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Data analysis

Distal hyperintense vessels influence white matter hyperintensities association with clinical outcome

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Abstract
Distal hyperintense vessels (HV) and white matter hyperintensities (WMHs) were frequently observed in intracranial artery stenosis patients on MRI. We usually diagnose stroke radiologically focus mainly on the infarction itself, but it is imperative to keep in mind that the additional changes that take place are worthy and important and add a high value in the prognosis of stroke. WMHs and HV were frequently observed in most situations in middle cerebral artery occlusion patients, but were paid no major attention. All acute stroke patients with routine MRI of middle cerebral artery (MCA) M1 occlusion from January 2012 to October 2014 were recorded. The extent of HV, p-WMHs and d-WMHs were taken into consideration. The clinical severity and prognosis were measured in accordance to ASPECTS score, NIH Stroke Scale (NIHSS) and modified Rankin Scale (mRS). More prominent HV were associated with younger age. Higher grade of WMHs was related to the relatively lower grade of HV, and bad prognosis. The presence of abundant HV with alleviated WMHs can help in the prediction of good stroke prognosis.
Keywords: White matter hyperintensities, hyperintense vessels, acute stroke, collateral circulation

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Introduction

The sensitivity to hyperacute cerebral infarction and radiationless examination methods made magnetic resonance imaging (MRI) the most widely used and irreplaceable tool in the intracranial disease detection clinically. Usually, in the diagnosis of stroke radiologically, we focus mainly on the infarction itself while some frequently observed relative phenomenal values that provide additional information are ignored. White matter hyperintensities (WMHs), usually accompanied with lacunes are regarded as the main MRI representatives of small vessel disease (SVD) [1]. The association with cognitive dysfunction, dementia, body incoordination and occurrence of stroke, further promotes the exploration of WMHs [2]. Increasing studies lay more emphasis on WMHs with severe vascular stenosis rather than SVD [3], in that intracranial artery stenosis is independently associated with WMHs lesions leading to severe infarction [4]. Distal hyperintense vessels (HV) are popular on fluid-attenuated inversion recovery (FLAIR) sequence among acute ischemic patients with proximal arterial occlusions, which own the reputation as a symbol of collateral circulation [5, 6]. The above mentioned MRI phenomena (WMHs, HV) share a common characteristic that both appear frequently among proximal arterial occlusive patients and are closely related to the stroke extent.

The relationship of WMHs and HV to the volume of infarction increases the ability of MRI in the evaluation for the prognosis of stroke patients. To clarify better, the relation between HV and WMHs with individual stroke differences, we assessed the ASPECT score and final infarct score for 90 days in M1 occlusive patients without acute thrombolysis therapy.

Methods

Patient selection

From January 2012 to October 2014, a total of 3525 patients with consecutive first acute ischemic stroke were evaluated in Jiangsu Province People's Hospital and The First Hospital of Nanjing (Fig. 1). The patients, which can meet the standards of completely occlude of the M1 and acute stroke were relatively less. Among those, 157 patients had ipsilateral M1 occlusion within 7 days from stroke onset. A total of 43 patients were excluded as they have undergone acute thrombolysis therapy and had no complete data that was required for the study, so 114 patients were included in our research.

Clinical data

Patient demographics, laboratory data and all the clinical data required for the study were collected by reviewing the electronic medical records. Neurological deficits of the patients were assessed according to the National Institutes of Health Stroke Scale (NIHSS) at presentation [7]. Stroke etiology was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) [8]. The follow-up were obtained after 90 days to classify nondisabling (score 0-2) and disabling (score 3-5) according to modified Rakin Scale (mRS) [7, 9].

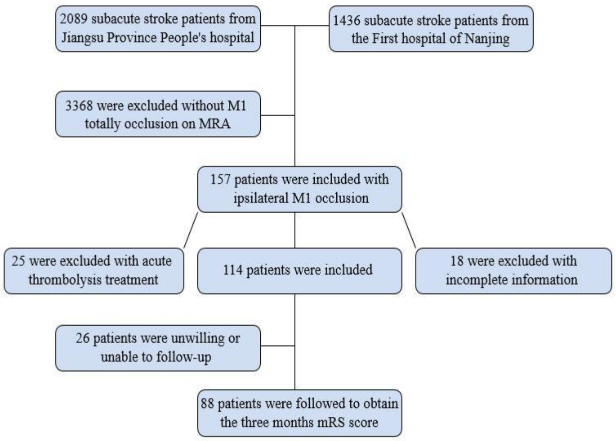

Fig 1 Flowchart summarizing the patient's selection criteria.

Radiological data

The WMHs were considered as hyperintensity on FLAIR without prominent hypo intensity on T_1WI and were assessed by the raters which were blind to clinical information. The severity of p-WMHs and d-WMHs was rated ranging from 0 to 3 by the method of Fazekas scale [10].

Distal hyperintense vessels (HV) are tubular or serpentine hyperintensities in the subarachnoid space, usually in the Sylvian fissure [11]. Subtle HV was defined as hyperintensity lines with an extension of less than 1/3 of middle cerebral artery (MCA) territory, whereas prominent HV were present more than 1/3 of the territory and extend to the frontal, parietal and occipital regions [6].

Early signs of ischemia were retrospectively semi-quantitatively evaluated by DWI sequence by Alberta Stroke Program Early CT Score (ASPECTS) [12], which is a 10 point scoring system used to denote affected extent and predict functional outcome [13], [14]. Two experienced radiologists classified the data independently. If there was a dispute, those were discussed together for consistency.

MRI scans

All the patients were imaged with 3.0T (Siemens Medical Solutions, Erlangen, Germany) using an 8-channel coil. The imaging protocols were standardized and consisted of regular T1, T2, diffusion-weighted imaging (DWI) (TR 4800 ms, TE 100 ms, field of view = 230 mm, b values of 0 and 1000 s/mm^2), fluid-attenuated inversion recovery (FLAIR) (TR 8000 ms, TE 97 ms, TI 2371 ms, field of view = 230 mm), MR angiography (MRA) (TR 22 ms, TE3.6 ms, field of view = 210 mm).

Statistical analysis

Statistical analysis was performed using SPSS 18.0 software. ANOVA test or the Kruskal-Wallis H test was used to compare continuous variables (age, WMHs, ASPECT score, NIHSS score, time from onset to MRI), and the X^2 test to compare categorical variables (gender, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, coronary artery disease, smoking, alcohol abuse, stroke etiology) between absent, subtle or prominent HV sign groups. Univariate and multivariate logistic regression analysis was applied to evaluate the predictive values of risk factors associated with poor outcome. Factors with $P<0.1$ were added into multivariate model.

Results

Clinical data

Out of the all first-time acute stroke patients admitted in the two hospitals from January 2012 to October 2014, a total of 114 were selected with complete and standard required information. Baseline characteristics of the classified HV groups are shown in Table 1. More prominent HV was associated with younger age (P=0.032). However, gender, clinical risk factors, stroke etiology and image time did not show any significant differences (Table 1).

Radiological data

Distal hyperintense vessels (HV) were observed in 86 (75.4%) patients, of which 37 (32.5%) were subtle and 49 (43.0%) were prominent. White matter hyperintensities (WMHs) were dichotomized into p-WMHs 85 (74.6%) and d-WMHs 50 (43.9%) groups. Higher grades of WMHs were related to the relatively lower grade of HV (P=0.004, P=0.002) (Fig. 2 and 3).

Stroke prognosis

The results of follow-up by modified Rankin Scale (mRS) evaluation were mainly conducted via out-patient review or telephone and out of 88 (77.2%), ten people died due to the severity of the stroke. Among the patients with different prognosis, prominent HV accounts obviously were more in the patients with better prognosis (52.6%) than bad prognosis (32%) (Fig 4). HV (odds ratio: 0.469, 95% confidence interval: 0.261-0.841, P=0.011), P-WMHs (odds ratio: 2.607, 95% confidence interval: 1.514-4.488, P=0.001), D-WMHs (odds ratio: 2.30,

Table 1 Baseline characteristics, radiological features and clinical data administered by HV groups.

	Absent HV n=28	Subtle HV n=37	Prominent HV n=49	*P* Value
Demographic data and risk factors				
Age (mean ± SD)	68.3±12.5	63.3±13.3	59.5±15.3	0.032*
Male, n (%)	14(50.0)	26(70.3)	31(63.3)	0.244
Hypertension, n (%)	23(82.1)	30(81.1)	34(69.4)	0.318
Diabetes mellitus, n (%)	11(39.3)	11(29.7)	18(36.7)	0.690
Dyslipidemia, n (%)	6(21.4)	6(16.2)	15(30.6)	0.283
Atrial fibrillation, n (%)	10(35.7)	7(18.9)	16(32.7)	0.252
Coronary artery disease, n (%)	10 (35.7)	11(29.7)	11(22.4)	0.443
Smoking, n (%)	14(50.0)	12(32.4)	16(32.7)	0.251
Alcohol abuse, n (%)	7(25.0)	8(21.6)	10(20.4)	0.895
Stroke etiology				
Atherothrombotic, n (%)	7(25.0)	15(40.5)	13(26.5)	
Cardioembolic, n (%)	11(39.3)	9(24.3)	21(42.9)	0.398
Cryptogenic, n (%)	10(35.7)	13(35.1)	15(30.6)	
Features of WHMs on MRI				
p-WMHs, (median, IQR)	2(1-2)	1(1-2)	1(1-1)	0.004*
d-WMHs, (median, IQR)	1(1-2)	1(0-1)	1(0-1)	0.002*
Clinical data				
Time from onset to MRI, h, (mean ± SD)	135.0±61.0	145.8±68.1	125.6±72.8	0.429
ASPECTS score (median, IQR)	5(4-6)	6(5-6)	7(6-7)	0.002*
Baseline NIHSS score (median, IQR)	9(7-12)	6(4-7)	5(4-7)	0.024*

* Statistically significant; HV = hyperintense vessel; p-WMHs = periventricular white matter hyperintensities; d-WMHs = deep white matter hyperintensities; mRS = modified Rankin Scale; ASPECTS = Alberta Stroke Program Early CT Score; NIHSS = National Institutes of Health Stroke Scale.

Table 2 Binary logistic regression analysis associated with poor outcome after 90 days.

Parameters	Univariate Logistic Analysis			Multivariate Logistic Analysis		
	OR	95% (CI)	*P* value	OR	95% (CI)	*P* value
HV	0.469	0.261-0.841	0.011	0.479	0.240-0.957	0.037
Diabetes	4.190	1.488-11.802	0.007	5.294	1.632-17.176	0.006
d-WMHs	2.300	1.379-3.837	0.001	1.525	0.734-3.167	0.258
P-WMHs	2.607	1.514-4.488	0.001	1.517	0.668-3.443	0.319
Age	1.050	1.016-1.086	0.004	1.019	0.974-1.065	0.424

HV = hyperintense vessel; p-WMHs = periventricular white matter hyperintensities; d-WMHs = deep white matter hyperintensities; OR = odds ratio. Only significant risks were listed in the table.

95% confidence interval: 1.379-3.837, *P*=0.001), and age (odds ratio: 1.050, 95% confidence interval: 1.016-1.086, *P*=0.004) were associated with poor outcome after 90 days in the univariate model. In the multivariate model, HV (odds ratio: 0.479, 95% confidence interval: 0.240-0.957, *P*=0.011) and diabetes (odds ratio: 5.294, 95% confidence interval: 1.632-17.176, *P*=0.006) were independent factors associated with poor outcome after 90 days (Table 2).

Discussion

Additional valuable information detected from routine MRI images are also worth noticing especially the frequently observed phenomena. White matter hyperintensities (WMHs) which had been proved to have relationship with large vessel occlusive lesions frequently emerged in the elderly, particularly in the patients with hypertension or diabetes mellitus [15]. Notably, HV is also common among the large vascular occlusive lesions and can significantly affect infarcted extent which may be crucial for prognosis [16]. In this research, the patients were restricted to the same large vessel occlusive extent. Firstly, we want to find out the relationship of frequently appeared, but easily ignored hidden information on MRI and secondly to compare the influential factors on prognosis since the proximal artery supply state was the same.

Regarding the selected patients in our research with different infarcted extent, the mechanism which attributed to extent difference can be explored further. The HV has been confirmed by recent angiographic studies to reflect the slow arterial blood flow in the leptomeningeal collateral circulation [11]. Importantly, HV can exhibit the value of predicting acute ischemic stroke [17], transient ischemic attack

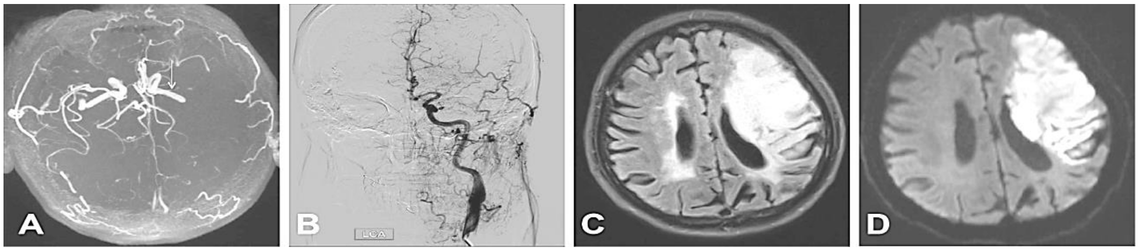

Fig. 2 A male patient (45 years old) with right limb weakness for three days. **A**: arrow denotes M1occlusion on MRA maximum intensity projection (MIP) images. **B**: abundant collateral vessel can be seen from angiography. **C**: arrows on FLAIR show prominent HV. Both P-WMHs and d-WMHs score are 0. **D**: acute stroke ASPECT score is 9 with only one area affected.

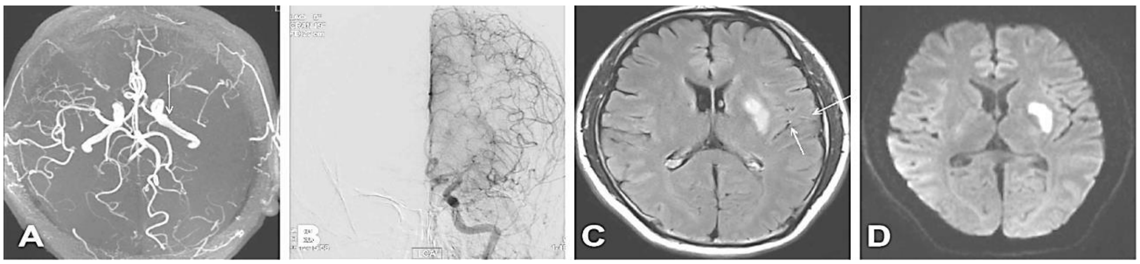

Fig. 3 A male patient (45 years old) right limb movement disturbance for one day. **A**: arrow denotes M1occlusion on MRA maximum intensity projection (MIP) images. **B**: scarcely any collateral vessel can be seen from angiography. **C**: FLAIR shows absent HV. Irregular p-WMHs score 3 and punctate foci d-WMHs score 1. **D**: acute stroke ASPECT score is 2.

[18], and diffusion-perfusion mismatch [19]. In conclusion, an acute cerebral ischemia state signs and collateral small vessel formation signs on MRI. The proximal artery supply was totally blocked; smaller infarction of the patients was attributed to the abundant distal potential collaterals reflected by HV. The observation of HV is important in prognosis evaluation.

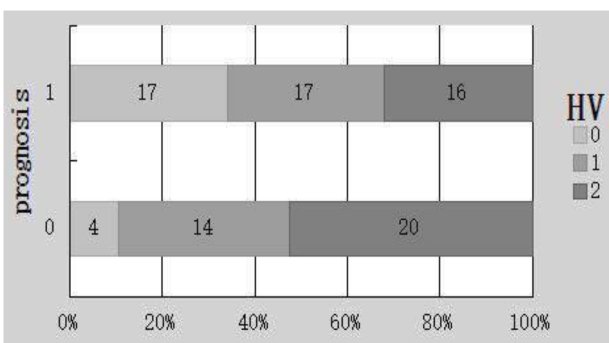

Fig. 4 The percentage comparison of different HV grades between good prognosis (0) and bad prognosis (1) patients. Prominent HV=2; subtle HV=1; absent HV=0.

Absent HV patients were easier to form sever WMHs, the reasons can be explained as follows. The WMHs were commonly emerged in the elderly, hypertension or diabetes mellitus patients. These were risk factors for small vessel injury. Collaterals were the formation of micro-vascular network which need angiogenic microenvironment. If this environment was disturbed as reflected by WMHs, the formation of small vessels reflected by HV was also influenced. As reflected by our results, severe WMHs tend to lose the ability of forming HV. The affected vessels of WMHs were not only limited to deep white matter (d-WMHs), but also to cortical vessels (p-WMHs), which can also reflect insufficient cortical collaterals from a different perspective [20].

In this study, a relative large number of unified standard patients from different hospitals were selected, and we blindly assessed two frequently observed phenomenon that rarely been linked before. Unfortunately, our research still contains some limitations. The first limitation is that about 77% of the patients had the mRS results owing to imperfect follow-up mechanisms. Secondly, although our data demonstrate a strong association between HV, WMHs, and prognosis, the potential mechanisms are needed to be explained more intensively. Finally, though HV signs have been proved by a lot of researches to reflect collaterals, it's just a proved assumption and we don’t have the cerebral angiography material for every patient.

Conclusively, the data demonstrate that the appearance of prominent HV together with the less severe WMHs result in a good functional outcome of the stroke patients. These findings may help in early diagnosis of patients with high risk and poor outcome meanwhile increasing the routine MRI ability in the evaluation of stroke prognosis clinically.

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