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# Association of lower serum Brain-derived neurotrophic factor levels with larger infarct volumes in acute ischemic stroke

Hui-Jie Qiao[a], Zhen-Zhi Li[a], Li-Ming Wang[a], Wei Sun[a], Jin-Chao Yu[a], Bin Wang[b,*]

[a] Department of Radiology, Weihai Municipal Hospital, Binzhou Medical University, Weihai, China
[b] Medical Imaging Research Institute, Binzhou Medical University, Yantai, China

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ABSTRACT

*Objective:* Brain-derived neurotrophic factor (BDNF) plays a potential role in stroke recovery, as it promotes plasticity. The aim of this study is to investigate the association between infarct volume using DWI and BDNF at admission in patients with acute ischemic stroke (AIS).

*Methods:* The study population comprised consecutive patients with an AIS diagnosis who had been referred to our hospital between January 2015 and June 2016. The severity of stroke was evaluated by the National Institutes of Health Stroke Scale (NIHSS) at admission. Infarct volumes indicated by DWI were measured with MIPAV software. The relationship between median DWI infarct volume and serum BDNF level quartiles was evaluated using a semiparametric approach with univariate and multivariate quartile regression analysis.

*Results:* In this study, 270 patients were included and met the study criteria. The median DWI infarct volumes for the serum BDNF level quartiles (lowest to highest) were 10.56, 5.13, 3.75 and 2.43 ml. Nonparametric Spearman rank correlation revealed a statistically significant negative correlation between serum BDNF level and DWI infarct volume ($r = -0.363$; $P < 0.001$). The median DWI infarct volume in the lowest BDNF quartile was significantly larger than those in the upper 3 quartiles ($P < 0.001$). Further, median adjusted DWI infarct volumes (IQR) for each of the BDNF level quartiles were 7.77, 4.56, 3.75, and 2.43 ml from lowest to highest quartiles.

*Conclusions:* Larger stroke infarct volumes using DWI are associated with lower levels of BDNF at admission. Further investigations are suggested to elucidate the role of BDNF as part of a potential neuroprotective strategy.

## 1. Introduction

Stroke is the leading cause of adult disability in the world. In China, 2.5 million people suffer a stroke each year and there are 7.5 million stroke survivors (Qiu et al., 2016). Approximately 15% to 30% of stroke survivors will be permanently disabled (Bonita et al., 2004). Those patients are a huge financial burden for health care systems.

Neurotrophins are an important class of signaling molecules in the brain responsible for axon targeting, neuron growth, maturation of synapses during development, and synaptic plasticity (Autry and Monteggia, 2012). Brain-derived neurotrophic factor (BDNF) is a member of a family of neurotrophins related by sequence homology and was originally identified as a factor that promoted the survival of cultured embryonic chick sensory neurons (Molendijk et al., 2011). BDNF is involved in neuronal survival, synaptic plasticity, learning and memory, and neuroplasticity. Previous observational studies have suggested that low circulating levels of BDNF concentrations were associated with brain injury (Pikula et al., 2013), functional outcome (Wang et al., 2016; Stanne et al., 2016) and post-stroke depression following stroke (Li et al., 2014).

Interestingly, one study identified a critical role for BDNF in rehabilitation-induced recovery after stroke (Ploughman et al., 2009). Similarly, another study found that enhancement of BDNF production after stroke could be a useful means of improving neuroprotection and recovery after stroke (Chan et al., 2015). Furthermore, Schabitz et al., 1997 shown that pretreatment with intraventricular BDNF reduces infarct size after focal cerebral ischemia in rats. However, the relationship between BDNF and actual volumetric measurements of infarct size by diffusion-weighted imaging (DWI) has not been assessed previously in patients with ischemic stroke. In the present study, we therefore investigate the association between infarct volume using DWI and BDNF at admission in patients with acute ischemic stroke (AIS).

## 2. Materials and methods

The study population comprised consecutive patients with an AIS

* Corresponding author at: No.346, Guanhai Road, LaishanDistrict, Yantai 264003, Shandong Province, China.
*E-mail address:* Zluoybsh@126.com (B. Wang).

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diagnosis who had been referred to our hospital between January 2015 and June 2016. Ischemic stroke was defined according to World Health Organization recommendations (defined stroke as a "neurological deficit of cerebrovascular cause that persists beyond 24 h or is interrupted by death within 24 h") (Hatano, 1976). The clinical diagnoses were validated by magnetic resonance imaging (MRI). The exclusion criteria were malignant tumor, renal insufficiency (creatinine > 1.5 mg/dl), severe edema, without informed consents, lost blood samples, or current medications that influence serum BDNF levels and incomplete workups for cerebrovascular status.

One hundred healthy subjects were recruited at the same period from the Physical examination center in our hospital, and matched for sex and age. The control subjects had no subjective symptoms of stroke, and had similar exclusion criteria as the stroke patients. The median age was 65 (IQR, 56–72) years and 47% were women. The present study has been approved by the ethics committee of the Weihai municipal hospital of Binzhou Medical University. All participants or their relatives were informed of the study protocol, and their written informed consents were obtained.

Demographic data (age, sex, body mass index [BMI]) and the following vascular risk factors were collected: alcohol abuse, smoking habit, hypertension, diabetes mellitus, hypercholesterolemia, atrial fibrillation, previous myocardial infarction, peripheral vascular disease (PVD), and a history of transient ischemic attack (TIA). Pre-stroke therapy (anticoagulants and/or statins) and acute treatment (Tissue plasminogen activator-treated [TPA-T]) were also recorded. Stroke severity was assessed on admission using the National Institutes of Health Stroke Scale (NIHSS) by a neurologist. Strokes were classified according to the criteria of the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification and the clinical stroke syndrome was determined applying the criteria of the Oxfordshire Community Stroke Project (OCSP).

All blood samples were collected on the first day of admission under fasting state. Serum samples were kept at − 80 °C until assay. BDNF serum levels were measured with sandwich-ELISA, using a commercial kit according to the manufacturer instructions (DuoSet ELISA Development, R & D Systems, Inc., USA). The lower detection limit was 2.0 ng/ml and the line range was 2.0–100 ng/ml. Results of the other blood analyses, such as high-sensitivity-C-reactive protein (Hs-CRP), fasting blood glucose (FBG) and homocysteine (HCY) were also measured using routine laboratory methods.

Patients underwent imaging before receiving any reperfusion therapy using a 3.0-T scanner (Siemens Vision; Siemens Medical Systems, Erlangen, Germany) within 24 h of hospitalization. Infarct volumes indicated by DWI were measured with MIPAV software (Medical Image Processing, Analysis, and Visualization, version 3.0; NIH, Bethesda, MD) (Buck et al., 2007). Acute diffusion lesions were identified on a slice-by-slice basis using a semiautomatic segmentation method, consulting apparent diffusion coefficients to distinguish acute from nonacute diffusion signals. DWI infarct volumes were calculated by multiplying slice thickness by total areas of lesions.

Results are expressed as percentages for categorical variables and as medians (interquartile ranges, IQRs) for the continuous variables. The Mann-Whitney *U* test and Chi-square test were used to compare the two groups. Correlations among laboratory parameters were analyzed using Spearman's rank correlation test. The relationship between median DWI infarct volume and serum BDNF level quartiles was evaluated using a semiparametric approach with univariate and multivariate quartile regression analysis (Koenker and Hallock, 2001). For the multivariate models, the median DWI infarct volumes were corrected for potential confounding variables. Categorical variables (sex, stroke subtype, stroke syndrome, vascular risk factors, and prior or acute treatment) and continuous variables (age, BMI, time from onset to blood collection, time to MR imaging, NIHSS score and serum levels of Hs-CRP, HCY and FBG) were used as covariates. Results were expressed as adjusted odds ratios (OR) with the corresponding 95% Confidence interval (CI). All statistical analysis was performed with SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was defined as $P < 0.05$.

**Table 1**
Baseline characteristics of patients with stroke.

| | N = 270 |
|---|---|
| Age, years medians (IQRs) | 65(56–73) |
| Female, (%) | 126(46.7) |
| BMI, medians (kg/m$^2$, IQR) | 26.8(25.4–27.3) |
| Vascular risk factors, n (%) | |
| Hypertension | 175(64.8) |
| Diabetes | 106(39.3) |
| Coronary heart disease | 76(28.1) |
| Hypercholesterolemia | 85(31.5) |
| Atrial fibrillation | 38(14.1) |
| Previous TIA | 45(16.7) |
| Smoking habit | 56(20.7) |
| Pre-stroke treatment | |
| Antithrombotic use | 145(53.7) |
| Statin use | 84(31.1) |
| Acute treatment, TPA-T no. (%) | 58(21.5) |
| NIHSS at admission, medians (IQR) | 7(4–12) |
| Lesion volumes, median (ml, IQR) | 5.32(1.67–14.77) |
| Time from onset to inclusion (hr, IQR) | 5.1(2.8–7.5) |
| Time from admission to MR imaging, median (hr, IQR) | 7.5(4.6–12.5) |
| Stroke etiology no. (%) | |
| Cardioembolic | 80(29.6) |
| Small-vessel disease | 68(25.2) |
| Large-vessel atherosclerosis | 67(24.8) |
| Other | 32(11.9) |
| Unknown | 23(8.5) |
| Laboratory findings, medians (IQR) | |
| Hs-CRP, mg/dl | 0.42(0.21–1.24) |
| HCY, umol/l | 19.2(14.8–23.6) |
| FBG, mmol/l | 5.48(4.86–6.65) |
| BDNF, ng/ml | 22.1(14.5–27.5) |

IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; TPA-T: Tissue plasminogen activator-treated; Hs-CRP, high C-reactive protein; HCY, homocysteine; FBG, fasting blood glucose.

## 3. Results

### 3.1. Baseline characteristics of study samples

In this study, from 328 screened patients with acute ischemic stroke, 270 patients (24 with onset of symptoms > 24 h, 6 without informed consent, 8 without blood samples, 3 with malignant tumor, 4 with renal insufficiency and 13 unavailability of MRI results were not analyzed) were included and met the study criteria. Among 270 study patients, the median age was 65 years (IQR, 56–73 years), and 126 (46.7%) were women. The median (quartiles) NIHSS score on admission was 7 (4–12), and 102 patients (37.8%) had a minor stroke (NIHSS score ≤ 5). The baseline characteristics of the 270 patients presenting with acute ischemic stroke are described in Table 1.

Serum levels of BDNF were obtained at a median of 11.5 h (IQR, 4.5–16.8 h) after the stroke onset. Serum BDNF levels in patients with stroke were significantly lower than those controls [22.1(IQR, 14.5–27.5)ng/ml *vs.* 28.1(IQR, 18.1–36.8)ng/ml; $Z = 8.95$, $P < 0.001$]. There was a significantly negative correlation between levels of BDNF and NHISS ($r$ [spearman] $= -0.305$; $P < 0.001$). Further, there was still a significant negative trend between serum BDNF levels and NIHSS score ($P = 0.015$), using ordered logistic regression after multivariate adjustment for possible confounders: sex, age, BMI, lesion volumes, risk factors, stroke subtype and syndrome. There was significantly negative correlations between levels of BDNF and BMI ($r = -0.186$, $P = 0.011$), age ($r = -0.201$; $P = 0.003$) and HS-CRP ($r = -0.223$, $P < 0.001$). In addition, BDNF levels were with