	0.129	0.003	0.132	0.004
DGM						
K_{trans} (10^{-4} min^{-1})	−0.437	0.002	−2.322	0.011	−1.346	0.132
AUC	−0.288	0.049	−0.317	0.054	0.006	0.971
V_p (10^{-2})	0.267	0.070	0.085	0.237	0.056	0.449

Abbreviations: *MoCA* Montreal Cognitive Assessment, *NAWM* normal-appearing white matter, *WMH* white matter hyperintensities, *CGM* cortex grey matter, *DGM* deep grey matter, K_{trans} leakage rate, *AUC* area under the leakage curve, V_p fractional blood plasma volume

[a]Univariable linear regression analysis with MoCA as dependent variable, and K_{trans}, AUC, and V_p respectively, as independent variable

[b]Multivariable linear regression analysis with MoCA as dependent variable, and K_{trans}, AUC, V_p, age, sex, vascular risk factors, and education years as independent variables

β, Unstandardized regression coefficient

Li *et al. BMC Neurology*　　(2021) 21:159

Page 6 of 8

Correlation between BBB leakage and cognitive function

Spearman correlation analysis showed that BBB leakage rate and leakage volume was negatively correlated with MoCA in all ROIs. Multivariable linear regression analysis revealed that the MoCA scores decreased with the increase of leakage rate in WMH to correct sex, age, vascular risk factors, and education years (Table 4).

Discussion

In this study, it was found that BBB leakage rate rose in WMH, NAWM, CGM, and DGM in vMCI patients compared with the controls. Additionally, leakage volume in vMCI patients also increased in NAWM and WMH relative to controls. MoCA was negatively correlated with the leakage rate in WMH after correcting sex, age, vascular risk factors, and education years. These results indicated that BBB leakage was elevated widespread in brain parenchyma in vMCI patients and was independently related to cognitive decline.

DCE-MRI, as the most reliable noninvasive quantitative neuroimaging method to quantify BBB leakage in vivo [21],has been used to show BBB breakdown in mild cognitive impairment patients in some studies, but only a few studies focused simply on vascular factor. One study paid attention to the white matter area and found evaluated BBB permeability in white matter in VCI using DCE-MRI [13], but failed to quantify BBB permeability in grey matter which was also involved in VCI [22, 23]. A recent study found the increase of BBB leakage volume in CGM, WMH, and NAWM in vMCI and recent small subcortical infarct patients. In contrast, no differences were found in leakage rate [12], which was inconsistent with the results of this study. The disparity may be caused by different participant selection standard that only patients with vMCI diagnosed according to both cognitive function and MRI findings were included, as well as different image acquisition and postprocessing methods.

It was found that BBB leakage rate increased widespread in the brain in vMCI patients and cognitive function decreased with the increase of BBB permeability, which coincided with previous research hypotheses, and may be caused by the neurovascular unit (NVU) disruption [9, 24]. Endothelial cells are the most important NVU component, and their dysfunction usually occurs first [25]. Tight junctions (TJs) are located between endothelial cells, and their disruption allows paracellular diffusion of water-soluble molecules from the blood into brain [26], upsetting brain environment homeostasis and impairing BBB function in vMCI patients [27, 28]. These changes are widely distributed in the brain tissue, rather than limited. A recent study found that BBB damage was an early initiating factor of cognitive dysfunction, which was independent of Aβ and tau protein [7]. Alterations in cerebral microvascular structure and neurovascular coupling dysfunction can lead to micro-vascular thrombosis and BBB dysfunction [29, 30]. This process may trigger a series of biochemical events, including microglial and astroglial activation, deposition of blood-borne proteins in the brain, release of pro-inflammatory neurotoxic cytokines, edema, and hemorrhage, eventually leading to neuronal degeneration and cognitive decline [31–33].

VMCI patients had impaired cognitive domains in information processing speed, attention executive function, spatial function, and language function rather than memory. This is in agreement with previous study [34]. And BBB dysfunctions was only correlated with MOCA rather than MMSE. A previous study exhibited that the MoCA was more sensitive than MMSE in the assessment of vMCI, and it had preferential sensitivity to early screening of VCI and evaluation of global cognitive function [35]. In addition, the MOCA only decreased with the increase of leakage rate in WMH, which was consistent with the result of a previous study [12]. A possible reason was that BBB breakdown may result in deposition of harmful substances. It has been found that WMH can mediates iron deposition, thus leading to cognitive impairment [36].

The study also revealed that vMCI patients displayed lower fractional blood plasma volume in CGM, DGM, and NAWM compared with control participants, indicating cerebral vascular hypoperfusion throughout the brain (including white and grey matter) in vMCI patients, which was consistent with the result of a previous study using DCE-MRI in cSVD [11]. It may be caused by structural abnormalities of blood vessels, including narrowing of the lumen and thickening of the wall due to hyaline arteriolosclerosis [37]. Moreover, reduced vascular density and cerebral vascular reactivity would also lead to hypoperfusion [38, 39]. Microvascular endothelial cells can release vasoactive substances to modulate vessel tone and regulate other functional non-vascular cells [40], while pericytes degeneration changes energy matrix transfer to neurons, reducing of cerebral blood flow (CBF) response in brain activation [41]. Changes of these cerebral vessels and local inflammation induced by ischemia may aggravate white matter damage and cognitive dysfunction [38, 42].

However, WMH was not involved, which was consistent with the results of previous studies that CBF was not associated with total WMH volume at baseline [43]. As speculated, the compensatory effect of capillaries may lead to increased local perfusion in WMH. A longitudinal study found that white matter area with low CBF progressed to new WMH during follow-up [44], suggesting that white matter hypoperfusion may contribute to disease progression.

Li *et al. BMC Neurology*   (2021) 21:159

Page 7 of 8

In addition, vMCI is different from the non-amnestic mild cognitive impairment(MCI). MCI is divided into amnestic MCI and non-amnestic MCI with the subtypes of single or multiple domain impaired classification. Both multidomain non-amnestic MCI and multidomain amnestic MCI may be vMCI which is identified based on the evidence of presumed vascular etiology(See Supplementary Figure 1, Additional file 2).

Although this study was limited by its small sample size, significant differences were revealed, indicating the sensibility of the method. It was also limited by the lack of neuropathological biomarkers for indicating increased BBB permeability. However, the results may be confounded by the differences in transport patterns between gadolinium contrast agents and neurobiological markers. Furthermore, the scan time was a bit short, but motion artifacts were reduced, while image signal-to-noise ratio was improved for the application of the 64-channel coil, and significant differences were obtained after multiple measurements, indicating that the method was feasible. Moreover, it is unsure whether the control group will have cognitive impairment in the future, and the control group will be follow up in further study. Finally, no causal relationship between BBB damage and cognitive function was established in this study, which should be further investigated through longitudinal studies.

Conclusions

The current study found that BBB leakage was higher in both grey matter and white matter in vMCI patients, and cognitive function decreased with the increase of BBB leakage in WMH, which indicated that generalized BBB disruption in vMCI patients could contribute to the pathophysiological mechanisms of impaired cognitive function.

Abbreviations
AUC: Area under the leakage curve; BBB: Blood-brain barrier; CGM: Cortical gray matter; CSF: Cerebrospinal fluid; cSVD: Cerebral small vessel disease; CBF: Cerebral blood flow; CDT: Clock drawing test; DCE-MRI: Dynamic contrast-enhanced-magnetic resonance imaging; DGM: Deep gray matter; DST: Digit span test; FOV: Field of view; MCI: Mild cognitive impairment; MoCA: Montreal Cognitive Assessment; MTA: Medial temporal lobe atrophy; NAWM: Normal-appearing white matter; NVU: Neurovascular unit; ROIs: Regions of interest; SDMT: Symbol digital modalities test; SCWT: Stroop color word test; TMT: Trail-making test; TR: Repetition time; TE: Echo time; TJs: Tight junctions; vMCI: Vascular mild cognitive impairment; Vp: Fractional blood plasma volume; VCI: Vascular cognitive impairment; VFT: Verbal fluency test; WMH: White matter hyperintensities

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12883-021-02189-6.

Additional file 1: Supplementary Table 1. Structural MRI scanning parameters.

Additional file 2: Supplementary Figure 1. How to distinguish different subtypes of MCI and how they can be paired with possible

---

etiologies. This is referenced from Petersen RC: Mild Cognitive Impairment. *Continuum (Minneap Minn)* 2016, **22**(2 Dementia):404–418.

Authors' contributions
Study design: ML and TJ. Data collection and analysis: ML, YL, and LZ. The drafting of the manuscript: ML and YL. Manuscript revision: ML, YL, LZ, WH, and TJ. All authors read and approved the final manuscript.

Availability of data and materials
All data derived from this study are available upon reasonable request.

Declarations

Ethics approval and consent to participate
Ethical clearance for this study was given by the institutional ethics committee of Beijing Chao-Yang Hospital, Capital Medical University. All participants provided signed informed consent before participating in the study. WH have ruled that all patients and participants have been deemed capable of ethically and medically consenting for their participation in the research presented in this manuscript.

Consent for publication
Not applicable.

Competing interests
All authors state that there is no competing interest.

Author details
[1]Radiology Department, Beijing Chao-Yang Hospital, Capital Medical University, No. 8, South Gongti Road, Chaoyang District, Beijing 100020, P.R. China. [2]Neurology Department, Beijing Chao-Yang Hospital, Capital Medical University, No. 8, South Gongti Road, Chaoyang District, Beijing, P.R. China.

References
1. van der Flier WM, Skoog I, Schneider JA, Pantoni L, Mok V, Chen CLH, et al. Vascular cognitive impairment. Nat Rev Dis Primers. 2018;4(1):18003. https://doi.org/10.1038/nrdp.2018.3.
2. Goodman RA, Lochner KA, Thambisetty M, Wingo TS, Posner SF, Ling SM. Prevalence of dementia subtypes in United States Medicare fee-for-service beneficiaries, 2011-2013. Alzheimer's Dement. 2017;13(1):28–37. https://doi.org/10.1016/j.jalz.2016.04.002.
3. Jia J, Zhou A, Wei C, Jia X, Wang F, Li F, et al. The prevalence of mild cognitive impairment and its etiological subtypes in elderly Chinese. Alzheimer's Demen. 2014;10(4):439–47. https://doi.org/10.1016/j.jalz.2013.09.008.
4. Rosenberg GA, Bjerke M, Wallin A. Multimodal markers of inflammation in the subcortical ischemic vascular disease type of vascular cognitive impairment. Stroke. 2014;45(5):1531–8. https://doi.org/10.1161/STROKEAHA.113.004534.
5. Wharton SB, Simpson JE, Brayne C, Ince PG. Age-associated white matter lesions: the MRC cognitive function and ageing study. Brain Pathol. 2015;25(1):35–43. https://doi.org/10.1111/bpa.12219.
6. Joutel A, Chabriat H. Pathogenesis of white matter changes in cerebral small vessel diseases: beyond vessel-intrinsic mechanisms. Clin Sci. 2017;131(8):635–51. https://doi.org/10.1042/CS20160380.
7. Nation DA, Sweeney MD, Montagne A, Sagare AP, D'Orazio LM, Pachicano M, et al. Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction. Nat Med. 2019;25(2):270–6. https://doi.org/10.1038/s41591-018-0297-y.
8. Bourassa P, Tremblay C, Schneider JA, Bennett DA, Calon F. Beta-amyloid pathology in human brain microvessel extracts from the parietal cortex:

Li et al. BMC Neurology   (2021) 21:159

Page 8 of 8

relation with cerebral amyloid angiopathy and Alzheimer's disease. Acta Neuropathol. 2019;137(5):801–23. https://doi.org/10.1007/s00401-019-01967-4.

9. Bowman GL, Dayon L, Kirkland R, Wojcik J, Peyratout G, Severin IC, et al. Blood-brain barrier breakdown, neuroinflammation, and cognitive decline in older adults. Alzheimer's Demen. 2018;14(12):1640–50. https://doi.org/10.1016/j.jalz.2018.06.2857.

10. Wang H, Golob EJ, Su MY. Vascular volume and blood-brain barrier permeability measured by dynamic contrast enhanced MRI in hippocampus and cerebellum of patients with MCI and normal controls. J Magnet Resonan Imaging. 2006;24(3):695–700. https://doi.org/10.1002/jmri.20669.

11. Wong SM, Jansen JFA, Zhang CE, Hoff EI, Staals J, van Oostenbrugge RJ, et al. Blood-brain barrier impairment and hypoperfusion are linked in cerebral small vessel disease. Neurology. 2019;92(15):e1669–77. https://doi.org/10.1212/WNL.0000000000007263.

12. Zhang CE, Wong SM, van de Haar HJ, Staals J, Jansen JF, Jeukens CR, et al. Blood-brain barrier leakage is more widespread in patients with cerebral small vessel disease. Neurology. 2017;88(5):426–32. https://doi.org/10.1212/WNL.0000000000003556.

13. Taheri S, Gasparovic C, Huisa BN, Adair JC, Edmonds E, Prestopnik J, et al. Blood-brain barrier permeability abnormalities in vascular cognitive impairment. Stroke. 2011;42(8):2158–63. https://doi.org/10.1161/STROKEAHA.110.611731.

14. Sachdev P, Kalaria R, O'Brien J, Skoog I, Alladi S, Black SE, et al. Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. Alzheimer Dis Assoc Disord. 2014;28(3):206–18. https://doi.org/10.1097/WAD.0000000000000034.

15. Skrobot OA, Black SE, Chen C, DeCarli C, Erkinjuntti T, Ford GA, et al. Progress toward standardized diagnosis of vascular cognitive impairment: guidelines from the vascular impairment of cognition classification consensus study. Alzheimer's Dement. 2018;14(3):280–92. https://doi.org/10.1016/j.jalz.2017.09.007.

16. Moleiro C, Madureira S, Verdelho A, Ferro JM, Poggesi A, Chabriat H, et al. Confirmatory factor analysis of the neuropsychological assessment battery of the LADIS study: a longitudinal analysis. J Clin Exp Neuropsychol. 2013; 35(3):269–78. https://doi.org/10.1080/13803395.2013.770822.

17. Larsson HB, Courivaud F, Rostrup E, Hansen AE. Measurement of brain perfusion, blood volume, and blood-brain barrier permeability, using dynamic contrast-enhanced T(1)-weighted MRI at 3 tesla. Magn Reson Med. 2009;62(5):1270–81. https://doi.org/10.1002/mrm.22136.

18. Lavini C, Verhoeff JJ. Reproducibility of the gadolinium concentration measurements and of the fitting parameters of the vascular input function in the superior sagittal sinus in a patient population. Magn Reson Imaging. 2010;28(10):1420–30. https://doi.org/10.1016/j.mri.2010.06.017.

19. Heye AK, Culling RD, Valdes Hernandez Mdel C, Thrippleton MJ, Wardlaw JM. Assessment of blood-brain barrier disruption using dynamic contrast-enhanced MRI. A systematic review. NeuroImage Clin. 2014;6:262–74. https://doi.org/10.1016/j.nicl.2014.09.002.

20. Scheltens P, Launer LJ, Barkhof F, Weinstein HC, van Gool WA. Visual assessment of medial temporal lobe atrophy on magnetic resonance imaging: interobserver reliability. J Neurol. 1995;242(9):557–60. https://doi.org/10.1007/BF00868807.

21. Smith EE, Beaudin AE. New insights into cerebral small vessel disease and vascular cognitive impairment from MRI. Curr Opin Neurol. 2018;31(1):36–43. https://doi.org/10.1097/WCO.0000000000000513.

22. Mufson EJ, Binder L, Counts SE, DeKosky ST, de Toledo-Morrell L, Ginsberg SD, et al. Mild cognitive impairment: pathology and mechanisms. Acta Neuropathol. 2012;123(1):13–30. https://doi.org/10.1007/s00401-011-0884-1.

23. Smallwood A, Oulhaj A, Joachim C, Christie S, Sloan C, Smith AD, et al. Cerebral subcortical small vessel disease and its relation to cognition in elderly subjects: a pathological study in the Oxford project to investigate memory and ageing (OPTIMA) cohort. Neuropathol Appl Neurobiol. 2012; 38(4):337–43. https://doi.org/10.1111/j.1365-2990.2011.01221.x.

24. Dudvarski Stankovic N, Teodorczyk M, Ploen R, Zipp F, Schmidt MHH. Microglia-blood vessel interactions: a double-edged sword in brain pathologies. Acta Neuropathol. 2016;131(3):347–63. https://doi.org/10.1007/s00401-015-1524-y.

25. Rajani RM, Quick S, Ruigrok SR, Graham D, Harris SE, Verhaaren BFJ, Fornage M, Seshadri S, Atanur SS, Dominiczak AF, Smith C, Wardlaw JM, Williams A. Reversal of endothelial dysfunction reduces white matter vulnerability in

cerebral small vessel disease in rats. Sci Transl Med. 2018;10(448):eaam9507. https://doi.org/10.1126/scitranslmed.aam9507.

26. Hawkins BT, Davis TP. The blood-brain barrier/neurovascular unit in health and disease. Pharmacol Rev. 2005;57(2):173–85. https://doi.org/10.1124/pr.57.2.4.

27. Nitta T, Hata M, Gotoh S, Seo Y, Sasaki H, Hashimoto N, et al. Size-selective loosening of the blood-brain barrier in claudin-5-deficient mice. J Cell Biol. 2003;161(3):653–60. https://doi.org/10.1083/jcb.200302070.

28. Montagne A, Barnes SR, Sweeney MD, Halliday MR, Sagare AP, Zhao Z, et al. Blood-brain barrier breakdown in the aging human hippocampus. Neuron. 2015;85(2):296–302. https://doi.org/10.1016/j.neuron.2014.12.032.

29. Snyder HM, Corriveau RA, Craft S, Faber JE, Greenberg SM, Knopman D, et al. Vascular contributions to cognitive impairment and dementia including Alzheimer's disease. Alzheimer's Dement. 2015;11(6):710–7. https://doi.org/10.1016/j.jalz.2014.10.008.

30. Iadecola C. The neurovascular unit coming of age: a journey through neurovascular coupling in health and disease. Neuron. 2017;96(1):17–42. https://doi.org/10.1016/j.neuron.2017.07.030.

31. Bennett C, Samikkannu M, Mohammed F, Dietrich WD, Rajguru SM, Prasad A. Blood brain barrier (BBB)-disruption in intracortical silicon microelectrode implants. Biomaterials. 2018;164:1–10. https://doi.org/10.1016/j.biomaterials.2018.02.036.

32. Lv J, Hu W, Yang Z, Li T, Jiang S, Ma Z, et al. Focusing on claudin-5: a promising candidate in the regulation of BBB to treat ischemic stroke. Prog Neurobiol. 2018;161:79–96. https://doi.org/10.1016/j.pneurobio.2017.12.001.

33. Montagne A, Nikolakopoulou AM, Zhao Z, Sagare AP, Si G, Lazic D, et al. Pericyte degeneration causes white matter dysfunction in the mouse central nervous system. Nat Med. 2018;24(3):326–37. https://doi.org/10.1038/nm.4482.

34. Nordlund A, Rolstad S, Klang O, Lind K, Hansen S, Wallin A. Cognitive profiles of mild cognitive impairment with and without vascular disease. Neuropsychology. 2007;21(6):706–12. https://doi.org/10.1037/0894-4105.21.6.706.

35. Koski L. Validity and applications of the Montreal cognitive assessment for the assessment of vascular cognitive impairment. Cerebrovasc Dis. 2013; 36(1):6–18. https://doi.org/10.1159/000352051.

36. Valdes Hernandez M, Allerhand M, Glatz A, Clayson L, Munoz Maniega S, Gow A, et al. Do white matter hyperintensities mediate the association between brain iron deposition and cognitive abilities in older people? Eur J Neurol. 2016;23(7):1202–9. https://doi.org/10.1111/ene.13006.

37. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. Lancet Neurol. 2013;12(5):483–97. https://doi.org/10.1016/S1474-4422(13)70060-7.

38. Koizumi K, Hattori Y, Ahn SJ, Buendia I, Ciacciarelli A, Uekawa K, et al. Apoepsilon4 disrupts neurovascular regulation and undermines white matter integrity and cognitive function. Nat Commun. 2018;9(1):3816. https://doi.org/10.1038/s41467-018-06301-2.

39. Marstrand JR, Garde E, Rostrup E, Ring P, Rosenbaum S, Mortensen EL, et al. Cerebral perfusion and cerebrovascular reactivity are reduced in white matter hyperintensities. Stroke. 2002;33(4):972–6. https://doi.org/10.1161/01.STR.0000012808.81667.4B.

40. Hu X, De Silva TM, Chen J, Faraci FM. Cerebral vascular disease and neurovascular injury in ischemic stroke. Circ Res. 2017;120(3):449–71. https://doi.org/10.1161/CIRCRESAHA.116.308427.

41. Nagata K, Yamazaki T, Takano D, Maeda T, Fujimaki Y, Nakase T, et al. Cerebral circulation in aging. Ageing Res Rev. 2016;30:49–60. https://doi.org/10.1016/j.arr.2016.06.001.

42. Danton GH, Dietrich WD. Inflammatory mechanisms after ischemia and stroke. J Neuropathol Exp Neurol. 2003;62(2):127–36. https://doi.org/10.1093/jnen/62.2.127.

43. ten Dam VH, van den Heuvel DM, de Craen AJ, Bollen EL, Murray HM, Westendorp RG, et al. Decline in total cerebral blood flow is linked with increase in periventricular but not deep white matter hyperintensities. Radiology. 2007;243(1):198–203. https://doi.org/10.1148/radiol.2431052111.

44. Bernbaum M, Menon BK, Fick G, Smith EE, Goyal M, Frayne R, et al. Reduced blood flow in normal white matter predicts development of leukoaraiosis. J Cereb Blood Flow Metab. 2015;35(10):1610–5. https://doi.org/10.1038/jcbfm.2015.92.

Publisher's Note