Original Article

The association of white matter hyperintensities with stroke outcomes and antiplatelet therapy in minor stroke patients

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Background: To characterize the severity and distribution of white matter hyperintensities (WMHs) and to assess the relationship of WMHs with initial stroke severity, 3-month functional outcome, stroke recurrence and response to antiplatelet therapies.

Methods: In Clopidogrel High-risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial, 787 minor stroke patients with baseline magnetic resonance imaging (MRI) information were included in this analysis. Deep and periventricular WMHs (DWMHs and PVWMHs) were rated using the Fazekas scale and categorized into mild (grades 0–2), moderate (grades 3–4) and severe (grades 5–6). Multivariable logistic regression was used to examine the associations between WMHs severities and outcomes, including initial stroke severity by the National Institutes of Health Stroke Scale (NIHSS) scores, 3-month functional outcome by modified Rankin Scale (mRS), and stroke recurrence. Cox proportional hazards model was used to assess the treatment-by-subgroup interaction effect.

Results: Among the 787 patients in this analysis, 432 (54.9%) had moderate or severe WMHs (3-6). Compared with mild WMHs, the adjusted odds ratio (OR) of severe WMHs for risk of higher NIHSS was 2.10, 95% confidence interval (CI), 1.26–3.48 (P=0.004). Both severities of SDWMHs (OR 1.66; 95% CI, 1.15–2.40; P=0.007) and PVWMHs (OR 1.47; 95% CI, 1.02–2.10; P=0.04) were associated with higher NIHSS scores. There were no statistically significant associations of WMHs with 3-month functional outcome and stroke recurrence. There were no significant interactions between WMHs and antiplatelet therapy.

Conclusions: In patients with minor stroke, both SDWMHs and PVWMHs might related with initial stroke severity. No interaction was detected between the severity of WMHs and antiplatelet treatment.

Trial registration: ClinicalTrials.gov identifier: NCT00979589. Date of registration: Sep 18, 2009.

Keywords: White matter hyperintensities (WMHs); minor stroke; stroke severity; functional outcome; antiplatelet therapy

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Introduction

White matter hyperintensities (WMHs) or leukoaraiosis, as one of the main magnetic resonance imaging (MRI) expressions of cerebral small vessel disease (CSVD) (1), are detected in 64–86% of stroke patients (2,3). WMHs may have important clinical implications as predictors of poor functional outcome, increased mortality, and long-term recurrence after ischemic stroke (2,4,5). However, the clinical significance of WMHs on stroke outcomes was inconclusive (6).

Data also suggest that stroke patients with WMHs may respond differently to treatment and secondary prevention (7-9). However, the therapeutic effect of stroke preventive therapies in patients with WMHs have yet to be reported from a randomized controlled trial. However, the interaction of WMHs severities with antiplatelet therapies for stroke outcomes has rarely been reported.

Moreover, the distribution of WMH seems to be an even more critical factor. Periventricular white matter hyperintensities (PVWMHs) and subcortical deep white matter hyperintensities (SDWMHs) are supposed to have different pathophysiological significance, thus distribution of WMHs may be a critical factor for clinical consequences after stroke (10-13). Investigations on WMHs will help to stratify risks in stroke patients.

Accordingly, we sought to characterize WMHs in a population of CSVD by examining minor stroke patients within the Clopidogrel in High-risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial and assess the relationship between WMHs and outcomes of stroke, as well as response to antiplatelet treatments.

Methods

Study design and participants.

We derived data from the CHANCE trial. Details about the rationale, design, and results of the trial have been published elsewhere (14,15). In brief, CHANCE was a randomized, double-blind, placebo-controlled clinical trial conducted in China between October 2009 and July 2012 to compare the efficacy and safety of combination therapy with Clopidogrel and Aspirin (Clopidogrel: loading dose of 300 mg followed by 75 mg daily for 90 days; Aspirin: loading dose of 75–300 mg followed by 75 mg daily for 21 days) *vs.* aspirin alone (loading dose of 75–300 mg followed by 75 mg daily for 90 days) in patients with minor stroke or high-risk TIA (transient ischemic attack). The inclusion criteria were as followed: age 40 years or older and diagnosis of an acute minor ischemic stroke (NIHSS ≤3) or high-risk TIA (ABCD2 ≥4) (16) within 24 hours after symptom onset. A total of 5,170 patients with minor stroke or TIA were included in the trial.

Standard protocol approvals, registrations, and patient consents

The CHANCE trial is listed on clinicaltrials.gov (NCT00979589). The protocol and data collection of the trial were approved by the ethics committee of Beijing Tiantan Hospital and all participating centers. All participants or their representatives provided written informed consent before inclusion into the study.

Data collection

The data were collected through face-to-face interview by trained and certified neurologists who were blinded to patients' treatment allocation and clinical information. Patient demographic information, vascular risk factors, symptoms of the qualifying event, pretreatment modified Rankin Scale score, stroke severity, treatment allocation, and time from index event to randomization were collected. Vascular risk factors included history of stroke or TIA, myocardial infarction, angina, known atrial fibrillation, hypertension, diabetes, hyperlipidemia, and smoking.

Participants of the imaging subgroup

Patients who were required to undergo magnetic resonance (MR) examinations (3.0 or 1.5 T) at baseline with the following sequences were included in the imaging subgroup: T1 weighted imaging, T2 weighted imaging, fluid-attenuated inversion recovery (FLAIR), diffusion weighted imaging (DWI), and 3D time-of-flight MR angiography (MRA). Those without any of the aforementioned sequences of MR examinations at baseline were excluded from the imaging subgroup. As reported in our previous article (17), baseline characteristics of patients in the trial with and without the MR sequences were similar.

Image analysis and interpretation

All images were centrally read by 2 readers (L Zong and

C Zhang), who were blinded to patient information. Neuroimage markers of CSVD including WMHs, lacunes, cerebral microbleeds (CMBs), and perivascular spaces (PVSs) were evaluated.

FLAIR sequences were used to evaluate the degree and distribution of WMHs. WMHs were scored using Fazekas scale (18). PVWMHs were defined as lesions contiguous with the margins of the lateral ventricles and extending up to and including 10 mm from the lateral ventricle into the white matter. SDWMHs were defined as lesions that were separated from the margins of the lateral ventricles, regardless of their distance to the margins of the lateral ventricles. PVWMHs and SDWMHs were evaluated separately and totaled as Fazekas scores. The severity of WMHs was rated by Fazekas scores (mild 0–2; moderate 3–4; severe 5–6). PVWMHs and SDWMHs were both divided into low [0–1] and high [2–3] groups.

The inter-rater agreement for the rating of WMHs was assessed on a random sample of 100 subjects at 8-week intervals. The intrareader reliability analysis showed a good reliability with κ values of 0.73 and 0.79 for PVWMHs and SDWMHs respectively.

Other neuroimaging markers of CSVD were assessed as following standards (19). Lacunes were defined as focal lesions 3 to 15 mm in size, with the same signal characteristics as cerebrospinal fluid on all MRI sequences, and surrounded by a hyperintense rim on FLAIR images, mainly situated in basal ganglia or white matter. Lacunes were initially assessed on T1WI. CMBs were defined as a round or ovoid area of homogeneous signal loss on SWI, 2 to 10 mm in diameter with blooming effect. Multiple CMBs were defined as ≥5 CMBs. PVSs were defined as small (<3 mm) punctate (if perpendicular to the plane of scan) or linear (if longitudinal to the plane of scan) hyperintensities on T2WI in the basal ganglia or centrum semiovale. Burden of PVSs was then stratified into 4 groups: 0, 1–10, 11–20, >20. Severe PVSs were defined as >10 PVSs in the basal ganglia, or >20 in the centrum semiovale.

Outcomes

Stroke outcomes included initial stroke severity measured by the NIHSS at admission, functional stroke outcome measured by 3-month mRS, and stroke recurrence (ischemic stroke and hemorrhagic stroke). The initial stroke severity was categorized as low (NIHSS 0–1) and high (NIHSS 2–3) levels. Patients' functional outcomes were dichotomized into good and poor categories by applying the mRS score cutoff 1 (no significant disability)/2 (slight disability).

Statistical analysis

We presented categorical variables as percentages and continuous variables as mean with SD or median with interquartile range. The continuous variables between the 3 groups were compared by one-way analysis of variance or Kruskal-Wallis test. Categorical variables were compared by the χ^2 test. We assessed the associations between WMHs (including Fazekas scale score ≥2 for the PVWMHs and SWMHs) and outcomes (NIHSS, mRS, and stroke recurrence) using multivariable Logistic regression models. Adjusted factors for NIHSS included age, gender, medical history, smoking, multiple CMBs, lacunes, and severe PVSs. Adjusted factors for mRS and stroke recurrence included age, gender, medical history, baseline NIHSS, smoking, antiplatelet therapy within 90 days, multiple CMBs, lacunes, and severe PVSs. In addition, we assessed whether the treatment effect differed in certain prespecified subgroups by testing the treatment-by-subgroup interaction effect with the use of Cox models. The level of significance was P<0.05 (2-sided). All analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Study participants and characteristics

Among the 5,170 patients enrolled in the CHANCE trial, 1,089 patients at 45 sites underwent MR examinations at baseline. After excluding TIA patients and those without Fazekas scores and mRS at 3 months, 787 patients undergoing baseline MR examinations with all the required sequences were included in this subgroup analysis (*Figure 1*).

Among the 787 patients, there were 355 (45.1%), 263 (33.4%), and 169 (21.5%) patients identified as mild level [0–2], moderate level [3–4], and severe level [5–6] based on Fazekas scores respectively. Patients with higher Fazekas scores were older, more likely to be female (P=0.01), and had more vascular risk factors, such as ischemic stroke history (P<0.001), hypertension (P<0.001), and smoking (P<0.003) (*Table 1*). Patients with severe WMHs were more likely to have multiple CMBs (P<0.001), lacunes (P<0.001), severe PVSs (P<0.001), and worse functional outcomes (P=0.04). There was no statistic difference in NIHSS scores and stroke recurrence among 3 groups. Recurrent ischemic

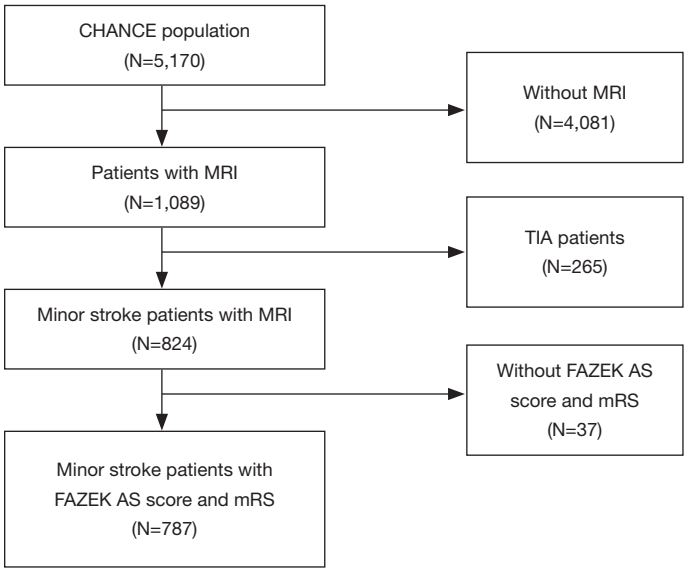

Figure 1 Flow diagram of participants in the imaging subgroup analysis. CHANCE, Clopidogrel in High-risk Patients with Acute Nondisabling Cerebrovascular Events.

stroke occurred in 90 (8.7%) patients, and none developed hemorrhage stroke (*Table 1*).

Association of WMHs with stroke outcomes

Table 2 shows associations of the severity and location of WMHs with outcomes. After adjustment for age, gender, final diagnosis, medical history, antiplatelet therapy within 90 days, and other CSVD markers (multiple CMBs, lacunes, and severe PVSs), severity of WMHs (OR 2.10; 95% CI, 1.26–3.48; P=0.004), SDWMHs (OR 1.66; 95% CI, 1.15–2.40; P=0.007) and PVWMHs (OR 1.47; 95% CI, 1.02–2.10; P=0.04) were associated with higher NIHSS scores. After adjustment, the severity and location of WMHs were not related to higher mRS scores and stroke recurrence.

Effect of randomized interventions

The risk of stroke recurrence and functional outcome did not differ for dual antiplatelet therapy versus aspirin alone amongst patients with different WMH features. There were no significant interactions in any of the subgroups (P>0.10 for all comparisons) (*Table 3*). Since none of patients developed hemorrhage stroke, there was no suggestion that the dual antiplatelet therapy increased intracranial hemorrhage in patients with severe WMHs.

Discussion

Our study reveals that high WMHs burden, especially SDWMHs burden, substantially impacts initial stroke severity in minor stroke; WMHs might not be a predictor of mRS and stroke recurrence in 3 months.

Our results agree with findings from the studies showing that the WMHs were highly predictive for NIHSS on admission (20,21). The probable reason is that loss of white matter tract organization resulted in reduced functional network integrity. It is difficult to compensate for deficits caused by acute ischemic stroke. This hypothesis will require confirmation in additional studies. One intriguing finding is that SDWMHs and PVWMHs both predict severe NIHSS, while SDWMHs might be more relevant. The two subtypes of WMHs have different but converging trajectories, possibly because of overlapping but not identical mechanisms and pathogenesis involved (22). Neuropathological differences are reported that PVWMHs are more likely due to diminished cerebral vasomotor reactivity and subsequent hypoperfusion, while SDWMHs are related to microangiopathy (22). In addition, the functional significance of the two subtypes is possible to be

Table 1 Baseline characteristics and outcomes according to WMH severities

Characteristics	FAZEKAS score (n=787)			P value
	0–2 (n=355)	3–4 (n=263)	5–6 (n=169)	
Age	59.1±9.7	65.1±10.1	70.1±8.8	<0.001
BMI	24.5±3.2	24.3±3.4	23.9±3.0	0.34
Female, No. (%)	104 (29.3)	105 (39.9)	64 (37.9)	0.01
Medical history, No. (%)				
Ischemic stroke	39 (11.0)	41 (15.6)	46 (27.2)	<0.001
TIA	3 (0.8)	6 (2.3)	2 (1.2)	0.31
Myocardial infarction	4 (1.1)	6 (2.3)	7 (4.1)	0.08
Atrial fibrillation or flutter	4 (1.1)	5 (1.9)	7 (4.1)	0.07
Hypertension	202 (56.9)	180 (68.4)	121 (71.6)	<0.001
Hyperlipidemia	43 (12.1)	30 (11.4)	18 (10.7)	0.88
Diabetes mellitus	79 (22.3)	53 (20.2)	36 (21.3)	0.82
Current or previous smoking, No. (%)	169 (47.6)	105 (39.9)	55 (32.5)	<0.003
Antiplatelet therapy, No. (%)				
Aspirin alone	185 (52.1)	130 (49.4)	85 (50.3)	0.79
Aspirin plus Clopidogrel	170 (47.9)	133 (50.6)	84 (49.7)	
Time to randomization	13.0±6.7	13.7±6.7	13.9±6.5	0.25
Other CSVD image markers, No. (%)				
Multiple CMBs[†]	1 (0.3)	9 (3.4)	20 (11.8)	<0.001
Lacunes	145 (41.3)	174 (66.7)	148 (88.6)	<0.001
Severe PVSs[‡]	148 (41.7)	161 (61.2)	123 (72.8)	<0.001
Outcomes, No. (%)				
NIHSS				
0–1	123 (34.6)	91 (34.6)	44 (26.0)	0.11
2–3	232 (65.4)	172 (65.4)	125 (74.0)	
mRS				
0–1	322 (90.7)	221 (84.0)	147 (87.0)	0.04
2–6	33 (9.3)	42 (16.0)	22 (13.0)	
Ischemic stroke, No. (%)	30 (8.5)	31 (11.8)	13 (7.7)	0.26
Hemorrhage stroke	0	0	0	–

[†], multiple CMBs: cerebral microbleeds ≥5; [‡], severe PVSs: >10 perivascular spaces in the basal ganglia, or >20 in the centrum semiovale.

different. In a study involving stroke patients, SDWMHs had a stronger association with cortical perfusion, although SDWMHs counted for only 1/3 of the total WMHs volume, with PVWMHs counting for 2/3 (23,24). That supports our finding, that the two subtypes are differently associated with initial stroke severity in CSVD.

Some studies suggested that patients with WMHs have a higher risk of intracranial hemorrhage and disability after stroke (25,26). Particularly, periventricular WMH volume was associated with accelerated functional decline (27).

Table 2 Associations of CSVD image markers with initial stroke severity and outcomes within 90 days

CSVD image markers	NIHSS[§]		mRS[¶]		Stroke recurrence	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Fazekas						
0–2	1		1		1	
3–4	1.12 (0.82–1.74)	0.35	1.49 (0.86–2.57)	0.16	1.16 (0.65–2.06)	0.61
5–6	2.10 (1.26–3.48)	0.004	0.84 (0.40–1.71)	0.62	0.65 (0.28–1.48)	0.30
SDWMHs[†]	1.66 (1.15–2.40)	0.007	0.81 (0.48–1.37)	0.43	0.68 (0.68–1.22)	0.19
PVWMHs[‡]	1.47 (1.02–2.10)	0.04	1.35 (0.79–2.32)	0.27	0.99 (0.55–1.78)	0.98

[†], SDWMHs: Fazekas score 2-3 *vs.* 0-1 in the subcortical area; [‡], PVWMHs: Fazekas scale 2-3 *vs*. 0-1 in the periventrcular area; [§], NIHSS score 2-3; [¶], mRS score 2-6.

Table 3 Hazard ratio for the stroke recurrence in prespecified subgroups

Subgroup	No. of patients	No. of events ()		Hazard ratio (95% CI)	P value for interaction
		Asprin	Clopidogrel-Asprin		
Overall	787	43 (10.8)	31 (8.1)	0.78 (0.48–1.27)	–
Fazekas					0.66
0–2	355	19 (10.3)	11 (6.5)	0.94 (0.41–2.15)	
3–4	263	18 (13.9)	13 (9.8)	1.15 (0.50–2.65)	
5–6	169	6 (7.1)	7 (8.3)	3.21 (0.53–19.27)	
SDWMHs					0.84
0–1	463	27 (11.3)	19 (8.5)	0.80 (0.41–1.54)	
2–3	324	16 (9.9)	12 (7.4)	0.74 (0.29–1.87)	
PVWMHs					0.76
0–1	364	18 (9.5)	12 (6.9)	0.92 (0.40–2.11)	
2–3	423	25 (11.9)	19 (8.9)	0.92 (0.47–1.77)	

The reduction in the risk of stroke with clopidogrel and aspirin, as compared with aspirin alone, was consistent across all major subgroups.

However, we demonstrated that WMHs has no impact on short-term functional outcome. In addition, several studies indicate that PVWMHs were significantly associated with poor functional outcome at 3 months (12,13,28). However, mRS does not seem to corelate with the location of WMHs in our study. This might be due to the fact that we exclusively included patients with minor stroke who have relatively good functional outcomes. Because of the limited sample size, the result is not conclusive. Further studies are needed to fully understand the association and mechanism.

Whether WMHs are risk factors of intracranial hemorrhage is controversial in prior studies (6,25). We did not observe a statistically significant treatment interaction between WMHs and dual *vs.* mono antiplatelet therapy. Therefore, the presence of WMHs might not impact on clinical decision making regarding the second preventive treatment.

Our study had several limitations. First, potential selection bias might have existed since this subgroup analysis included only approximately 20% of patients from 45 of 114 participating sites providing MRIs. However, baseline characteristics of patients in the trial with and without the MR sequences were similar (*Table S1*). Second, the CHANCE trial enrolled only Chinese patients. Hence

the external generalizability of the findings of this subgroup analysis needs further validation in Western populations. Third, MRI-based WMHs grading using the Fazekas scale is well established, frequently used in clinical research, and has been shown to correlate well with the WMHs volume. However, the volume of WMHs might be a more precise way to define the severity of CSVD (29). Forth, some patients were scanned with 1.5 T MRI and some other with 3.0 T MRI. This might cause inconsistency in the evaluation of image markers of CSVD. Fifth, in CHANCE study, minor stroke was defined as an acute ischemic stroke with NIHSS ≤3. However, the standardized surrogate information of the stroke severity might include infarct size on DWI at presentation. Sixth, in our study, stroke subtypes were not determined based on the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. There are suggestions that stroke outcomes may be affected by WMHs differentially depending on stroke subtypes (29).

Conclusions

In summary, in patients with minor stroke, both SDWMHs and PVWMHs were predictors for initial stroke severity. WMHs might not be associated with the effect of secondary stroke preventative therapies.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The protocol and data collection of the trial were approved by the ethics committee of Beijing Tiantan Hospital and all participating centers. All participants or their representatives provided written informed consent before inclusion into the study.

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Supplementary

Table S1 Characteristics of WHMs subgroup and overall minor stoke

Characteristics	Subgroup, N=787	Overall, N=2,938	P value
Age	63.4±10.6	62.4±10.7	0.01
BMI	24.3±3.2	24.7±3.0	<0.001
Female, n (%)	273 (34.7)	956 (32.5)	0.25
Medical history, n (%)			
Ischemic stroke	126 (16.0)	655 (22.3)	<0.001
TIA	11 (1.4)	61 (2.1)	0.22
Myocardial infarction	17 (2.2)	57 (1.9)	0.69
Known atrial fibrillation or flutter	16 (2.0)	53 (1.8)	0.67
Hypertension	503 (63.9)	1,893 (64.4)	0.79
Hyperlipidemia	91 (11.6)	283 (9.6)	0.11
Diabetes mellitus	168 (21.3)	597 (20.3)	0.53
Current or previous smoking, n (%)	329 (41.8)	1,304 (44.4)	0.20
Antiplatelet therapy, n (%)			0.55
Aspirin alone	400 (50.8)	1,458 (49.6)	
Aspirin plus Clopidogrel	387 (49.2)	1,480 (50.4)	
Time to randomization	13.4±6.7	13.1±6.8	0.24
Baseline NIHSS	2 [1–3]	2 [1–3]	0.33
Outcomes within 90 days, n (%)			
Ischemic stroke	74 (9.4)	294 (10.0)	0.61
TIA	8 (1.0)	20 (0.7)	0.33
Any bleeding	17 (2.2)	52 (1.8)	0.47
Hemorrhage stroke	0	14 (0.5)	0.052
Secondary combined outcome	75 (9.5)	312 (10.6)	0.37
mRS, n (%)			0.75
0–1	690 (87.7)	2,539 (87.3)	
2–6	97 (12.3)	371 (12.7)	