Reduced Serum Adiponectin Level and Risk of Poststroke Depression in Patients with Ischemic Stroke

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Background and Aims: Decreased adiponectin (APN) level has been indicated to be associated with depression. In the present study, we aimed to investigate whether serum APN could predict poststroke depression (PSD) at 3 months in patients with acute ischemic stroke. *Method:* Patients with first-ever ischemic stroke and hospitalized within 24 hours of symptoms onset were enrolled prospectively during March 2017 to September 2017. Serum APN level was measured at admission by enzyme-linked immunosorbent assay. Neuropsychological evaluations were performed at the 3-month follow-up. PSD was diagnosed using the Chinese version of the Structured Clinical Interview for DSM-IV. The association between APN level and predict PSD was analyzed by binary logistic regression analysis. *Results:* Of the 255 acute ischemic stroke patients included, the median (interquartile range) APN level was 5.4 (3.0-7.5) μg/mL. PSD was observed in 69 patients, which accounted for 27.1% (95% confidence interval, 24.3%-29.9%) of the cohort. Patients with PSD showed lower level of APN (3.5 [2.5-6.3] μg/mL versus 6.2 [3.5-8.0] μg/mL, $P = .001$) at admission. Univariate logistic regression analysis indicated that patients with APN level in the first tertile compared with the third tertile were more likely to have PSD (odds ratio, 3.550; 95% confidence interval, 1.732-7.276; $P = .008$). The association remained significant even after multivariable adjustment for potential confounders. *Conclusions:* This study demonstrated that decreased APN level at admission might be associated with PSD in patients after acute ischemic stroke.

Key Words: Adiponectin—poststroke depression—ischemic stroke—Biomarker

Introduction

Stroke has been ranked as the first leading cause of mortality and long-term disability in China.[1] Poststroke depression (PSD) is the most frequent affective disorder that affects approximately a third of stroke survivors.[2-4] The recognition and diagnosis of PSD is important because it may portend a higher risk of mortality and increased dependency in daily living.[4-6] PSD has also been reported as an independent risk factor for recurrent stroke.[7] However, the potential pathophysiological mechanisms involved in PSD still remained unclear.

Adiponectin (APN) is the most abundant circulating adipocytokine synthesized and secreted from the adipose tissue. It operates on many processes such as insulin resistance, systemic inflammation, and endothelial function.[8-10] In humans, it has been consistently indicated that low APN concentration is associated with metabolic syndrome, atherosclerosis, and cardiovascular disease.[11-14] Moreover, regarding the involvement of APN in

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hypothalamic-pituitary-adrenal axis, the level of APN has been hypothesized to be correlated with the development of psychiatry diseases.[15] Previous studies have reported that decreased circulating level of APN in adult patients was associated with major depression.[16-18] To date, however, the influence of APN on the development of PSD has not yet been clarified.

We therefore performed this prospective study to evaluate the possible association between serum APN level and PSD in the Chinese cohort with acute ischemic stroke.

Methods

Study Populations

The subjects were first-ever acute ischemic patients who were hospitalized at Sichuan Provincial People's Hospital during the period from March 2017 to September 2017. Those who aged 18 years or older and received evaluations within 24 hours of symptom onset were included in the study. Exclusion criteria were: prestroke diagnosis of any psychiatric illness, decreased level of consciousness and severe aphasia that precluded us from performing the evaluation, history of any central nervous system disease, severe hepatic or renal disease, autoimmune disease, thyroid hormone disorders, life expectancy less than 3 months, and lost to follow-up. We also excluded the patients who were using psychotropic drugs prior to stroke onset. The study protocol was approved by the institutional review board of Sichuan Provincial People's Hospital. All subjects provided written informed consent before entering the study.

Clinical Data

Data collection was performed using a standardized case report form. Demographic characteristic, vascular risk factors (including hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, current smoking, and drinking), systolic and diastolic blood pressure, body mass index, stroke severity and etiology, imaging data, and laboratory results were all recorded. Stroke severity was assessed by certified neurologist using National Institutes of Health Stroke Scale (NIHSS) at admission. Stroke etiology was classified according to TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria.[19]

Blood Collection and APN Level Measurement

Blood samples were obtained from each subject within 24 hours after admission. The specimens were centrifuged at 1500 g for 10 minutes and the isolated serum frozen at −80°C for later analysis. APN concentration was measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits (EZHMWA-64K, Merck Millipore, Burlington, MA). The variation coefficients of intra- and interassay for the biochemical assays were 3.0%-8.8% and 1.8%-6.1%, respectively. All procedures were performed in strict accordance to manufacturers' instructions.

Psychological Evaluation

Psychological evaluation was performed at 3 months after stroke by the same trained psychologist who was blinded to the laboratory results and clinical data. All patients were screened for depressive symptoms using the 17-item Hamilton Depression Scale.[2] Patients with a Hamilton Depression Scale score greater than or equal to 7 were further assessed using the Chinese version of structured clinical interview of DSM-IV, for diagnosing the PSD.[3,20,21] Limited intrarater reliability testing (50 patients) demonstrated a good reliability with kappa values of .89 for the diagnosis of PSD.

Statistical Analysis

The statistical analysis was performed using SPSS version 23.0 (SPSS Inc., Chicago, IL). Continuous variables were presented as the means (standard deviation, SD) or median (interquartile range, IQR), and categorical variables were expressed as n (%). Differences in baseline variables stratified by tertile of APN level were determined using χ^2, analysis of variance, or Kruskal-Wallis where appropriate. Binary logistic regression analysis was performed for the evaluation of possible risk factors for PSD after acute ischemic stroke. Multivariable logistic regression analysis was performed adjusting the potential confounders with the P value less than .10 in the univariate analysis. We also performed the receiver operating characteristic (ROC) curves to describe APN concentration as a potential predictive factor for PSD. The area under curve (AUC) was calculated based on the ROC curves. The level of statistical significance was set at $P < .05$.

Results

In general, 255 patients (mean age, 62.1 ± 9.5 years; 45.9% female) with acute ischemic stroke were enrolled in this study. Of them, hypertension was present in 157 (61.6%), diabetes mellitus in 65 (25.5%), and hyperlipidemia in 44 (17.3%). The median (interquartile range) APN level was 5.4 (3.0-7.5) μg/mL, and the median (interquartile range) NIHSS score at admission was 4.0 (2.0-6.0) points. At the 3 months of follow-up, PSD was observed in 69 patients (27.1%). Among them, 30 patients (11.8%) had major depression, and 39 (15.3%) had minor depression.

Baseline epidemiological and clinical characteristics of the study population stratified by the APN tertile were shown in Table 1. Decreasing tertile of APN was associated with male sex ($P = .013$), diabetes mellitus ($P = .004$), coronary heart disease ($P = .013$), white matter lesions ($P = .003$), PSD ($P = .001$), and higher level of body mass index ($P = .011$), triglyceride ($P = .008$), hypersensitive C-reactive protein ($P = .003$), fasting blood glucose ($P = .004$), and homocysteine ($P = .023$).

Table 1. *Baseline characteristics of the study population according to the APN tertile*

Variable	Total patients (n = 255)	APN tertile			*P* value
		1st (<3.7 μg/mL, n = 85)	2nd (3.7-6.8 μg/mL, n = 85)	3rd (>6.8 μg/mL, n = 85)	
Age, year	62.1 ± 9.5	61.6 ± 9.0	61.1 ± 10.0	63.6 ± 9.5	.191
Female sex, %	117 (45.9)	28 (32.9)	45 (52.9)	44 (51.8)	.013
Risk factors, %					
Hypertension	157 (61.6)	60 (70.6)	50 (58.8)	47 (55.3)	.100
Diabetes mellitus	65 (25.5)	33 (38.8)	20 (23.5)	12 (14.1)	.004
Hyperlipidemia	44 (17.3)	16 (18.8)	16 (18.8)	12 (14.1)	.644
Coronary heart disease	23 (9.0)	14 (16.5)	4 (4.7)	5 (5.9)	.013
Current smoking	106 (41.6)	33 (38.8)	40 (47.1)	33 (38.8)	.453
Current drinking	69 (27.1)	22 (25.9)	29 (34.1)	18 (21.2)	.158
Clinical data					
NIHSS, score	4.0 (2.0, 6.0)	5.0 (3.0, 8.0)	4.0 (2.0, 6.0)	4.0 (2.0, 6.0)	.066
White matter lesions, %	108 (42.4)	48 (56.5)	34 (40.0)	26 (30.6)	.003
Silent lacunar infarcts, %	126 (49.4)	38 (44.7)	43 (50.6)	45 (52.9)	.542
Previous antiplatelet, %	78 (30.6)	24 (28.2)	26 (30.6)	28 (32.9)	.801
Previous statin, %	65 (25.5)	23 (27.1)	24 (28.2)	18 (21.2)	.527
Poststroke depression, %	69 (27.1)	35 (41.2)	20 (23.5)	14 (16.5)	.001
Systolic blood pressure, mmHg	136.9 ± 16.8	135.4 ± 16.4	136.4 ± 17.4	139.0 ± 16.7	.350
Diastolic blood pressure, mmHg	80.9 ± 9.9	80.9 ± 10.0	81.8 ± 8.9	80.1 ± 10.9	.587
Body mass index, kg/m^2	24.8 ± 3.0	25.4 ± 3.7	25.3 ± 3.2	24.1 ± 3.0	.011
Stroke etiology, %					.484
Large artery atherosclerosis	140 (54.9)	50 (58.8)	48 (56.5)	42 (49.4)	
Cardioembolism	19 (7.5)	6 (7.1)	5 (5.9)	8 (9.4)	
Small artery occlusion	73 (28.6)	20 (23.5)	23 (27.1)	30 (35.3)	
Other determined	9 (3.5)	2 (2.4)	5 (5.9)	2 (2.4)	
Undetermined	14 (5.5)	7 (8.2)	4 (4.7)	3 (3.5)	
Laboratory data					
Total cholesterol, mmol/L	4.0 ± 1.0	3.9 ± .9	4.0 ± 1.0	4.1 ± 1.2	.863
Triglyceride, mmol/L	1.4 (1.1, 1.8)	1.5 (1.1, 2.6)	1.4 (1.0, 1.8)	1.4 (1.0, 1.7)	.008
Low-density lipoprotein, mmol/L	2.3 (1.9, 2.9)	2.4 (1.7, 2.9)	2.4 (1.9, 2.9)	2.3 (1.8, 2.9)	.087
High-density lipoprotein, mmol/L	1.0 (.9, 1.2)	1.0 (.8, 1.2)	1.1 (.9, 1.2)	1.0 (.9, 1.2)	.641
Hs-CRP, mg/L	4.1 (2.0, 8.7)	8.6 (3.7, 12.7)	2.9 (1.5, 6.7)	2.8 (1.5, 5.8)	.003
Fasting blood glucose, mmol/L	5.6 ± 2.2	6.3 ± 2.6	5.5 ± 1.7	5.1 ± 2.1	.004
Homocysteine, mmol/L	15.4 ± 4.9	16.4 ± 4.6	15.6 ± 4.7	14.4 ± 5.1	.023

Abbreviations: APN, adiponectin; Hs-CRP, hypersensitive C-reactive protein; NIHSS, National Institutes of Health Stroke Scale.

Table 2 summarized the results of the binary logistic regression of PSD. Univariate logistic regression analysis demonstrated that advanced age, NIHSS score, white matter lesions, silent lacunar infarcts, high level of hypersensitive C-reactive protein, and low APN level were associated with increasing risk of PSD. Moreover, after adjusting for potential confounders, the lowest tertile of APN level (odds ratio [OR], 3.225; 95% confidence interval [CI], 1.440-7.218; $P = .004$) was identified as a risk factor of PSD. The ROC curve analysis demonstrated the optimal cut-off value of serum APN level as a 3-month PSD indicator was estimated to be 3.5 μg/mL, which yielded a sensitivity of 74.7% and a specificity of 52.5%, with the area under curve at .640 (95% CI, .565-.746).

Discussion

In this hospital-based study of acute ischemic stroke patients, we demonstrated that APN level is an important biological marker of the risk for PSD.

APN has been reported to possess anti-inflammatory, antiatherogenic, and insulin-sensitizing properties.[8-10,13] Its expression is significantly and inversely associated with metabolic syndrome, traditional risk factors for cardiovascular disease, and carotid intima-media thickness,[11-14,22] suggesting a favorable cardiovascular effect of APN. In our present study, lower serum level of APN within 24 hours after admission was found in patients with worse neurological deficit. However, it has been

Table 2. *Univariate and multivariate logistic regression analysis for risk factors with PSD*

	Univariate logistic regression analysis		Multivariate logistic regression analysis	
Variable	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.031 (1.000-1.063)	.049	1.042 (1.006-1.079)	.021
Female sex	1.028 (.590-1.789)	.923		
Risk factors				
Hypertension	1.769 (.975-3.211)	.061	1.861 (.943-3.671)	.113
Diabetes mellitus	1.157 (.619-2.160)	.648		
Hyperlipidemia	1.504 (.750-3.016)	.250		
Coronary heart disease	1.200 (.471-3.054)	.703		
Current smoking	.737 (.417-1.302)	.293		
Current drinking	1.141 (.618-2.109)	.673		
Clinical data				
NIHSS	1.086 (1.005-1.173)	.036	1.079 (.988-1.177)	.090
White matter lesions	1.873 (1.072-3.272)	.028	1.669 (.860-3.327)	.130
Silent lacunar infarcts	1.889 (1.076-3.317)	.027	2.107 (1.089-4.078)	.041
Previous antiplatelet	.842 (.484-1.236)	.164		
Previous statin	.674 (.345-1.316)	.248		
Systolic blood pressure	.998 (.983-1.016)	.909		
Diastolic blood pressure	.991 (.964-1.019)	.536		
Body mass index	1.019 (.931-1.116)	.679		
Stroke etiology				
Large artery atherosclerosis	.677 (.389-1.179)	.168		
Cardioembolism	1.637 (.617-4.345)	.322		
Small artery occlusion	1.127 (.616-2.064)	.697		
Other determined	2.428 (.793-9.090)	.109		
Undetermined	.800 (.214-2.997)	.741		
Laboratory data				
Total cholesterol	.880 (.665-1.164)	.369		
Triglyceride	1.029 (.774-1.369)	.842		
Low-density lipoprotein	.954 (.698-1.304)	.766		
High-density lipoprotein	1.489 (.766-2.893)	.240		
Hypersensitive C-reactive protein	1.037 (1.012-1.065)	.007	1.031 (1.007-1.055)	.011
Fasting blood glucose	1.005 (.889-1.137)	.935		
Homocysteine	1.031 (.975-1.092)	.282		
Adiponectin level				
First tertile	3.550 (1.732-7.276)	.008	3.225 (1.440-7.218)	.004
Second tertile	1.560 (.729-3.341)	.252	1.529 (.656-3.566)	.325
Third tertile	Reference		Reference	

Abbreviations: CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PSD, poststroke depression.

Multivariable analysis was further adjusted for age, hypertension, NIHSS score, white matter lesions, silent lacunar infarcts, and hypersensitive C-reactive protein levels.

reported that patients with higher APN level were susceptible to develop severe stroke at admission or impaired neurological function during their recovery.[23] These distinct findings may be due to different study design, criteria for the recruitment of study populations, and time of assessment.

Our results showed that 27.1% of patients who suffered an acute ischemic stroke present with depression at 3 months, which is consistent with earlier studies.[3,24-26] We also found that patients with lower APN concentration had higher NIHSS score, and increased prevalence of diabetes mellitus and white matter lesions. Severe neurological deficit is a well-established risk factor for PSD. Moreover, cerebral small vessel disease markers, including white matter lesions, were proved to be positively correlated with PSD occurrence.[3] The relationship between APN and PSD might be explained by the abovementioned factors. Whereas, APN level at baseline was associated with PSD after controlling for potential confounders, for instance: age, hypertension, NIHSS score, white matter lesions, silent lacunar infarcts, and hs-CRP level. Therefore, other possible mechanisms should be considered.

Our main findings indicated that decreased serum APN level might be associated with the development PSD at 3 months. Although the biological mechanisms by which decreased APN concentration affects PSD are not entirely clear, several findings may support the association. First, chronic inflammation has been widely recognized as an important mechanism related to PSD.[27] Acute ischemic stroke triggers a widespread inflammatory response, characterized by rapid upregulation of proinflammatory cytokines,[28] disrupting blood-brain barrier and contributing to neurodegeneration.[29] However, APN might induce the production of anti-inflammatory molecules, such as Interleukin-1 and Interleukin-10 receptor antagonist.[30] APN-deficient mice showed an activation proinflammatory cascade, a higher expression of tumor necrosis factor, for instance.[31] Second, oxidative stress has received considerable attentions as an important contributor involved in PSD.[32-34] Previous evidence suggested that APN could attenuate NADPH oxidase-mediated oxidative stress and neuronal damage induced by cerebral ischemia-reperfusion injury.[35] Therefore, the anti-inflammatory and antioxidative stress characteristics of APN may protect against depression development after ischemic stroke. In addition, adipose PPARγ-adiponectin axis plays an important role in the pathophysiology of depression/anxiety-related behaviors.[36] Downregulated APN expression in peripheral circulation was noted in patients with depression.[36,37] This also provides the basis for a correlation between APN and PSD.

The strengths of our study include using a standardized research method, recruiting a homogeneous group of ischemic stroke patients, and the extensive neuropsychological assessment, all of which made it possible to evaluate associations between APN and PSD. Additionally, the demographic characteristics, clinical information, and laboratory results of all patients were collected in a prospective design. Nevertheless, our study had several limitations. First, the study was conducted in only 1 center with small sample size. Second, APN concentration was measured only once at admission. Assessing longitudinal changes of APN level could provide meaningful insights into the presence of PSD. Third, patients with severe aphasia, severe neurological deficits, and died before the 3-month follow-up were all excluded, which might underestimate the prevalence of PSD and limit the generalizability of our findings. Finally, we did not include information that may influence depression, including socioeconomic status and premorbid personality. These issues should be addressed in future large longitudinal studies.

In summary, the present study showed that decreased APN level is significantly associated with the development of PSD at 3 months. Given the association of PSD with unfavorable functional outcomes, APN level may be a valuable predictor of prognosis in patients with acute ischemic stroke. Further longitudinal studies with large sample size are warranted to evaluate these associations comprehensively.

Conflict of Interest

All the authors declare that there is no conflict of interest.

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