Hemoglobin is Associated with Periventricular but Not Deep White Matter Hyperintensities in Lacunar Ischemic Stroke

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White matter hyperintensities (WMHs), also known as leukoaraiosis (LA), are strongly linked to the cerebral small vessel disease, which increases the risk of stroke, cognitive decline, and dementia [1]. These high signal abnormalities are often divided into two categories: periventricular WMH (PVWMH), which occurs adjacent to the cerebral ventricles, while deep WMH (DWMH), which occurs in subcortical white matter distinct from the periventricular area [2]. PVWMH differs from DWMH in that it has consistently clinical, histopathological, and etiological correlates. In the nondemented elderly, cognitive impairment (especially psychomotor speed), rate of cognitive decline, and medial temporal lobe atrophy were preferentially associated with the severity of PVWMH, but not with that of DWMH. In contrast, the risk and outcomes of mood disorders were preferentially associated with DWMH [2]. The pathophysiological mechanisms underlying the occurrence of WMH are largely unknown. Available information indicates that WMH is commonly seen in aging, hypertension, diabetes mellitus, cerebral vessel atherosclerosis, and genetic diseases [3,4]. Recent studies show that hemoglobin (Hb), the iron-containing oxygen-transport metalloprotein in the red blood cells, may be associated with cerebral vascular diseases [5]. To the best of our knowledge, no studies have been taken to investigate the relationship between Hb and different types of WMH. In this study, we investigated the relationship among hemoglobin, cognitive function, PVWMH, and DWMH in acute lacunar infarct patients.

We prospectively recruited consecutive patients who had been admitted to our university hospital stroke service with a clinical syndrome of acute stroke between January 2010 and December 2011. MRI scans were coded for the presence, location and size of the recent infarct by a neuroradiologist. An experienced stroke

physician classified patients into lacunar stroke clinical syndromes according to the Oxfordshire Community Stroke Project classification. PVWMH and DWMH were evaluated on FLAIR sequences and classified by a neurologist according to the Fazekas scale, which rates lesions in both regions from 0 to 3 [6]. We excluded patients with contraindications to MRI, hemorrhage, severe stroke, and nonstroke diagnoses. The history of hypertension, diabetes, stroke, ischemic heart disease (IHD), and smoking was documented. Hb was measured with the Beckman Coulter MAXM/HMX analyzer (Beckman Coulter, Miami, FL, USA), using the manufacturer's reagents and methods. The cognitive function of the participants was evaluated by the Mini-Mental State Examination (MMSE). This study was approved by the hospital's research ethics committee, and all patients provided written informed consent. Chi-squared test and Student's *t*-test were used to compare between two groups. A multivariable linear regression model was used to assess the relationship among hemoglobin, MMSE and severity of PVWMH and DWMH on the first MRI scan. Statistical significance was defined as a two-tailed $P < 0.05$ using SPSS ver 15.0 (SPSS Inc., Chicago, IL, USA).

A total of 189 patients were identified [age: 68.4 ± 12.4 years, mean $\pm$ standard deviation] in which 34% of patients were women. 29.5% (43/189) of patients were anemic at the baseline level based on World Health Organization criteria. Patients with anemia at entry were older and had lower levels of glomerular filtration rate (GFR) and higher scores of PVWMH when compared with the patients who were not with anemia. Tracking the past medical history, there were no significant differences between the two groups (Table 1). 21.2% (40/189) of patients had lacunar infarct located in brain stem while the others were in cerebral

hemisphere. The average diameter of infarct was 1.91 ± 0.27 mm (data not shown).

Multivariable regression model demonstrated that increased PVWMH scores were significantly associated with decreased Hb levels. There was no association between Hb and DWMH scores. Age was associated with WMH scores which was consistent with prior reports [3]. History of stroke was also an important issue, which is associated with increased PVWMH and DWMH scores in all patients (Tables 1 and 2). We found that the location and size of infarct did not correlate WMH scores as well as MMSE and Hb levels. For MMSE, there is no statistically significant association between Hb and MMSE after adjustment for age, GFR, and past medical history factors (data not shown).

Our results indicate that lower Hb levels were associated with severity of PVWMH in all patients. The mechanisms by which lower Hb associates with severe WMH are still not clear. Since the primary function of Hb is to carry oxygen to tissues, this means that lower Hb levels may influence oxygen metabolism. Several studies have showed that LA may be linked to cerebral hypoperfusion [7]. Age-related thickening of the vessels wall and narrowing of the vascular lumen may reduce blood flow in small penetrating arteries and arterioles in the white matter [8]. Pathological changes in extracranial or intracranial large arteries might induce extensive white matter changes by interrupting blood flow to the white matter [9]. These mechanic obstacles affecting blood flow to white matter determined by multiple risk factors could induce an increased sensitivity to a further reduction of oxygen supply when Hb concentration is lower.

Interestingly, Hb levels on admission were independently associated with PVWMH without DWMH in our patients. Pathological

Table 1 Baseline characteristics of the patients

Characteristic	Anemia	Normal	P value
n	43	146	
Sex, female (%)	16 (37.2)	49 (33.6)	0.658
Mean age (SD), years*	74.7 (10.4)	65.3 (12.2)	0.000
Total bilirubin (SD), $\mu\text{mol/L}$	12.5 (6.76)	13.6 (5.86)	0.297
MPV(SD), fl	11.1 (1.21)	12.2 (13.12)	0.599
GFR(SD), mL/min per 1.73 m^2 *	93.0 (26.7)	107. (28.3)	0.005
PVWMH score (SD)*	2.58 (0.88)	1.59 (0.94)	0.000
DWMH score (SD)	1.53 (0.91)	1.36 (1.14)	0.365
MMSE (SD)	25.6 (3.27)	25.7 (3.46)	0.865
MMSE (SD)	25.4 (3.62)	26.2 (2.91)	0.053
Past medical history of			
Hypertension, n (%)	29 (67.4)	109 (74.7)	0.349
Diabetes mellitus, n (%)	13 (30.2)	41 (28.1)	0.784
Stroke, n (%)	7 (16.3)	28 (19.2)	0.667
IHD, n (%)	3 (7.0)	7 (4.8)	0.574
Smoking, n (%)	13 (30.2)	60 (41.1)	0.198

PVWMH, periventricular white matter hyperintensity; DWMH, deep white matter hyperintensity; MPV, mean platelet volume; GFR, glomerular filtration rate; IHD, ischemic heart disease. Values are percentages, unadjusted means (SD). The difference between anemic group and normal group was tested using the *t*-test. Chi-squared tests were used to compare the proportions.

* $P < 0.01$, versus normal group.

Table 2 Multivariable adjusted associations with Hgb in patients

Variable	PVWMH		DWMH	
	β -Coefficient	P value	β -Coefficient	P value
Age	0.498	0.000	0.49	0.000
Total bilirubin	0.054	0.361	-0.082	0.204
MPV	-0.052	0.37	-0.017	0.783
GFR	-0.025	0.698	-0.076	0.28
Hemoglobin	-0.222	0.001	0.058	0.416
Past medical history of				
Hypertension	-0.047	0.425	0.078	0.23
Diabetes mellitus	0.053	0.365	0.071	0.263
Stroke	0.26	0.000	0.232	0.000
IHD	-0.079	0.179	-0.059	0.355
Smoking	0.049	0.407	0.036	0.574

PVWMH, periventricular white matter hyperintensity; DWMH, deep white matter hyperintensity; MPV, mean platelet volume; GFR, glomerular filtration rate; IHD, ischemic heart disease. All values are corrected for the presence of all of the other variables in the table.

studies suggested that both types of WMH shared the same ischemic etiology while there were anatomical differences in the vascular supply between PVWMH and DWMH [10]. There is little collateral blood supply for arterioles (diameter $< 200 \mu\text{m}$) penetrating from pial surface arteries from 20 to 50 mm deep into white matter. Thus, periventricular white matter is more vulnerable to ischemia [8]. In our research, the relationship between Hb levels and MMSE scores was not statistically significant.

While our study provides important information regarding the role of Hb levels in PVWMH, we still need to take cautious when interpreting our data. First, the study subjects were patients who received their services in a single hospital, and the study population may not represent the general population, which likely limits our study power. However, our study provides important clues to the direction of future research in this important area. Second, we used only MMSE to evaluate cognitive function. Several evaluating batteries, more sensitive than the MMSE, may be needed for evaluating mild cognitive change in further studies.

In summary, our data demonstrate that lower Hb levels are associated with severity of PVWMH which have never been reported before. Future studies focusing on investigating the mechanism of this association would ultimately guide potential treatment options.

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Conflict of Interest

The authors declare no conflict of interest.

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