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Correlation between acute stroke-induced white matter lesions and insulin resistance

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Abstract

The present study was to examine the relationship between white matter lesions (WMLs) and insulin resistance (IR) in patients with acute stroke and evaluate clinical prognosis.

Around 200 patients with initial onset of acute stroke including 146 patients (73.0%) with WMLs and 54 patients (27%) without WMLs were analyzed by neuropsychological scales. Fasting blood glucose (FBG), fasting insulin, blood lipid, homocysteine (Hcy), high-sensitivity C-reactive protein (hs-CRP), creatinine, and uric acid, diabetes mellitus (DM), prediabetes (PD), and normal glucose (NG) were determined according to HbA1c levels. According to homeostasis model assessment (HOMA)-IR index of IR, HOMA-IR index ≥2.5 indicated IR, and HOMA-IR index < 2.5 represented noninsulin resistance (NON-IR).

IR values and the proportion of patients with IR, HbA1c levels and the quantity of DM patients, the levels of low-density lipoprotein cholesterol, Hcy, and hs-CRP of patients with WMLs were significantly higher than those in patients without WMLs (all $P < .05$). OR value of IR exposure and WMLs was 1.862 (1.235–2.236). OR values of level 1, level 2, and level 3 WMLs were 1.632 (1.032–2.532), 1.328 (1.152–2.865), and 1.158 (0.639–3.526), respectively. Regarding WMLs patients, MoCA and MMSE scores were significantly decreased, and Hamilton Depression Scale scores were significantly increased (all $P < .05$). National Institutes of Health Stroke Scale and modified Rankin scale scores of patients with WMLs were significantly increased, and BI scores were significantly decreased (all $P < .05$).

IR is intimately correlated with the WMLs of acute stroke. The incidence and severity of WMLs are significantly associated with cerebral arterial thrombosis, neuropsychology, and neurological scores.

Abbreviations: BI = Barthel index, DM = diabetes mellitus, DWI = diffusion weighted imaging, DWMH = deep white matter hyperintensity, FBG = fasting blood glucose, FLAIR = fluid attenuated inversion recovery, HAMD = Hamilton Depression Scale, Hcy = homocysteine, HDL-C = high-density lipoprotein cholesterol, HGF = hepatocyte growth factor, hs-CRP = high-sensitivity C-reactive protein, IR = insulin resistance, LDL-C = low-density lipoprotein cholesterol, MMSE = mini-mental state examination, MoCA = Montreal Cognitive Assessment, MRA = magnetic resonance angiography, MRI = magnetic resonance imaging, MRS = modified Rankin scale, NG = normal glucose, NIHSS = National Institutes of Health Stroke Scale, NON-IR = noninsulin resistance, PD = prediabetes, PVH = periventricular hyperintensities, TC = total cholesterol, TG = triglyceride, WMH = white matter hyperintensity, WMLs = white matter lesions.

Keywords: acute stroke, insulin resistance, neurological function, neuropsychology, white matter lesion

1. Introduction

White matter lesions (WMLs) are also known as leukoaraiosis (LA) and white matter hyperintensity (WMH). The magnetic resonance T2-weighted images and fluid attenuated inversion recovery (FLAIR) array are present as high signals.[1] WMLs have been recognized as the imaging characteristics of cerebral small vessel diseases.[2] WMLs are closely related to the disorders of cognitive function, gait, emotion, and urination, and are a major factor associated with functional disability of older people.[3] The risk of stroke recurrence in patients with severe WMLs is increased and the risk of early stage cerebral ischemic stroke recurrence can be independently predicted according to the severity of WMLs.[4] Age and hypertension are independent risk factors for determining WMLs.[5] Stroke history, diabetes, and hyperglycemia are risk factors that accelerate WMLs.[6] However, it is unclear if diabetes mellitus (DM) is a risk factor for WMLs, and the exact conclusions have not been reached in spite of the association between DM and severe WMLs.[7] There are few studies on the relationship between insulin resistance (IR), which is the primary mechanism of DM and WMLs. Therefore, this prospective cohort case-control study was performed to analyze the relationship between acute stroke WMLs and IR, and evaluate the clinical prognosis of acute stroke patients.

2. Methods

2.1. Patients and methods

2.1.1. Patients. A total of 200 patients initially diagnosed with acute stroke admitted to our hospital from January 2015 to June 2016 were consecutively selected. The study procedures were approved by the Ethics Committee of our hospital. Inclusion

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criteria: aged from 45–75 years; duration of acute stroke ≤ 1 week; complete data of imaging examination, blood biochemistry examination, and various assessment scales; the informed consent form was signed. Exclusion criteria: those with DM, and taking insulin or hypoglycemic drugs; those with cardioembolic stroke or hemorrhagic stroke; contraindications for undergoing inspection by magnetic resonance imaging (MRI), or cannot undergo MRI inspection; other secondary cerebral WMLs, such as multiple sclerosis, metabolic encephalopathy, toxic encephalopathy, tumors, familial diseases of the central nervous system, degenerative diseases, and infectious diseases; coma, epilepsy, dementia, and mental diseases; severe functional disorders of the heart, liver, kidney, and lung; simultaneous participation in other studies.

2.1.2. Research methods. The head MRI, magnetic resonance angiography (MRA), and diffusion weighted imaging (DWI) were performed within 24 hours after admission by 2 MRI physicians. The periventricular hyperintensities (PVH) and deep white matter hyperintensity (DWMH) were divided into 4 levels (levels 0–3) according to the Fazekas method. PVH: 0 referred to no lesion; 1 referred to calyptriform or pencil thin layer lesions; 2 referred to lesions that present as a smooth halo; 3 referred to irregular ventricular high signals, extending to the deep white matter. DWMH: 0 referred to no lesion; 1 referred to the punctiform lesion; 2 referred to lesion fusion; 3 referred to large-scale fusion of the lesion. Furthermore, 0 meant WML-negative while 1 to 3 meant WML-positive. Two physicians independently completed the analysis; when there was disagreement on the results, analysis was performed by a third MRI physician. The majority opinion was considered as the final result to judge the positive rate and degree of WMLs.

Assessment by neuropsychological scales included the Montreal Cognitive Assessment (MoCA), mini-mental state examination (MMSE), and Hamilton Depression Scale (HAMD). MoCA comprised 11 parameters in 8 cognitive fields including attention and concentration, executive function, memory, language, visual structure skill, abstract thought, calculation, and orientation. The total score was 30, and a normal score was ≥ 26. When the period of education of the tested patients was < 12 years, 1 point was added to the total score. The test time was 10 minutes. For MMSE, a score of 27 to 30 was considered normal; a score of < 27 was considered as cognitive disorder. We used the version of the 17-item HAMD, and each of them adopted a 5-level scoring method with 0 to 4 points, where 0 referred to no depression; 1 referred to light degree of depression; 2 referred to medium degree of depression; 3 referred to severe degree of depression; and 4 referred to extremely severe degree of depression. Each estimation was performed for 20 minutes; the results were obtained according to the Davis JM method; total score ≥ 35 indicated severe depression; total score ≥ 20 indicated medium depression; and total score < 8 indicated no depression.

Neurological function was scored using the National Institutes of Health Stroke Scale (NIHSS), modified Rankin scale (MRS), social participation ability, and Barthel index (BI). NIHSS comprised consciousness, stare, vision, facial paralysis, upper and lower limb movement, ataxia, feeling, language, dysarthria, and neglect; higher score implied poorer function. The levels ranged from 0 to 6 (no symptoms to death); lower score implied better prognosis. BI comprised 10 parameters such as control of defecation, make up, going to the washroom, eating, moving a bed and chair, exercise on the ground, putting on clothes, walking up and down stairs, and taking a shower; each parameter was divided into 4 levels: 0, 5, 10, and 15 points, with 100 points in total. A higher score implied better clinical prognosis.

Routine analysis included fasting blood glucose (FBG), fasting insulin, total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), homocysteine (Hcy), high-sensitivity C-reactive protein (hs-CRP), creatinine, and uric acid.

Diabetes mellitus (DM), prediabetes (PD), and normal glucose (NG) were determined according to the level of HbA1c. DM referred to HbA1c ≥ 6.5%; PD was 5.7% to 6.4%; and NG was < 5.7%. The homeostasis model assessment (HOMA)-IR index of insulin resistance was calculated as follows: HOMA-IR = FIN (μU/mL) × FBG (mmol/L) / 22.5; HOMA-IR index ≥ 2.5 indicated IR, while HOMA-IR index < 2.5 indicated noninsulin resistance (NON-IR).

2.1.3. Statistical analysis. Data were analyzed with SPSS 18.0 statistical software. Continuous variables with normal distribution are presented as mean ± standard deviation, and were compared by *t*-test. Continuous variables with skewed distribution are presented as the P25–P75 and were compared with the Mann–Whitney *U* test. Classified variables are presented as percentage and were compared by χ^2-test. The dichotomy logistic method was adopted to analyze the relationship between IR and the risk of WMLs. The classified logistic approach was adopted to analyze the relationship between IR and different severity of WMLs. The linear dependence/curvilinear correlation or rank correlation analysis were employed to analyze the dependency of the measurement data. $P < .05$ was considered as statistically significant.

3. Results

3.1. The relationship between WMLs and IR

A total of 146 patients were diagnosed with WMLs (73.0%) and 54 patients without WMLs. Among them, 130 patients with PVH (36.11%) including 40 patients with level 1, 52 with level 2 and 38 with level 3. There were 133 patients with DWMH (36.94%) including 45 patients with level 1, 48 with level 2, and 40 with level 3. IR values and the proportion of IR patients among those with WMLs were significantly higher than those in patients without WMLs. The levels of HbA1c and proportion of DM patients among those with WMLs were significantly higher compared with those in patients without WMLs. The levels of LDL-C, Hcy, and hs-CRP in patients with WMLs were significantly higher than those in patients without WMLs (all $P < .05$). FBG, fasting insulin, TC, TG, HDL-C, and creatinine levels did not significantly differ between patients with and without WMLs (all $P > .05$), as illustrated in Table 1. OR value between IR exposure and WMLs was 1.862 (95% CI=1.235–2.236). OR value between IR exposure and level 1 WMLs was 1.632 (95% CI=1.032–2.532). OR value for level 2 was 1.328 (95% CI=1.152–2.865), and 1.158 for level 3 (95% CI= 0.639–3.526).

3.2. The relationship between WMLs and neuropsychological scale scores

The MoCA and MMSE scores of patients with WMLs were significantly decreased (both $P < .05$). The HAMD scores were considerably increased with statistical significance ($P < .05$), as demonstrated in Table 2.

Table 1

Relationship between WMLs and IR.

Group	WML (n = 146)	No WML (n = 54)	$t/\chi 2$	P
Male/female	85/61	36/18	1.177	.278
Age, years	62.4 ± 12.3	53.2 ± 11.7	7.624	.000
Hypertension [percentage (%)]	80 (54.8)	20 (37.0)	4.972	.026
HbA1c (%)	6.3 ± 0.5	5.9 ± 0.6	6.539	.008
DM [percentage (%)]	67 (45.9)	9 (16.7)	24.027	.000
PD [percentage (%)]	51 (34.9)	17 (31.5)		
NG [percentage (%)]	28 (19.2)	28 (51.9)		
FBG, mmol/L	6.2 ± 1.3	6.0 ± 1.2	0.236	.852
Fasting insulin, μU/mL	16.7 ± 4.5	14.2 ± 3.8	0.362	.754
IR	2.9 ± 0.7	2.3 ± 0.5	5.964	.012
IR [percentage (%)]	80 (54.8)	14 (25.9)	13.188	.000
TC, mmol/L	5.8 ± 1.3	5.6 ± 1.4	0.321	.743
TG, mmol/L	1.3 ± 0.3	1.2 ± 0.4	0.206	.832
LDL-C, mmol/L	4.7 ± 1.1	4.2 ± 1.3	5.532	.019
HDL-C, mmol/L	0.8 ± 0.2	0.7 ± 0.2	0.182	.934
Hcy, μmol/L	26.4 ± 6.3	18.2 ± 6.7	6.235	.008
hs-CRP, mg/L	15.3 ± 5.4	7.6 ± 3.2	6.954	.000
Creatinine, μmol/L	126.5 ± 35.4	133.8 ± 42.2	0.268	.765
Uric acid, mmol/24 h	2.2 ± 0.6	2.1 ± 0.7	0.163	.867

DM = diabetes mellitus, FBG = fasting blood glucose, HbA1c = glycosylated hemoglobin, Hcy = homocysteine, HDL-C = high-density lipoprotein cholesterol, hs-CRP = high-sensitivity c-reactive protein, IR = insulin resistance, LDL-C = low-density lipoprotein cholesterol, NG = normal glucose, PD = prediabetes, TC = total cholesterol, TG = triglyceride, WML = white matter lesion.

3.3. The relationship between WMLs and neurological score

The NIHSS and MRS scores in patients with WMLs were significantly increased, whereas the BI score was significantly decreased with statistical significance (all $P < .05$), as shown in Table 3.

4. Discussion

The incidence rate of WMLs is 27% to 95.6% in the elderly population, aged > 65 years. The onset rate of WMLs in patients with cerebral ischemic stroke and transient ischemic attack is 42.4% to 52.6%, approximately 2/3 of patients with dementia and 1/3 of patients with Alzheimer's disease are complicated with WMLs.[8] The morbidity rate associated with WMLs increases over aging, which is referred as "age-related white matter lesions."[9] The WMLs adjacent to the ventricle are related to the decline of cognitive function. However, WMLs in the subcortex may be associated with the late-onset of depression.[10] A meta-analysis that included 23 cross-sectional and 14 longitudinal studies, consisted of 8685 and 7731 patients and indicated that WMLs were significantly related to the damage of all cognitive domains including general intelligence, memory, speed of processing information, attention, executive function, and cognitive restructuring.[11] Furthermore, the development of WMLs is correlated with severe cognitive impairment, such as general intelligence, attention, and executive function. By applying BI and MRS to evaluate neurological function after acute stroke, PVH has been found to be related to poor functional results.[12] The loose volume of cerebral white matter is a factor for predicting the clinical outcomes after acute stroke. Such relationship still exists after the adjustment of prognostic factors, such as age, severity of initial onset of stroke and cerebral infarction volume.[13]

Table 2

Relationship between WMLs and neuropsychological scale scores.

Group	WMLs	No WMLs	t	P
MoCA	22.5 ± 5.7	25.6 ± 6.3	5.632	.015
MMSE	23.5 ± 6.2	26.8 ± 6.7	5.847	.010
HAMD	28.7 ± 9.2	21.5 ± 8.3	6.231	.006

HAMD = Hamilton Depression Scale, MMSE = mini-mental state examination, MoCA = Montreal Cognitive Assessment, WML = white matter lesion.

Table 3

Relationship between WMLs and neurological scores.

Group	WML	No WML	t	P
NIHSS	65.6 ± 13.2	45.3 ± 12.5	6.539	.004
MRS	52.8 ± 14.5	36.9 ± 11.3	6.214	.008
BI	73.5 ± 14.3	82.3 ± 13.9	5.823	.011

BI = Brathel score, MRS = modified Rankin scale, NIHSS = National Institute of Health Stroke Scale, WML = white matter lesion.

The metabolic syndrome includes abdominal obesity, hypertension, hyperglycemia, and dyslipidemia, which are significantly associated with WMLs.[14] Portet et al[15] analyzed 308 participants in the French ESPRIT longitudinal study and found that the WML volume of patients with metabolic syndrome was two times of that without metabolic syndrome after the adjustment of potential confounding factors. Furthermore, metabolic syndrome is related to increasing WML volume of the temporal and parietal lobes. The relationship between IR and stroke is not completely understood. Rundek et al[16] performed follow-up studies on subjects without stroke and patients with DM from multiple countries. They have found that IR is a primary factor for increasing the risk of stroke in subjects without DM. However, Wieberdink et al[17] performed a prospective cohort study on the elderly patients without DM and yieled the conflicting results that IR is not related to the risk of stroke and stroke subtype. Anan et al[18] performed a study on Japanese patients with type 2 diabetes mellitus (D2TM), and found that the IR of patients with positive WMLs was significantly increased compared with those with negative WMLs. Additionally, IR, high-sensitivity C-reactive protein, hepatocyte growth factor (HGF), hyperhomocysteinemia, microalbuminuria, and visceral fat accumulation were not significantly related to WMLs.

In the present study, roughly 73.0% of patients with acute stroke presented with WMLs, among whom there were 36.5% with PVH and 36.5% with DWMH. Regarding patients with WMLs, IR values and the proportion of patients with IR were significantly increased. The levels of HbA1c and quantity of patients with DM were also significantly increased. The levels of LDL-C, Hcy, and hs-CRP were significantly increased. However, FBG, fasting insulin, TC, TG, HDL-C, creatinine, and uric acid did not significantly differ. The OR value of IR exposure and WMLs was 1.862. The OR value of level 1 WMLs was 1.632. The OR value of level 2 was 1.328. The OR value of level 3 was 1.158. Regarding patients with WMLs, MoCA and MMSE scores were significantly decreased, whereas the HAMD scores were increased. The NIHSS and MRS scores were significantly increased, whereas the BI scores were decreased.

In conclusion, insulin resistance is significantly correlated with WMLs in patients diagnosed with acute stroke. The incidence and severity of WMLs are intimately related to the

neuropsychology and neurological scores of cerebral arterial thrombosis.

5. Study limitation

The sample size in current study is relatively small, and more studies with larger sample size are urgently required to further validate the hypothesis and conclusion. In addition, this is a single center study. Multicenter clinical trials remain to be performed.

Author contributions

Conceptualization: C.-j. You, G. Li.
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