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ORIGINAL ARTICLE

Susceptibility-weighted imaging and transcranial Doppler ultrasound in patients with cerebral small vessel disease

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Abstract

Introduction Cerebral small vessel disease (SVD) is a common accompaniment to aging. Magnetic resonance imaging (MRI) features of SVD include lacunar infarcts (LI) and white matter hyperintensity (WMH). Brain iron deposition is also a known marker of SVD that is associated with cognitive impairment and can be detected with susceptibility-weighted imaging (SWI) MRI technique. According to recent studies, the pulsation of cerebral blood flow can be one of the main factors of the development of pathological brain changes in elderly patients. The objective of this study was to investigate the relationship between the brain iron deposition, cerebral blood flow pulsation, and cognitive impairment in patients with SVD.

Materials and methods For the study, 97 patients with diagnosed SVD were selected. The patients were divided into two groups based on the Montreal Cognitive Assessment (MoCA) test scores. All patients underwent MRI in the SWI sequence. Pulsatility index (PI) and resistivity index (RI) were recorded from the middle cerebral artery bilaterally using transcranial Doppler (TCD).

Results The linear regression model showed that the pulsatility index (PI) and resistivity index (RI) were associated with cognitive impairment and brain iron deposition in basal ganglia. The most significant association was found between left globus pallidus severe hypointensity voxels count and left middle cerebral artery (MCA) RI ($p = 0.009$).

Conclusion The results of the study provide information that TCD indicators may be associated with brain iron deposition and cognitive decline in patients with SVD. Our findings suggest that both brain iron deposition and cerebral hemodynamics abnormalities may play an important role in the pathophysiological mechanisms of SVD.

Keywords Small vessel disease · Brain iron deposition · Transcranial Doppler · Cognitive decline

Introduction

Hypertension and cerebral atherosclerosis can often result in a cerebral small vessel disease (SVD). SVD is a common accompaniment to aging and is associated with increased risk of cognitive decline. The most common neuroimaging markers of SVD that can be seen on MRI include lacunar infarcts (LI) and white matter hyperintensity (WMH) or leukoareosis (LA).

Brain iron deposition is also a known marker of SVD that is associated with cognitive decline and can be detected with the novel MRI techniques such as susceptibility-weighted imaging (SWI) [1].

The most probable cause of morphological changes related to SVD is insufficient arterial blood supply and ischemia caused by it. However, the pulsation of cerebral blood flow can be one of the main factors of the development of pathological brain changes in aging population [2, 3].

Arterial blood flow has a pulsating character and causes a periodic increase in the volume of blood entering the intracranial cavity. Under normal physiological conditions, it is compensated by the outflow of cerebrospinal fluid and venous outflow from the cranial cavity. In the process of aging, the

Highlights
1. Brain iron deposition is a marker of cerebral small vessel disease.
2. Basal ganglia hypointensity at SWI MRI is associated with cognitive decline.
3. TCD parameters are associated with basal ganglia SWI MRI hypointensity.
4. Cognitive status of elderly patients is associated with TCD parameters.

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effectiveness of such a compensatory mechanism decreases that can lead to brain tissue damage, causing the development of pulse wave encephalopathy [4].

Many studies have found a strong relationship between LA and abnormal cerebral blood flow, as well as the connection of the latter with cognitive decline in patients with SVD [4, 5]. Transcranial Doppler Ultrasound (TCD) is widely used to determine the pulsation of cerebral arteries. According to recent studies, cognitive impairment of both neurodegenerative and vascular origins is characterized by microangiopathy, which can lead to vasoconstriction, atherosclerotic processes, and decreased vascular elasticity, thus resulting in decreased arterial diameter and cerebral blood flow [6]. Significantly higher rates of middle cerebral artery (MCA) and internal carotid artery (ICA) pulsation were found in patients with vascular dementia comparing with non-demented age-matched controls [7–9].

Therefore, the study of cerebral blood flow pulsation and neuroimaging markers association may be essential for better understanding of SVD mechanism and its clinical manifestation.

SWI MRI technique can provide important neuroimaging markers for understanding of SVD. The method is based on the detection of iron-containing molecules in brain tissue, which is a proven marker of neurodegeneration [1, 10].

During image processing, the degree of hypointensity of the selected area is measured in SWI intensity units, where 0 corresponds to the intensity of Galen's veins, 200—the intensity of the cerebrospinal fluid(CSF) [11].

Brain contains iron predominantly in the form of neuromelanin and it is necessary for neurometabolism, but its excess may be harmful [12, 13]. Mechanism of iron transport through nervous tissue may be disrupted with aging, which leads to iron accumulation. Excessive accumulation of iron causes the formation of free radicals, lipid peroxidation, and nerve damage [14].

The aim of this study is to identify the relationship between brain iron deposition, cerebral blood flow pulsation, and cognitive impairment in patients with SVD.

Materials and methods

The present study included 98 patients with the diagnosis of SVD. All the patients attended neurological department of the Feofaniia Clinical Hospital in Kyiv, Ukraine. Inclusion criteria were (1) the age of 65–90 years old, (2) presence of leukareosis of any severity and/or presence of one or more lacunar infarctions in neuroimaging, (3) presence of acute (transient ischemic attacks in history) or subacute (cognitive decrease) signs of SVD. The primary criteria were the neuroimaging features of SVD because clinical symptoms of SVD are more heterogeneous and typically mild at the onset of cerebral SVD [12].Exclusion criteria were (1) clinical dementia, dementia was excluded according to DSM-V (Diagnostic and Statistical Manual for Mental Disorders—Fifth Edition) criteria [15]; (2) clinical parkinsonism; (3) intracranial hemorrhage; (4) intracranial space-occupying lesion; (5) (psychiatric) disease interfering with cognitive testing; (6) use of acetylcholinesterase inhibitors, neuroleptic agents, L-dopa, or dopa-a(nta)gonists; (8) non-SVD related WMLs (e.g., multiple sclerosis, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy[CADASIL], and Fabry disease); (9) severe visual and hearing impairment; (10) contraindications to MRI examination; (11) gait and balance disorders unrelated to SVD (psychogenic gait and balance disorders, acute musculoskeletal disorders).

All the patients had a clinical assessment at baseline by means of standardized history taking and neurologic examination; the estimated demographic and clinical parameters included age, gender, hypertension stage, cardiac rhythm disturbance, and presence of diabetes mellitus. Cognitive status was assessed using the MoCA test.

MRI scans of all participants were acquired on a single 1.5 T Avanto scanner (Siemens Medical Solutions, Erlangen, Germany). The following parameters were used to obtain SWI images: TE/TR = 40/50 ms, flip angle of 25°, voxel size 0.5 mm × 0.5 mm × 2 mm, field of view 20.1 × 23.0 cm.

The 3D Slicer 4.7.0-2017-06-06 software was used for SWI images post-processing. Four regions of interest (ROIs) were drawn bilaterally according to the anatomical structures, in the basal ganglia: putamen (PUT), globus pallidus (GP), on the slice where they were best visualized. When analyzing images, the edge of the studied structure was bypassed, sections with the most anatomically clear contours and with the highest degree of hypointensity were selected for evaluation [12–14] (Fig. 1). The hypointensity was graded according to the criteria proposed by Gupta et al.: Grade 0: signal intensity (SI) similar to CSF intensity (SI > 200). Grade 1: mild hypointensity (SI > 150 but < 200). Grade 2: moderate hypointensity (SI > 5 but < 150). Grade 3: severe hypointensity (SI < 75). In each ROI, number of voxels with Grade 3 hypointensity was counted [11] (Fig. 1).

Patients were divided in two groups, depending on the severity of cognitive impairment evaluated using Montreal Cognitive Assessment (MoCA) test. Group A included patients who scored less than 22 points inclusive. Group B included patients who scored more than 22 points.

The threshold of 22 was empirically selected. In this study, we found that the most statistically significant differences between groups were seen when subdividing them according to the MoCA score higher/lower than 22. Also, MoCA score of 21–22 is often chosen as a cut off score for identifying mild cognitive impairment [16, 17].

TCD sonography was performed using a Hitachi HI VISION Ascendus sonographer. The blood flow velocity of

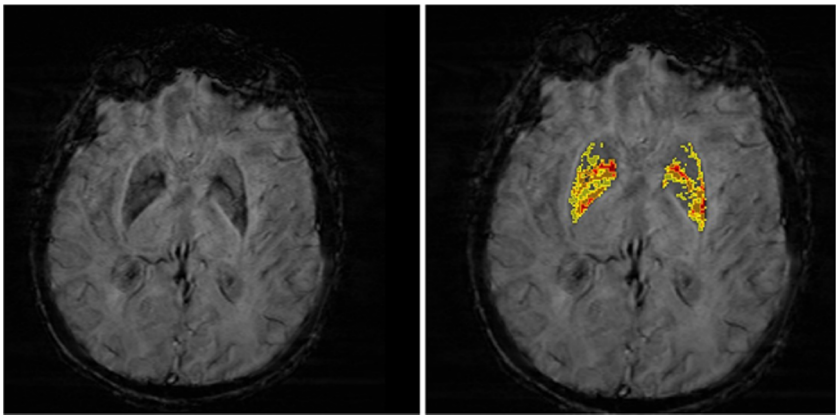

Fig. 1 The same SWI MRI image with unhighlighted (left) and highlighted (right) hypointense voxels in the regions of interest: putamen (PUT) and globus pallidus (GP) bilaterally, on the slice where they were best visualized.Voxels highlighted in yellow—Grade 1: mild hypointensity (SI >150 but<200). Voxels highlighted in orange—Grade 2: moderate hypointensity (SI >75 but < 150). Voxels highlighted in red—Grade 3: severe hypointensity (SI < 75)

the proximal tract (M1) of the middle cerebral artery (MCA) was recorded from two sides using portable 2-MHz ultrasound probes through the temporal bone window at rest and at a depth that provided the best signal (50–60 mm). The following parameters were evaluated: peak systolic blood flow velocity (PSV), end diastolic blood flow rate (EDV), mean blood flow rate (MBFV), pulsatility index (PI) calculated according to the formula (PSV−EDV)/MBFV, and Pourcelot resistivity index (RI) calculated according to the formula (PSV−EDV)/PSV. TCD values were obtained after a 30-s stable recording period and lasted for at least 10 cardiac cycles.

Statistical analysis

The SPSS software, version 23.0, was used for statistical analysis. Data were presented as mean and standard deviation (age) or median and interquartile range (MoCA scale, TCD parameters, number of hypo-intensive voxels on SWI images). Patients' data were compared using the Mann-Whitney test for skewed continuous data and the chi-square test for categorical variables. Spearman correlation coefficient (ρ) was used to determine the correlation between the basal nuclei hypointensity and the TCD parameters.

Linear regression models corrected for age and degree of hypertension were used to assess the association between TCD parameters and basal nuclei hypointensity or score on MoCA test. A p value < 0.05 was considered a statistically significant difference.

Results

Patients in group A were older ($p < 0.001$) and were more likely to have grade 3 hypertension ($p = 0.04$). Also, patients in group A had higher SWI intensities in all studied structures ($p = 0.001$–0.002) and had higher left MCA RI (Table 1).

Data represent number (percentage), mean ± standard deviation, or median (interquartile range)

MoCA Montreal Cognitive Assessment, *MCA* middle cerebral artery, *PI* pulsatility index, *RI* resistivity index

The Spearman correlation detected a positive correlation between RI in the left MCA and the number of severe hypointensity voxels in the left ($p = 0.013$; $\rho = 0.33$) and right ($p = 0.019$; $\rho = 0.31$) GP. There was also a negative correlation between MoCA score and RI in the left MCA ($p = 0.028$; $\rho = -0.29$). A negative correlation was also found between the MoCA score and the number of severe hypointensity voxels in all the studied ROIs ($p = 0.001$–0.002). The most significant association was found between the MoCA score and the number of severe hypointensity voxels in the right PU ($p < 0.001$; $\rho = -0.38$).

Table 2 presents the linear regression models for both groups of patients adjusted for age and degree of hypertension. A statistically significant association was found between the number of severe hypointensity voxels in the right globus pallidus and the left MCA RI ($p = 0.009$). The number of severe hypointensity voxels in the left globus pallidus was significantly associated with the right MCA PI ($p = 0.01$), left MCA PI ($p = 0.028$), right MCA RI ($p = 0.028$), and left MCA RI ($p = 0.009$).

A MoCA score was significantly associated with left MCA RI ($p = 0.028$) and right MCA PI ($p = 0.05$) (Table 3).

Discussion

SVD refers to the slowly progressing disorders of the cerebral blood circulation. Arterial hypertension, atherosclerosis, diabetes mellitus, and other diseases affecting the vessels of the brain play an important role in SVD development. It is worth noting that the most common causes of SVD are recurrent transient ischemic attacks and "small strokes", less often the

Table 1 Clinical-demographic characteristics, neuroradiological features, MoCA test scores, and TCD values of all participants

	MoCA ≤ 22 ($N = 51$)	MoCA > 22 ($N = 53$)	p
Age (years)	77.7 ± 6.9	71.7 ± 8.1	< 0.001
Female gender (%)	55.6	44.4	0.24
Hypertension stage 3 (%)	68	32	0.04
Diabetes mellitus (%)	54.2	45.8	0.48
Cardiac rhythm disturbance (%)	41.7	58.3	0.64
MoCA test score	19 (3)	25 (2)	< 0.001
Right globus pallidus severe hypointensity voxels count	8 (18)	1 (6.75)	0.001
Left globus pallidus severe hypointensity voxels count	8 (24.5)	0.5 (4.25)	0.002
Right putamen severe hypointensity voxels count	4(19.5)	0 (19.5)	0.001
Left putamen severe hypointensity voxels count	3 (22)	0 (0.01)	0.002
Right MCA RI	0.65 (0.07)	0.61 (0.1)	0.22
Left MCA RI	0.68 (0.02)	0.62 (0.01)	0.05
Right MCA PI	1.2 (0.34)	1.1 (0.3)	0.08
Left MCA PI	1.1 (0.02)	1.1 (0.01)	0.47

disease develops due to gradual brain ischemia. MRI is one of the most widely used techniques for diagnosing pathological brain conditions, including SVD [18, 19].

Susceptibility-weighted imaging provides a quick snapshot of the state of the brain for existing microbleeds and brain structure hypointensities, which are the novel neuroimaging markers of SVD [20]. Also, SWI is feasible for the early evaluation of cerebral infarct size and clinical prognosis of patients with acute cerebral infarction and a useful predictor of early infarct growth and early-stage outcome [21]. The use of iron-sensitive MRI sequences such as SWI may also be of therapeutic interest [22].

It is also known that pre-existing SVD burden, mainly driven by brain atrophy, negatively affects early and late clinical outcomes in anterior circulation ischemic stroke treated with endovascular therapy [23].

To the best of our knowledge, this is the first study investigating the relationship between brain iron deposition and cerebral hemodynamics in patients with SVD. Also, the novel method of brain structures SWI hypointensity assessment was used. SWI hypointensity was measured by counting hypointensive voxels in the structure, not by measuring the level of hypointesity of the whole structure, though the limitation of this method may be that the only one MRI slice was used for analysis in each case.

The main finding of this study was that the parameters of cerebral perfusion and vascular resistance are associated with SWI intensity of brain basal nuclei, namely with intensity of the right and left globus pallidus. Increased SWI hypointensity is a result of excessive brain iron deposition, which has been shown to correlate with cognitive decline in patients with SVD [11, 24, 25]. In this study, we also found significant correlation between globus pallidus hypointensity and MoCA test score. It is worth noting that in this study, no association was found between the right and left putamen SWI hypointensity and cerebral hemodynamics.

Increased pulsation indices and vascular resistance are most likely to reflect microcirculatory pathology associated with lesions of small vessels and capillaries. Deposition of iron-containing molecules in subcortical ganglia is also a proven marker of neurodegeneration. The connection between these two phenomena may be due to extreme sensitivity of subcortical structures to hypoperfusion. Hypoperfusion causes ischemic lesions of subcortical structures, which leads to pathology of iron metabolism in the basal nuclei and its excessive deposition.

Table 2 Linear regression corrected for age and degree of hypertension: significant predictors of SWI MRI parameters in patients with SVD (Group A + B)

Dependent variables	Predictors	Std β	p	Adjusted R^2
Right globus pallidus severe hypointensity voxels count	Right MCA RI	0.210	0.111	0.098
	Left MCA RI	0.313	0.009	0.164
	Right MCA PI	0.230	0.09	0.107
	Left MCA PI	0.241	0.081	0.126
Left globus pallidus severe hypointensity voxels count	Right MCA RI	0.296	0.028	0.141
	Left MCA RI	0.360	0.009	0.167
	Right MCA PI	0.358	0.01	0.173
	Left MCA PI	0.306	0.028	0.133

Table 3 Linear regression corrected for age and degree of hypertension: significant predictors of MoCA score in patients with SVD (Group A + B)

Dependent variable	Predictors	Std β	p	Adjusted R^2
MOCA score	Right MCA RI	−0.129	0.333	−0.001
	Left MCA RI	−0.297	0.028	0.071
	Right MCA PI	−0.254	0.05	0.048
	Left MCA PI	0.04	0.77	−0.11

The areas of increased SWI hypointensity and associated RI and PI parameters in the MCA did not always coincide anatomically. This is likely to reflect the complex nature of the relationship between cerebral perfusion changes and the pathology of iron metabolism. The results could also have been influenced by the not very large number of patients studied. However, the more significant correlation between the parameters of cerebral perfusion and the SWI hypointensity of the left globus pallidus probably testifies the leading role of the dominant hemisphere in the development of SVD and concomitant cognitive decline.

The findings could contribute to further understanding of the small vessel disease development and its clinical features.

Conclusions

TCD indicators may be associated with the cognitive decline caused by small vessel disease and the deposition of iron-containing molecules in the subcortical ganglia, which is a marker of this pathology. According to the results of this study, level SWI indices of left pale ball hypointensity were more related to changes in perfusion and to a degree of cognitive decline. Because cerebral hypoperfusion and the deposition of iron-containing molecules are risk factors for cognitive decline in patients with small vessel disease, further studies in this area are needed to understand more about the complex relationship between these parameters.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants This study was approved by the ethics committee of the Shupyk National Medical Academy of Postgraduate Education. Written informed consent was obtained from all patients who participated in the study.

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