Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

Research Report

Brain-derived neurotrophic factor G196A polymorphism predicts 90-day outcome of ischemic stroke in Chinese: A novel finding

Jing Zhao, Hui Wu, Lan Zheng, Yingfeng Weng, Yanqing Mo*

Department of Neurology, Minhang District Central Hospital, 170 Xinsong Road, Shanghai 201100, China

ARTICLE INFO

Article history:
Accepted 31 August 2013
Available online 11 September 2013

Keywords:
BDNF polymorphism
Ischemic stroke
Outcome
Chinese

ABSTRACT

Background and purpose: Recovery after stroke varies considerably between individuals. An abundance of evidence suggests that genetic factors contribute to stroke recovery. The aim of this study was to determine whether or not the *BDNF* G196A polymorphism independently influences the occurrence, severity, and 90-day functional outcome in Chinese patients with ischemic stroke (IS).

Methods: *BDNF* G196A genetic variants were investigated in 494 IS and 346 controls. Severity was assessed by the National Institutes of Health Stroke Scale at the time of admission. Three hundred and eight patients were assessed 90 days post-stroke using the Modified Rankin Scale to determine stroke outcome.

Results: We showed that a significant association existed between the *BDNF* G196A AA genotype and the occurrence of IS ($P=0.021$), even after adjustment for covariates ($P=0.028$). The AA genotype of the *BDNF* G196A was associated with a poor outcome of recovery 3 months after stroke onset ($P=0.008$) was a novel finding, independent of other known predictors of poor outcome ($P=0.012$).

Conclusions: The *BDNF* G196A polymorphism was significantly associated with the occurrence and long-term outcomes of IS, thus *BDNF* G196A may be used as a prognostic biomarker and therapeutic target in IS.

1. Introduction

There are 2.5 million stroke patients in China and 1 million die from stroke-related causes per year (Cohen-Cory et al., 2010). Stroke is also the second most common cause of death worldwide and is the major cause of serious, permanent disability requiring institutional long-term care. There is an increasing evidence that pathologic brain damage is surprisingly plastic, but the rates and extent of recovery vary considerably between individuals. This phenomenon led us to hypothesis that differences in genetic factors may influence an individual's capacity for brain plasticity, thus contributing to different outcomes. Polymorphisms in the gene encoding brain-derived neurotrophic factor (BDNF) are good candidates for playing this role.

A previous study reported that BDNF exerts strong survival and differentiation function during the development of the nervous system (Tunstall-Pedoe et al., 1994). BDNF and its

*Corresponding author. Fax: +86 21 64923400.
E-mail address: zhaojingssmu@163.com (J. Zhao).

0006-8993/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.brainres.2013.08.061

receptor (TrkB) have previously been used as markers of motor neuron survival and neuronal plasticity (Sendtner et al., 1992; Yan et al., 1993). BDNF also represents a crucial signaling molecule in adaptative brain plasticity after stroke (Cowansage et al., 2010; Lipsky and Marini, 2007; Mattson, 2008). Animal studies have shown that BDNF reduces ischemic injury and improves functional recovery and post-injury regeneration (Almeida et al., 2005; Schabitz et al., 1997). The *BDNF* gene is located in the short arm of chromosome 11p13–p14. A common single nucleotide polymorphism (SNP; G196A orVal66Met, dbSNP: rs6265) in the *BDNF* gene leading to a valine (Val) to methionine (Met) substitution in codon 66 of the prodomain affects the regulated secretion and neuroplastic effect of mature BDNF (Egan et al., 2003), and has a beneficial activity influencing plasticity in the motor cortex (Kleim et al., 2006). This functional polymorphism was recently shown to be associated with unstable angina (Jiang et al., 2009), episodic memory (Egan et al., 2003), hippocampal volume (Hariri et al., 2003), and Alzheimer's disease (Huang et al., 2007). Emerging studies, however, indicate that the *BDNF* G196A polymorphism predicts poor outcome of aneurysmal subarachnoid hemorrhage (Siironen et al., 2007), and is associated with the severity of reversible cerebral vasoconstriction syndrome (RCVS) (Chen et al., 2005).

Given the important role of the *BDNF* gene in adaptative brain plasticity after stroke, we hypothesized that polymorphisms in the *BDNF* gene may play important role in IS. however, no association has yet been demonstrated between the *BDNF* polymorphism and the occurrence, severity, and long-term functional outcome of IS in Chinese.

2. Results

2.1. *Characteristics and risk factor profiles in the cases and controls*

Table 1 summarizes the baseline characteristics and risk factor profiles in the cases and controls.

The IS group included 300 males and 194 females; the mean age of the IS group was 69.75±11.32 years, and the ages ranged between 40 and 85 years. The control group included 185 males and 152 females; the mean age was 68.96±9.99 years, and the ages ranged between 40 and 85 years. There were no statistically significant differences in age ($P=0.303$) or gender ($P=0.094$) between the case and control groups. Traditional cerebrovascular risk factors in the case group were as follows: hypertension, $n=374$ (75.7%); DM, $n=168$ (34.0%); hypercholesterolemia, $n=164$ (33.2%) and smoking, $n=202$ (40.9%). The control group was matched for histories of hypertension, $n=205$ (60.8%), DM, $n=56$ (16.6%), hypercholesterolemia, $n=80$ (23.7%), and smoking, $n=91$ (27.0%). The prevalence of the risk factors (hypertension, DM, hypercholesterolemia, and smoking) was significantly overrepresented in the case group.

IS was also classified into subtypes according to the TOAST criteria. Subtype analysis was limited to LAA ($n=200$), SAO ($n=165$), and cardioembolism ($n=82$) because of the small sample sizes of the other subtypes ($n=47$). No significant difference was noted in age or gender between the

Table 1 – Baseline characteristics of IS cases and controls.

Characteristic	Control ($n=337$)	Total		TOAST subtype				
		Ischemic stroke ($n=494$)	P	LAA ($n=200$)	P value	SAO ($n=165$)	P value	Cardioembolism ($n=82$)	P value
Age (years)	68.96±9.99	69.75±11.32	0.303	70.03±10.721	0.067	68.39±10.78	0.362	70.99±13.09	0.124
Gender, M/F	185/152	300/194	0.094	129/71	0.098	100/65	0.162	42/40	0.319
Hypertension	205(60.8%)	374(75.7%)	<0.0001*	152 (76%)	<0.0001*	130(79.8%)	<0.0001*	57 (69.5%)	0.145
DM	56 (16.6%)	168(34.0%)	<0.0001*	65 (32.5%)	<0.0001*	54 (33.1%)	<0.0001*	30 (36.6%)	<0.0001*
Hypercholesterolemia	80(23.7%)	164(33.2%)	0.003*	56 (28.1%)	0.258	51 (30.9%)	<0.0001*	22 (26.8%)	0.019*
Smoking	91(27.0%)	202(40.9%)	<0.0001*	108(54%)	<0.0001*	79 (49.4%)	0.309	37 (45.7%)	0.849

LAA, large artery atherosclerosis; SAO, small artery occlusion; DM, diabetes mellitus.
* Significant difference compared with control and $P<0.05$ is considered statistically significant