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Association between red blood cell distribution width (RDW) and carotid artery atherosclerosis (CAS) in patients with primary ischemic stroke

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ABSTRACT

Background: The present study aimed to explore the association between RDW and CAS in patients with ischemic stroke, expecting to find a new and significant diagnosis index for clinical practice.
Methods: This cross-sectional study involves 432 consecutive patients with primary ischemic stroke (within 72 h). All subjects were confirmed by magnetic resonance imaging, and underwent physical examination, laboratory tests and carotid ultrasonography check. Finally, 392 patients were included according to the exclusion criteria. The odds ratios of independent variables were calculated using stepwise multiple logistic regression.
Results: Carotid intimal-medial thickness (IMT) and RDW are both significantly different between CAS group and control group. Univariate analyses show that high-sensitive C-reactive protein (Hs-CRP) and RDW ($r = 0.436$) are both in significantly positive association with IMT. Stepwise multiple logistic regression shows that RDW is an independent protective factor of CAS in patients with ischemic stroke. Compared with the lowest quartile, the second to fourth quartiles are 1.13 (95% CI: 1.13–3.05), 2.02 (95% CI: 1.66–4.67), and 3.10 (95% CI: 2.46–7.65), respectively.
Conclusion: The present study suggested that RDW level were higher than non-CAS in patients with primary ischemic stroke. Our results facilitated a bridge to connect RDW with ischemic stroke and further confirmed the role of RDW in the progression of the ischemic stroke.

1. Introduction

RDW is an index of blood routine examination. It is usually used for the diagnosis of different types of anemia. RDW is recently suggested as an important factor of adverse events in the general population (Perlstein, Weuve, Pfeffer & Beckamn, 2009; Patel, Ferrucci, Ershler, Longo & Guralnik, 2009). RDW is also associated with many clinical outcomes of cardiovascular events, such as early-stage renal function damage and CAS in hypertensive patients (Li, Chen, Yuan, Zhou & Kuang, 2014; Wen, 2010), acute myocardial infarction (Sangoi et al., 2014; Sun et al., 2014) and heart failure (Shao, Li, Li & Liu, 2015). Since the confirmation of its association with inflammatory status (Lappe et al., 2011), growing attention has been paid to RDW in various fields.

Ultrasound examination of carotid IMT and carotid plaque is widely used in quantification of atherosclerosis, evaluation of future risk of stroke, and as surrogate endpoints for clinical diseases. Carotid plaque and IMT are associated with subclinical atherosclerosis, a risk factor of cerebral infarction or ischemic stroke (Everson-Rose et al., 2014; Savoiu et al., 2009). CAS is significantly related with inflammatory response of the vascular endothelial injury, while RDW is also involved in the process of inflammation (Almer et al., 2013). Therefore, RDW might be associated with CAS, which has never been studied in patients with ischemic stroke. Identification of early risk factors is greatly important for diseases such as stroke, which is featured with high rates of mortality and stroke-induced disability. The present study aims to explore the relationship between RDW and CAS in patients

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with ischemic stroke, expecting to find a new significant diagnosis index for clinical practice.

2. Methods

2.1. Study population

In this cross-sectional study, totally 432 consecutive patients with primary ischemic stroke were recruited from the Second Affiliated Hospital of Zhengzhou University from November 2013 and October 2014. All subjects were confirmed by magnetic resonance imaging (MRI), and underwent physical examination, laboratory tests and carotid ultrasonography check. The exclusion criteria are as follows: (1) history of ischemic stroke; (2) hemorrhagic stroke, mixed stroke or adenomas apoplexy; (3) second stroke due to other factors (e.g. surgery); (4) severe renal function impairment, gout, diabetic ketoacidosis, coronary bypass surgery or angioplasty; and (5) incapability of communication due to severe stroke. According to the above criteria, 40 patients were excluded and 392 patients were included. The study protocol was approved by the Ethics Committee at Southern Medical School of Zhengzhou University.

2.2. Physical and laboratory examinations

The patients' demographic characteristics including age, sex, height, weight, waist circumference, alcohol use and smoking status were acquired through a standardized questionnaire. Smoking was defined as at least one cigarette daily for 1 year and drinking was defined as at least 50 g of alcohol daily for 1 year. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2).

Hypertension was defined as systolic blood pressure (SBP) $\geq$ 140 mmHg and (or) diastolic blood pressure (DBP) $\geq$ 90 mmHg (Chobanian et al., 2003). Diabetes was determined through self-reporting with a validated history or through new diagnosis by an oral glucose tolerance test (WHO: fasting plasma glucose $\geq$ 7.0 mmol/L, or 2-h postprandial glucose $\geq$ 11.1 mmol/L (Kuzuya et al., 2002). Coronary artery disease was diagnosed from history of myocardial infarction or more than 75% narrowing of coronary artery.

Blood routine indices including red blood cell (RBC) count, white blood cell (WBC) count, platelet count, hemoglobin count, RDW and mean corpuscular volume were tested using an automated biochemical analyzer. Serum creatinine level, plasma glucose level, serum lipid status (total cholesterol, low- and high-density lipoprotein and triglyceride) and inflammatory factors (e.g. high-sensitive C-reactive protein, Hs-CRP) were also determined.

2.3. Carotid ultrasonography

Carotid ultrasonography on each subject was performed by a single sonographer with a commercial machine (ALOCA Prosound α5) with a linear probe at frequency of 7.5–10.0 Hz. The distal walls from the anterior, lateral and posterior longitudinal walls were recorded for carotid IMT. Both the left and right common carotid arteries were examined. IMT was calculated as mean of the bulb and common carotid segment measurements. Carotid plaque was defined as plaque encroaching into the arterial lumen by at least 0.5 mm or 50% of the surrounding IMT and IMT $\geq$ 1.5 mm (Touboul et al., 2012).

2.4. Statistical analysis

The patients were divided into a CAS group and a non-CAS group. Data were reported as mean ± standard deviation for qualitative variables and as percentages for quantitative variables. Distributional normality of each continuous variable was assessed by the Kolmogorov–Smirnov test. Between-group differences were tested by Student's *t*-test or Chi-square test, as appropriate. Correlation coefficients between IMT and other variables were calculated with Pearson's or Spearman's test, as appropriate. Odds ratios (ORs) were computed with multiple logistic regressions. Collinearity diagnostics within variables was applied before the regression model was built. Statistical analyses were performed on SPSS 18.0 (SPSS Inc., Chicago, IL, USA), with the significance level at $P < 0.05$.

3. Results

3.1. Baseline characteristics of subjects

The baseline characteristics are shown in Table 1. Totally 180 CAS patients and 212 non-CAS patients were finally included. The patients were aged from 60 to 70 years old. The sex ratios were comparable between groups. IMTs and RDWs are both significantly different between groups (both $P < 0.001$). Compared with the control group, the CAS group tended to be smokers, hypertensive and higher levels in BMI, waist circumference, SBP, DBP, triglyceride, total cholesterol, 2hPG, serum creatinine, uric acid, blood urea nitrogen, Hs-CRP, WBC and hemoglobin ($P < 0.05$). There is no difference in other variables between groups ($P > 0.05$). The results were shown in Table 1.

3.2. Univariate analyses

In the whole study population, HDL-cholesterol is negatively associated with IMT. IMT is positively and significantly associated with BMI, smoking status, SBP, triglyceride, serum creatinine, uric

Table 1
Clinical characteristics of ischemic stroke patients with and without CAS.

Parameters	Carotid artery atherosclerosis		P
	No (n = 212)	Yes (n = 180)	
Age (year)	65.9 ± 10.2	64.8 ± 9.8	0.279
Sex (male)	107 (50.5%)	94 (52.2%)	0.729
Smoking (yes)	47 (22.2%)	61 (33.9%)	0.009
Drinking history (yes)	21 (9.9%)	27 (15.0%)	0.125
Hypertension (yes)	84 (39.6%)	94 (52.2%)	0.013
Coronary artery disease (yes)	25 (11.6%)	19 (10.6%)	0.699
Diabetes mellitus (yes)	28 (13.2%)	26 (14.4%)	0.723
Body mass index (kg/m^2)	25.8 ± 2.8	26.6 ± 2.5	0.003
Waist circumference (cm)	88.3 ± 8.0	91.4 ± 8.2	<0.001
Systolic blood pressure (mmHg)	138.8 ± 9.3	141.8 ± 10.5	0.003
Diastolic blood pressure (mmHg)	78.5 ± 10.6	80.8 ± 11.2	0.037
Triglyceride (mmol/dL)	1.4 ± 0.5	1.7 ± 0.5	<0.001
HDL-cholesterol (mmol/dL)	1.1 ± 0.2	1.0 ± 0.2	<0.001
LDL-cholesterol (mmol/dL)	3.2 ± 1.0	3.3 ± 0.9	0.302
Total cholesterol (mmol/dL)	5.2 ± 0.9	5.4 ± 0.9	0.029
Fasting plasma glucose (mmol/dL)	5.6 ± 2.1	5.9 ± 2.3	0.178
2 h postprandial glucose (mmol/dL)	9.9 ± 3.6	10.6 ± 2.8	0.035
HbA1c (%)	5.9 ± 1.2	6.2 ± 1.8	0.050
Serum creatinine (mmol/dL)	68.3 ± 9.0	74.1 ± 10.5	<0.001
Serum uric acid (μmol/L)	353.9 ± 126.3	396.2 ± 125.8	0.001
Blood urea nitrogen (mmol/L)	4.7 ± 1.2	4.9 ± 1.1	0.011
Hs-CRP (mg/dL)	2.3 ± 0.7	2.6 ± 0.9	<0.001
Red blood cell ($\times 10^{12}$/L)	4.4 ± 0.4	4.6 ± 0.4	<0.001
White blood cell ($\times 10^9$/L)	5.8 ± 2.4	6.4 ± 2.5	0.016
Red cell distribution width (%)	13.4 ± 0.2	14.2 ± 0.4	<0.001
Blood platelet ($\times 10^9$/L)	210.6 ± 64	205.4 ± 54	0.390
Hemoglobin (g/L)	155.6 ± 13.4	149.2 ± 14.8	<0.001
IMT (mm)	0.84 ± 0.19	0.98 ± 0.13	<0.001