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High serum nerve growth factor concentrations are associated with good functional outcome at 3 months following acute ischemic stroke

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ABSTRACT

Background: Previous studies in animal model have demonstrated that neurotrophins were associated with functional outcome following stroke. However, the relationship between serum nerve growth factor (NGF) and functional outcome in stroke patients has not been explored. Our objective was to investigate the association between serum NGF concentrations at admission and functional outcome of patients at 3 month after stroke.
Methods: One-hundred eight-five patients with acute ischaemic stroke were recruited in our study. Serum NGF concentrations were measured by ELISA at admission. The stroke severity at admission was assessed by the National Institute of Health Stroke Scale (NIHSS). The modified Rankin Scale (mRS) was used to assess the functional outcome of patients at 3 month after stroke. In addition, 100 healthy controls were recruited.
Results: Serum NGF concentrations were higher in good functional outcome group (mRS score of 0–2) than that in poor functional outcome group (mRS score of 3–6) (9.51 ± 2.33 vs. 8.12 ± 1.61, $P < 0.001$). Meanwhile, the serum NGF concentrations in healthy group were lower than that in acute ischemic stroke patients (7.17 ± 1.49 vs. 9.15 ± 2.24, $P < 0.001$). Moreover, our results demonstrated that high serum NGF concentrations (> 9.21 ng/l) were independently associated with the better functional prognosis at 3 months following the occurrence of stroke (OR 0.048, 95% CI 0.012–0.185, $P < 0.001$).
Conclusions: High concentrations of serum NGF at admission may predict good functional outcome of patients at 3 months after acute cerebral ischemia stroke.

1. Introduction

Reports have indicated that approximately a third of the stroke patients suffered permanent disability on account of neuronal damage and limited regeneration in the brain each year [1]. Neurotrophins, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3/neurotrophin-4 (NT-3/NT-4), have been found to be involved in the functional recovery after stroke [2,3]. For example, low serum BDNF concentrations were shown to be correlated with poorer functional outcome after stroke [2,4]. Studies in animal model also demonstrated that knockdown of BDNF had a negative effect on the functional recovery after stroke [5]. Neurotrophin-3/Neurotrophin-4 was also found to be involved in the regeneration and differentiation of neuron [6,7]. Meanwhile, it is reported in animal model that treatment of NT3 or NT4 contributed to the functional recovery after cerebral ischemia stroke [8].

Noteworthy, NGF, one member of neurotrophins, plays an important role in the functional outcome after stroke in animal model. NGF injection was found to protect against brain injury [9] and it was revealed that endogenous NGF signaling participated in neuroprotective and repair functions [10]. Besides, NGF was shown to stimulate the axonal sprouting formation and promote axonal functional reconnection, which was correlated with functional recovery after ischemia stroke [11–13]. Moreover, the neuroprotective effect of several therapies on cerebral ischemia was mediated by synthesis of NGF in brain [1,14–16]. Interestingly, NGF was also involved in other diseases including depression [17,18], Alzheimer disease [19] and drug abuse [20,21].

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; BI, Barthel Index; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NGF, nerve growth factor

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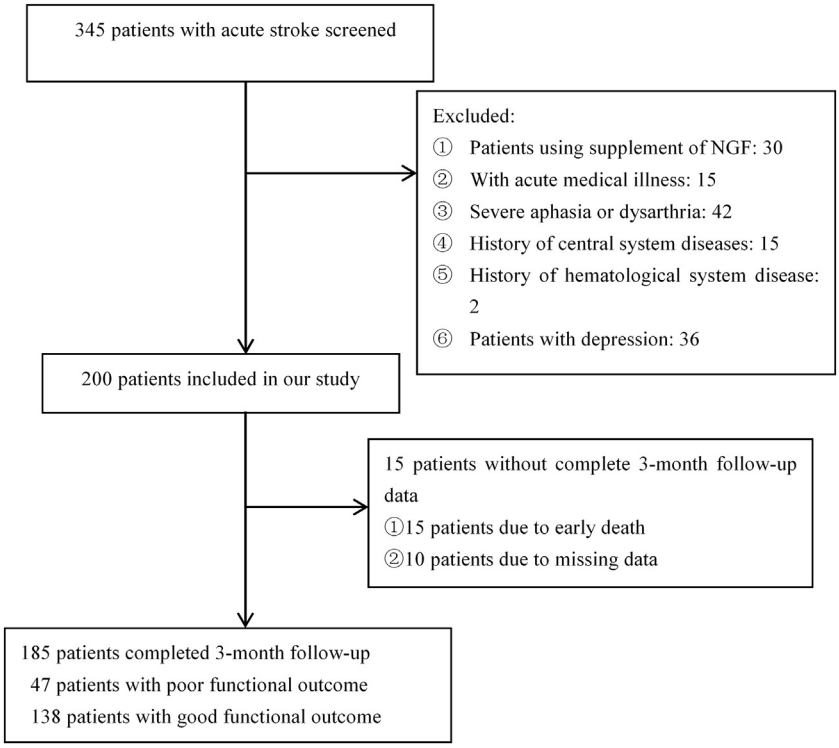

Fig. 1. Study recruitment profile. NGF, nerve growth factor.

Given the relationship between NGF and functional recovery in animal model, it would be interesting to investigate whether serum NGF concentrations were correlated with functional outcome of patients after ischemic stroke. To date, however, no research has been conducted to explore the relationship between serum NGF and functional outcome of patients with ischemia stroke.

2. Materials and methods

2.1. Study population

Patients with acute ischemic stroke were admitted to this study from the Stroke Unit of the First Affiliated Hospital of Wenzhou Medical University between January 2014 and May 2015. The inclusion criteria were: 1) age 18 to 80 y; 2) willing and competent to sign a consent form; 3) diagnosed with acute ischemic stroke within one week since stroke onset and confirmed by magnetic resonance imaging (MRI) reports or computed tomography (CT); The exclusion criteria were: 1) had the supplement of NGF; 2) patients who had recently received anti-inflammatory treatment or immune inhibitor; 3) failed to communication due to severe dysarthria or aphasia; 4) a history of mental disorder or who had recently accepted antipsychotics; 5) a history of central nervous system diseases, such as dementia, Parkinson disease, cerebroma, and cerebral trauma; 6) failed to finish the follow-up. In addition, 100 healthy controls were recruited from our hospital during physical check-ups and they were confirmed without severe physical diseases, including acute cerebral ischemia. This research was conducted in accordance with the principles of the Declaration of Helsinki and was approved by Medical Ethics Committee of our hospital. The researchers obtained the informed consent from each participant after a detailed description of the research.

2.2. Clinical variables

The National Institute of Health Stroke Scale (NIHSS) at admission was assessed by trained neurologists. Lesion location was confirmed by CT/MRI, which was performed within 1 to 3 days. The modified Rankin Scale (mRS) and the Barthel Index (BI) were applied by trained neurologists to evaluate functional outcome of patients at 3 months after stroke. Patients were divided into two groups according to the mRS scores at 3-month follow-up. Patients with mRS scores of 3–6 were defined as poor functional outcome group while those with mRS scores of 0–2 were defined as good functional outcome group.

2.3. NGF measurements

We collected blood samples within 24 h after admission. All the samples were processed by a laboratory technician who was blinded to all clinical data. Serum NGF concentrations were measured by enzyme-linked immunosorbent assay (ELISA) method, in which a double-antibody sandwich ELISA kit (Labsystems Multiskan MS) was used. Serum NGF was recorded in ng/l and 0.7 ng/l was the assay detection limit.

2.4. Statistical analysis

Categorical variables were indicated as percentages and continuous variables were expressed as mean plus SD, or median (interquartile range, IQR) on the basis of their normal distribution. Chi-squared test was applied for comparison of proportions between groups. Student's *t*-test, the Mann-Whitney *U* test or analysis of variance (ANOVA) was used for comparison of continuous variables between groups, as appropriate. Receiver-operating characteristic (ROC) curve analysis was applied to determine prognostic accuracy and the cut-off point for serum NGF concentrations was selected according to the Youden index. The effect of NGF on functional outcome was estimated by binary logistic regression analysis, adjusting for potential confounding variables (age and sex). The results were indicated as adjusted odds ratios (ORs) (95% confidence intervals, CIs). Statistical analyses were used in IBM SPSS software (ver. 21.0) and MedCalc ver. 12.7. All *P* values were 2-tailed, with the significance concentration set at 0.05.

Table 1
Clinical and demographic characteristics of the samples under study.

Baseline characteristics	MRS 0–2 (n = 138)	MRS 3–6 (n = 47)	Healthy controls (n = 100)
Demographic characteristics			
Male/Female	92/46	31/16	55/45
Age (y), mean ± SD	62.53 ± 10.39	61.85 ± 10.96	61.15 ± 9.27
Educational years, median (IQR)	4 (0–6)	3 (0–8)	
BMI (kg/m^2), mean ± SD	23.72 ± 2.97	24.39 ± 3.60	24.53 ± 3.06
Marital status, married, n (%)	128 (93.4)	44 (93.6)	
Vascular risk factors			
Hypertension, n (%)	99 (73.3)	29 (61.7)	
Diabetes mellitus, n (%)	28 (20.9)	13 (27.7)	
Coronary heart disease, n (%)	5 (3.8)	5 (2.1)	
Hyperlipidaemia, n (%)	7 (5.2)	3 (6.4)	
History of stroke, n (%)	16 (12.0)	3 (6.4)	
Current smoking, n (%)	73 (53.3)	20 (43.5)	
Current drinking, n (%)	49 (38.6)	12 (29.3)	
Lesion location, n (%)			
Frontal lobe	40 (18.1)	13 (16.7)	
Parietal lobe	25 (11.3)	10 (12.8)	
Temporal lobe	18 (8.1)	8 (10.3)	
Occipital lobe	21 (9.5)	7 (9.0)	
Basal ganglia	68 (30.8)	22 (28.2)	
Brainstem	22 (10.0)	9 (11.5)	
Cerebellum	19 (8.6)	6 (7.7)	
Other	8 (3.6)	3 (3.8)	
Neuropsychological function			
NIHSS score, median (IQR)	2 (1–4)	5 (3–9)[a]	
BI (IQR)	100 (95–100)	60 (50–75)[a]	
NGF, mean ± SD	9.51 ± 2.33[b]	8.12 ± 1.61[ab]	7.17 ± 1.49

BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; BI, modified Barthel Index; IQR, interquartile range; SD, standard deviation; NGF, nerve growth factor.
[a] $p < 0.001$ compared to MRS 0–2.
[b] $p < 0.001$ compared to healthy controls.

3. Results

3.1. Baseline characteristics

A total of 345 acute ischemic stroke patients were consecutively screened and 200 patients met the entry criteria at baseline. By the time of 3-month follow-up, 185 patients were finally enrolled in this study (Fig. 1). There was no difference between the included and the excluded patients in terms of baseline characteristics, such as age, sex and NIHSS score. No significant intergroup difference was observed in terms of age, sex and BMI among good functional outcome group, poor functional outcome group and healthy controls. Serum NGF concentrations in healthy controls were significantly lower than acute ischemic stroke patients (9.15 ± 2.24 vs. 7.17 ± 1.49, $P < 0.001$). Moreover, poor functional outcome group showed a lower serum NGF concentrations compared to good functional outcome group ($P < 0.001$). Meanwhile, the NIHSS score was significantly higher in poor functional outcome group than good functional outcome group [5(3–9) vs. 2(1–4), $P < 0.001$] (Table 1). Lower BI score was observed in good functional outcome group than poor functional outcome group [60 (50–75) vs. 100 (95–100), $P < 0.001$] (Table 1).

3.2. Association between serum NGF at admission and functional outcome at 3 months after stroke

There was a significant negative correlation between serum NGF and mRS score ($r = -0.372$, $P < 0.001$) in stroke patients. According to the ROC curve (Fig. 2), the optimal cutoff value of serum NGF concentrations as an indicator for an auxiliary diagnosis of 3-month functional prognosis was 9.21 ng/l, with a sensitivity of 85.4% and a specificity of 52.1% [AUC 0.712; 95% CI (0.641–0.776); $P < 0.001$], which was similar to the range of the NIHSS with an AUC of 0.767 (95% CI, 0.698–0.826). There was no significant difference in prognostic accuracy between NGF and the NIHSS (P = NS). In the logistic regression analysis, the serum NGF concentrations above the cut-off (9.21 ng/l) remained independently associated with good functional prognosis after adjustment for confounding variables (OR 0.048, 95% CI 0.012–0.185, $P < 0.001$). In addition, the NIHSS score at admission also remained significantly correlated with poor functional prognosis (OR 1.737, 95% CI 1.420–2.124, $P < 0.001$) (Table 2).

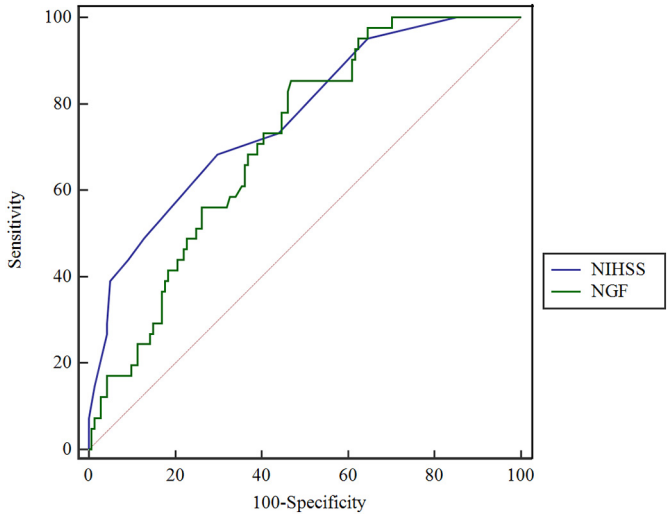

Fig. 2. Receiver operator characteristic curve demonstrating sensitivity as a function of 1-specificity for predicting functional prognosis based on the serum NGF levels and NIHSS score in stroke patients. NGF, nerve growth factor; NIHSS, National Institutes of Health Stroke Scale.

4. Discussion

Our results demonstrated that high NGF concentrations were

Table 2
Multivariate logistic model of the clinical determinants of functional outcome three months after stroke.

Variables	OR (95%CI)	*P* value
NGF (> 9.21 ng/l)	0.048 (0.012–0.185)	< 0.001
Age		NS
SEX		ND
NIHSS	1.737 (1.420–2.124)	< 0.001

NIHSS, National Institutes of Health Stroke Scale; NGF, nerve growth factor.

independently associated with better functional prognosis at 3 months following stroke onset. Increased serum NGF concentrations were observed in ischemic stroke patients comparing to healthy controls. This was in line with previous studies in animal model [22]. High regulation of mRNA for NGF was found in hippocampus, striatum and cortex following brain ischemia [23–25]. Besides, NGF was found to be increased after hypoxic brain injury [26]. The increased NGF serum concentrations in acute ischemic stroke patients might be explained by mechanisms of inflammation and immunity, which are shown to be involved in the pathophysiology of stroke [27,28]. It was reported that NGF played a vital role in tissue inflammation as well as neuroimmune interactions, in which NGF served as a general 'alert' molecule to recruite and trigger tissue defence processes following insult and systemic defensive mechanisms [29]. Additionally, neurotrophin response was found to be suppressed by interleukin-1 receptor antagonist in injured rat brain [30].

Furthermore, we found that high serum NGF concentrations were independently associated with better functional prognosis at 3 months following acute ischemic stroke. Several mechanisms might explain high NGF concentrations in patients with better functional prognosis after ischemic stroke. NGF was shown to stimulate axonal sprouting formation and promote axonal functional reconnection, which was associated with functional recovery after stroke [12,13]. Meanwhile, previous studies found that endogenous NGF signaling was involved in neuroprotective and repair functions [10,31,32]. Similarly, another study reported that NGF/receptor system might participate in the astrocyte/neuron interaction under cerebral ischemia [33]. In addition, delivery of NGF was shown to mitigate neuronal death after stroke and lead to detectable functional sparing [34].

There were several limitations in our study. Firstly, serious conditions such as severe aphasia were excluded, which might impose some bias on the results. Secondly, serum NGF concentrations was only tested at admission, which might make us fail to reveal the dynamic change of NGF concentrations. Thirdly, 3 months was chosen for the evaluation of functional outcome rather than six months or one year which might be more appropriate to assess functional recovery of patients after stroke.

In conclusion, despite these limitations, this study demonstrated that high NGF concentrations at admission were independently correlated with better functional prognosis of patients with ischemic stroke, which suggests a potential role of NGF in the pathophysiology of functional recovery in stroke patients. High serum NGF concentrations might be an independent prognostic marker of functional outcome after cerebral ischemia. In future, further prospective studies and randomized controlled trials are necessary to determine whether NGF is a causal agent in functional recovery after ischemic stroke.

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Conflicts of interest

All authors declare that they have no conflicts of interest.

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Authors Jincai He, Xiaoqian Luan, Chaowen Wu and Kai Zhao designed the study and wrote the protocol. Authors Huihua Qiu, Huijun Chen, Zhuoying Zhu, Xianmei Li conducted literature searches and provided summaries of previous research studies. Author XiaoqianLuan conducted the statistical analysis. Author Xiaoqian Luan wrote the first draft of the manuscript and all authors contributed to and have approved the final manuscript.

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