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Original Article

Association of white mater lesions with orthostatic hypotension

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Abstract: Objective: To reveal the cerebral hypoperperfusion characteristics of White matter lesions (WMLs), we monitored the blood pressure (BP) fluctuation in patients with orthostatic hypotension (OH) and WMLs. Methods: A total of 2265 syncope patients were enrolled in this retrospective study. Clinical outcomes of brain MRI or CT, tilt test and continuous electrocardiogram monitoring were reviewed. All patients were divided into two groups according to WMLs status, and the WMLs group was further classified into three subgroups according to Fazekas grade (1-3). BP fluctuation in these subgroups was compared. The risk factors of WMLs and OH were determined by a multivariate logistic regression test. Results: A total of 2265 syncope patients were enrolled, among which 56% patients were male. The average age of patients with WMLs was (61±12) years old. ΔTIME (Odds ratio [OR]: 1.014, 95% confidence interval [CI]: (1.005, 1.023), P=0.0015) and ΔSBP1 (OR: 0.990, 95% CI: (0.980, 1.000), P=0.0579) were demonstrated to be the risk factors of WMLs. The number of cases of repeated drops in blood pressure was twice as high as the cases with only drop in BP. The median and mean ΔSBP and ΔTIME of patients with WMLs were higher than those without WMLs. The incidence of diabetes, hypertension, age and Parkinson Plus Syndromes in patients with WMLs significantly decreased in comparison to those without WMLs (OR-diabetes: 2.558, OR-hypertension: 1.713, OR-age: 0.924 and OR-Parkinson Plus Syndromes: 0.476, P<0.05). Conclusion: WMLs occurs in patients with hypoperfusion of recurrent OH. Vascular WMLs is associated with diabetes, hypertension, and age is at higher risk than WMLs associated with Parkinson Plus Syndromes.

Keywords: White mater lesions, orthostatic hypotension

Introduction

White matter lesions (WMLs) are commonly observed with high-signal foci and blurred edges on T2-weighted and fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI), or hypoattenuations or hypodensities on computed tomography (CT) of the brain, especially in periventricular and subcortical areas [1-3]. Previous studies have focused on the genetic characteristics of WMLs, and the Fazekas scale has been widely used as a grading standard for disease severity [4-12]. Other research found that levels of systolic (SBP) and diastolic blood pressure (DBP) are associated with WML severity [13-16]. Reports on the relationship between BP change and WML progression are scarce [17]. Neither did these studies show relationship between the degree of blood pressure change with WMLs and the degree of hypoperfusion which is manifested as clinical symptoms, nor did they reflect the cerebral autoregulation that occurs when blood pressure changes. We usually use the increase of pulsatility index (PI) and the decrease of diastolic blood flow velocity by transcranial doppler (TCD) to estimate the change of intracranial pressure and reflect the fluctuation of cerebral perfusion pressure. However, PI value is affected by many factors (BP and cardiac output) which limit its clinical application. Diastolic blood flow velocity with TCD has not been popular either because of the degree of cerebrovascular disease and the failure ratio of detecting temple window.

We have found that many patients with syncope have WMLs as indicated by MRI. The various forms of syncope and transient loss of consciousness (TLOC) are due to cerebral hypoper-

fusion. The degree of hypoperfusion has not been quantitatively distinguished in the past literature. Orthostatic hypotension (OH) is confirmed when syncope occurs while standing [18-24]. The onset may occur within 3 minutes of a change in position (typical OH) or after long standing (delayed OH). Tilt testing may assist in finding such OH [18-22]. This method is practical and has rigorous standards, and parameters which can be used to quantify indicators.

Our aim was to determine whether blood pressure changes in OH patients with syncope are more representative to reflect the degree of hypoperfusion with WMLs.

Materials and methods

Patient profiles

This was a retrospective study. During June 2015 and March 2019, we recruited 2265 consecutive patients with syncope. All patients were informed and provided written consent before participating in the study, which was approved by the Ethics Committee of Beijing Tiantan Hospital Affiliated to Capital Medical University (approval No. KY2019-109-01). All the patients with syncope were referred to China National Clinical Research Center for Neurological Diseases by their neurologists or physicians, with confirmation of the referral diagnosis by clinical and laboratory evaluations.

Patient enrolment

Inclusion criteria: Patients with a history of syncope ranging from single to several times; patients with pressure alteration from lying to standing position (SBP decreased by ≥20 mmHg or DBP decreased by ≥10 mmHg or SBP was lower than 90 mmHg) in the upright tilt test, which meets the standard of upright hypotension.

Office hypertension, diabetes, Parkinson's disease (PD), Parkinsonian Syndrome and Parkinson Plus Syndromes (e.g. multiple system atrophy (MSA), dementia with Lewy bodies (DLB), corticobasal degeneration (CBD), and progressive supranuclear palsy (PSP)) were involved [22-27].

Exclusion criteria: Patients with any of the following conditions were excluded: leukodystrophy, heart disease or heart failure; low blood volume (after menstruation, intracerebral hemorrhage, gastrointestinal bleeding and diarrhea); renal insufficiency; unable or refuse to accept brain MRI or CT examination due to metal implants in the body or psychological and emotional problems.

Imaging data collection

The following protocols were recommended for all patients: brain imaging, including brain MRI (T1 weighted, T2 weighted, Fluid-attenuated Inversion Recovery (FLAIR)) or CT (if contraindicated to MRI). Image data were collected in DICOM format on discs and analyzed by the Image Research Centre in Beijing Tiantan Hospital. All patients were divided into two groups: WMLs group and non-WMLs group. And the WMLs group was classified into three subgroups according to Fazekas grade [11, 12].

Blood pressure data collection and data management

Heart examination included 12-lead ECG, precordial echocardiography, cardiac monitoring for ≥24 hours with automated rhythm detection. Antihypertensive drugs were prohibited on the day of monitoring. Head-up tilt test and continuous electrocardiogram monitoring were completed. Blood pressure was measured noninvasively by using a to nometric device placed on the radial pulse when underwent the head-up tilt test. The position of the arm was at heart level for measurements of blood pressure in both supine and upright positions. And then blood pressure was recorded sustained from supine to upright position. OH was defined as a decrease in SBP≥20 mmHg and/or DBP≥10 mmHg, or SBP<90 mmHg from supine to standing >60 minutes (or until symptomatic hypotension after standing) [18-22].

Symptoms of OH to end the head-up tilt test included dizziness, transient loss of consciousness (TLOC), and syncope.

Blood pressure outcomes

The angle of head-up tilt test was 70° by upright position. Blood pressure was recorded sustained from supine to upright position as diagram A and B. The monitored values are listed below: SBP_0/DBP_0: supine BP; $TIME_1$: the first time for falling down of upright BP; SBP_1/DBP_1: the first falling down of upright BP with or with-

Table 1. Comparison of the distribution of characteristics between individuals with and without WMLs

N=2265	with WMLs n=1342	without WMLs n=923
Age (year), $\bar{x}$±sd (median)	61±12 (62)	43±17 (45)
Male, n (%)	790 (34.9%)	468 (20.7%)
Symptom, n (%)	884 (39.0%)	576 (25.4%)
Hypertension, n (%)	536 (23.7%)	153 (6.8%)
Diabetes, n (%)	293 (12.9%)	59 (2.6%)
PD, n (%)	150 (6.6%)	78 (3.4%)
Parkinsonian syndrome, n (%)	197 (8.7%)	65 (2.9%)
Parkinson Plus Syndromes, n (%)	45 (2.0%)	34 (1.5%)

Note: Fisher test and Kruskal-Wallis test: P<0.05. WMLs: white matter lesions; PD: Parkinson's disease.

were a total of 2265 eligible patients with complete information. Overall, 56% patients were male, and the average age was 54 years old (7 to 92). 2010 OH patients were monitored by tilt test and divided into WMLs group and non-WMLs groups according to MRI.

Over half of the patients had symptoms such as dizziness, TLOC or syncope. There were 1342 patients with WMLs as presented in **Table 1**. Age, gender and diseases had significant difference between patients with and without WMLs.

out symptoms; $\Delta SBP_1/\Delta DBP_1$: the first BP fluctuation; $TIME_2$: the time for the maximum falling down of upright BP; SBP_2/DBP_2: the maximum falling down of upright BP with or without symptoms; $\Delta SBP_2/\Delta DBP_2$: the maximum BP fluctuation; ΔTIME: interval time of twice falling down of upright BP. All of ΔBPs are primary indicators, and ΔTIMEs are secondary one.

Statistical analysis

Quantitative data were expressed as median and mean ± standard deviation ($\bar{x}$±sd). Categorical variables were expressed as numbers (percentages). The outcomes were tested by the Wilcoxon test, Fisher's exact test, Kruskal-Wallis test, and Logistic regression analysis. All analyses were performed with SAS 9.4 Software, and values of P<0.05 were considered statistically significant.

Data availability

The clinical data involved in this paper were from the clinical databases of Beijing Tiantan Hospital and Beijing Chaoyang Hospital. Others who want to share information must first get approval from the two hospitals and the authors. This study was not involved in any industry-sponsored research and corporate activities.

Results

There were 3315 syncope patients who consented and were enrolled in this study during June 2015 and March 2019. We initially excluded 572 patients by exclusion criteria. After excluding 478 patients with missing data, there

Latencies and durations of orthostatic hypotension

Blood pressure was recorded from supine (0°) to upright position (70°) as shown in **Figures 1A** and **2A**. As shown in **Figures 1B** and **2B**, ΔTIME had two types: the one was that the blood pressure decreased repeatedly, and the other was that blood pressure dropped one and only, then ΔTIME is zero.

According to our calculations, the number of cases with BP decreased repeatedly was twice as much as the cases with BP dropped one and only (**Table 2**).

There were significant differences in BP, ΔSBP and ΔTIME between patients with and without WMLs. The median and mean of BP parameters of patients with WMLs were slightly higher than those without WMLs. The time parameters of patients with WMLs were slightly higher than or equal to those without WMLs (**Table 3**).

We compared differences in blood pressure fluctuations among patients with Fazekas scales (**Table 4**). Some parameters were of significant difference between patients with Fazekas 1 and Fazekas 2, and between patients with Fazekas 1 and Fazekas 3. There was faint difference between patients with Fazekas 2 and Fazekas 3.

Risk factors analysis

The multivariate analysis showed 5 impact factors: age, ΔTIME, hypertension, diabetes, and Parkinson Plus Syndromes had significant difference (all P<0.05) between patients with and

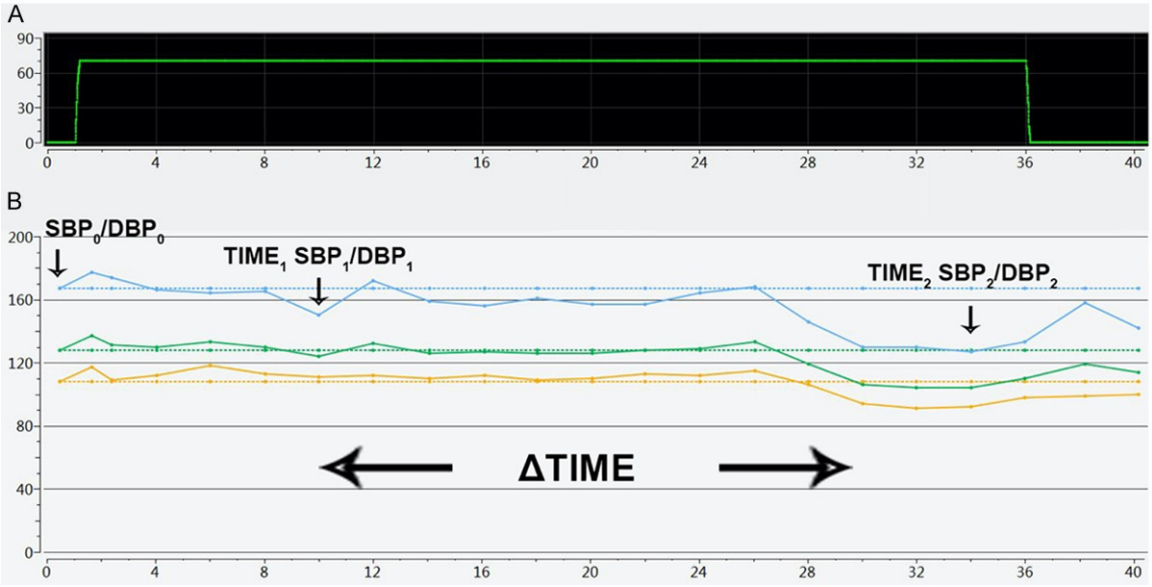

Figure 1. A (Time-angle): The X-axis was the time of tilt testing (minite), and the Y-axis was the angle of head-up tilt test; B (Time-BP mmHg): The X-axis was the time of tilt testing (minite), and the Y-axis was blood pressure. The three lines of the broken line diagram represented systolic blood pressure, mean blood pressure, and diastolic blood pressure. Blood pressure had decreased repeatedly and slowly.

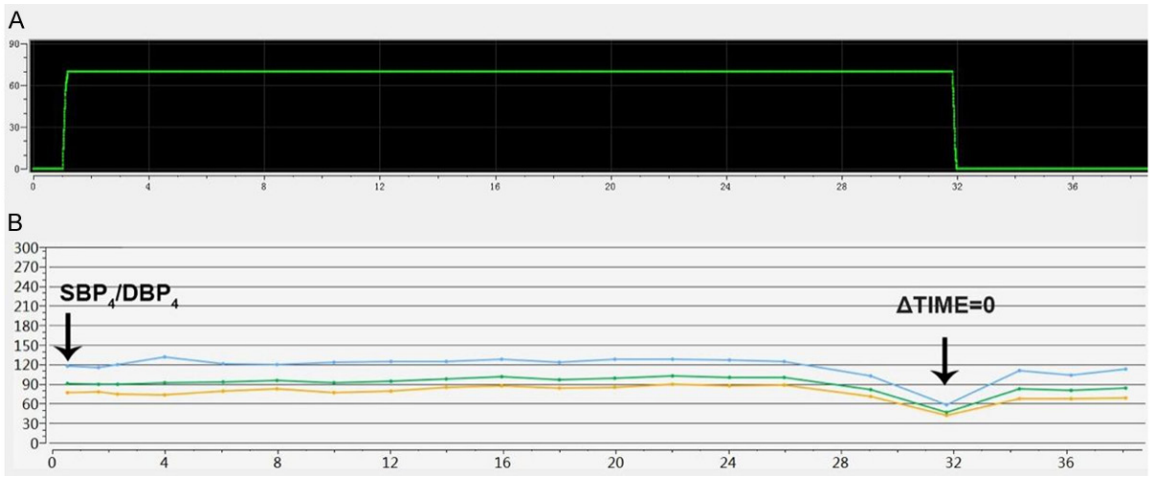

Figure 2. A (Time-angle): The X-axis was the time of tilt testing (minite), and the Y-axis was the angle of head-up tilt test; B (Time-BP mmHg): The X-axis is the time of tilt testing (minite), and the Y-axis is blood pressure. The three lines of the broken line diagram represent systolic blood pressure, mean blood pressure, and diastolic blood pressure. Blood pressure had dropped one and only, then ΔTIME is zero.

Table 2. Type for ΔTIME oforthostatic hypotension (n)

ΔTIME of OH	With WMLs	Without WMLs	Total
BP decreased repeatedly (non-zero)	734	656	1390
BP dropped one and only (zero)	468	152	620

Note: OH: orthostatic hypotension; WMLs: white matter lesions.

without WMLs (**Table 5**) after controlling for confounders. After we set sub-variables for BP fluctuations, there was faint difference in ΔSBP_1 (P=0.0579) between those with and without WMLs (**Table 5**).

Discussion

WMLs were commonly considered as a result of chronic cerebral ischemia [7-15]. We have shown that the median and mean of BP parameters in patients with WMLs were

Table 3. BP fluctuations in patients with or without WMLs (BP: mmHg, time: min)

n=2265	with WMLs (n=1342)		without WMLs (n=923)		P
	median	$\bar{x}$±sd	median	$\bar{x}$±sd	
SBP_0	131	134±18	122	123±14	<0.0001
DBP_0	82	82±11	77	78±11	<0.0001
SBP_1	104	104±25	101	100±22	<0.0001
DBP_1	72	70±17	70	68±17	0.0001
ΔSBP_1	25	30±21	21	23±19	<0.0001
ΔDBP_1	10	12±15	9	10±15	0.0050
SBP_2	95	93±25	92	91±23	0.0375
DBP_2	65	64±18	62	61±17	<0.0001
ΔSBP_2	36	40±25	28	32±23	<0.0001
ΔDBP_2	15	18±18	14	16±18	0.0908
$TIME_1$	35	27±17	35	28±15	0.9262
$TIME_2$	40	37±10	37.5	37±10	0.5310
ΔTIME	2.5	10±14	2.5	9±12	0.0110

Note: Kruskal-Wallis test: P<0.05; WMLs: white matter lesions.

higher than those without WMLs (**Table 3**). Most of the BP parameters of patients with Fazekas 2 and 3 of WMLs had similar trends to patients with Fazekas 1 of WMLs. The higher the WMLs scale is, the more obvious change in blood pressure (**Table 4**). Because Fazekas scale is a semi-quantitative judgment of the weight and degree of WMLs, there will be fuzzy transition between the levels of the score. The difference between patients with Fazekas 2 and 3 in our study was not as significant as that between patients with Fazekas 1 and 3 or Fazekas 1 and 2. Semi-quantitative methods cannot accurately estimate the decrease in cerebral perfusion. Primary and final levels of WMLs can be distinguished from measured changes, however, the intermediate transition levels cannot be easily distinguished. The BP level could not reflect hypoperfusion. So, variables for BP fluctuations were set, in which ΔSBP_1 (OR: 0.990, 95% CI: (0.980, 1.000), P=0.0579) did not significantly increase the risk of WMLs, and ΔDBP_1, ΔSBP_2 and ΔDBP_2 were not the impact factors (**Table 5**). The standard we applied was a drop of 20 mmHg in SBP and/or 10 mmHg in DBP, or SBP<90 mmHg after standing position. The data of ΔSBP_1 would be smaller when SBP dropped from 100 mmHg to 89 mmHg. So, there may be difference when *p* value close to 0.05.

In healthy people, upright positioning leads to decreased blood pressure (BP) in a transient period within 30 seconds, at the same time, intact cerebral auto-regulation maintained a constant cerebral perfusion through increased cardiac output and cerebral vasodilatation [28]. However, the responses to upright positioning may be disturbed due to diminished cerebral autoregulation or ischemic lesions that disturb autonomic nervous function [29-35]. So, we paid attention to the interval time (ΔTIME) of twice falling down of upright BP. $TIME_1$ and $TIME_2$, the time for falling down of upright BP, showed no specificity (P>0.05), but ΔTIME (P= 0.0110) had significant difference between those with and without WMLs in our present study. The risk of WMLs increased by 1.4% with each additional second in ΔTIME (OR: 1.014, 95% CI: 1.005, 1.023, P=0.0015) of twice falling down of upright BP. We found that the median and mean ΔTIME of patients with WMLs were equal to or longer than those without WMLs (P=0.0110, **Table 2**), suggesting that abnormality of autonomic nerve in patients with WMLs is breaking out later than those without WMLs. And recurrent hypotension is characteristic. Among the patients with WMLs, the number of non-zero ΔTIME cases far exceeded the number of zero ΔTIME cases (**Table 2**).

Our study showed that the OR of diabetes, hypertension, age and Parkinson Plus Syndromes for WMLs were 2.558, 1.713, 0.924 and 0.476 respectively (**Table 5**). This means that diabetes is the most distinct risk factor, but such comparisons have never been made before. Previous studies focused on the incidence, pathogenesis and baroreflex sensitivity of OH in patients with different age, hypertension and diabetes conditions [36-46]. Rotterdam Scan Study displayed that the middle-aged people with subcortical and periventricular WMLs were higher than those of old-aged people [47]. The three factors are all related to atherosclerosis. So, the reasons for hypoperfusion with WMLs might be that: (1) Atherosclerotic narrowing of the arteriole leads to decreased blood flow and leads directly to chronic hypoperfusion. (2) Atherosclerosis leads to dysfunction of the arterial baroreceptor which causes dysregulation of autonomic

Table 4. BP fluctuations in patients with different Fazekas scales (BP: mmHg, time: min)

n=2265	Fazekas 1 n=758		Fazekas 2 n=290		Fazekas 3 n=294	
	median	$\bar{x}$±sd	median	$\bar{x}$±sd	median	$\bar{x}$±sd
SBP_0	128	131±16	137	138±20	134	136±18
DBP_0	81	81±11	83	83±11	83	83±11
SBP_1	101	100±25	111	109±26	109	107±23
DBP_1	71	69±18	73	72±16	74	73±16
ΔSBP_1	24	31±22	25	30±20	25	29±18
ΔDBP_1	10	13±16	9	10±14	9	11±13
SBP_2	92	91±24	98	96±26	97	97±24
DBP_2	63	62±18	65	65±18	66	67±18
ΔSBP_2	35	40±25	38	43±26	33	39±24
ΔDBP_2	16	19±18	14	18±18	13	16±17
$TIME_1$	35	28±16	35	25±17	35	26±17
$TIME_2$	40	38±10	38	36±11	38	36±11
ΔTIME	2.5	10±14	2.5	11±14	2.5	10±14

Note: $\bar{x}$±sd: Mean ± standard deviation. P<0.05: between Fazekas 1 and Fazekas 2: SBP_0 (P<0.0001), DBP_0 (P=0.0167), SBP_1 (P<0.0001), DBP_1 (P=0.0010), ΔDBP_1 (P=0.0362), SBP_2 (P=0.0037), DBP_2 (P=0.0401), $TIME_1$ (P=0.0046), and $TIME_2$ (P=0.0020); between Fazekas 1 and Fazekas 3: SBP_0 (P<0.0001), DBP_0 (P=0.0108), SBP_1 (P<0.0001), DBP_1 (P=0.0005), SBP_2 (P=0.0003), DBP_2 (P=0.0008), and ΔDBP_2 (P=0.0071). P≈0.05: between Fazekas 2 and Fazekas 3: ΔSBP_2 (P=0.0558).

Table 5. Risk factors for WMLs

	WMLs	
	OR*(95% CI)	P
BP fluctuations		
ΔSBP_1	0.990 (0.980, 1.000)	0.0579
ΔDBP_1	0.991 (0.977, 1.004)	0.1749
ΔSBP_2	0.996 (0.987, 1.006)	0.4457
ΔDBP_2	1.010 (0.997, 1.024)	0.1450
ΔTIME	1.014 (1.005, 1.023)	0.0015
Age	0.924 (0.916, 0.932)	<0.0001
Sex	0.959 (0.777, 1.184)	0.6978
Hypertension	1.713 (1.342, 2.185)	<0.0001
Diabetes	2.558 (1.839, 3.558)	<0.0001
PD	0.577 (0.348, 0.957)	0.1901
Parkinsonian syndrome	0.683 (0.386, 1.209)	0.7859
Parkinson Plus Syndromes	0.476 (0.268, 0.846)	0.0208

Note: *OR: odds ratio; 95% CI: 95% confidence interval of the difference; WMLs: white matter lesions; PD: Parkinson's disease.

nervous system. (3) While blood-brain barrier permeability increased with vascular endotheliocyte incompetence, plasma protein components may leak into the perivascular of brain white matter [46].

Comprehensive analysis shows that PD and PD syndrome have no significant influence, regardless of the number of enrolled cases. The minimum impact factor of WMLs is Parkinson Plus Syndromes (OR: 0.476, 95% CI: (0.268, 0.846)). OH is one of the non-motor symptoms of movement disorders [23-27, 48, 49]. Although OH occurs in several diseases, Parkinson Plus Syndromes that progresses to autonomic failure has a OR value of 0.476 (95% CI: 0.268, 0.846, P<0.05) for WMLs (**Table 5**). Gregor KW found that long latencies of OH with PD (161 months) was significantly different with MSA (24 months), DLB (34 months), or PSP (30 months) [49]. Our study, as a cross-sectional design, was likely to be in the early stages of PD Syndrome. In addition, MDS Clinical Diagnostic Criteria for Parkinson's Disease defined an orthostatic decrease of at least 30 mmHg in systolic or 15 mmHg in diastolic to diagnose severe autonomic failure [23-27]. The standard we applied was a drop of 20 mmHg in SBP and/or 10 mmHg in DBP, or SBP<90 mmHg after standing position [18-21]. We think that autonomic dysfunction or autonomic disorder is equivalent to the latency period of PD or other diseases.

There are some limitations in this study. Firstly, it is uncertain whether the length of ischemia time is the only index to determine the degree of WMLs. In the future, we plan to solve it through animal experiments, such as making

animal models of different Fazekas grades of WMLs to study the relationship between ischemia and blood pressure change time (ΔTIME). Secondly, autonomic dysfunction or autonomic disorder could be reversed in a period of time, while the change in WMLs is irreversible. Autonomic disorder cannot define the pathological stage of the change about WMLs. Especially for those patients with improved symptoms of dizziness and syncope after treatment, quantitative indicators such as perfusion volume will be more useful to evaluate WMLs.

In conclusion, we have found indirect indices, as ΔSBP and ΔTIME, can reflect the change of scale of WMLs.

Disclosure of conflict of interest

None.

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