Risk of Acute Cerebral Infarction and Plasma Asymmetrical Dimethylarginine and Homocysteine Levels: A Clinical Correlation Analysis of Chinese Population

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Background: The aim of this study was to investigate the distribution of plasma asymmetrical dimethylarginine (ADMA) and homocysteine levels in Chinese patient with acute cerebral infarction (ACI) and their correlations with various risk factors. *Methods:* In total, 178 patients within the first 72 hours of ACI were assigned to 5 groups according to the Trial of Org 10172 in Acute Stroke Treatment classification and further divided into primary group and recurrent group; 52 healthy controls were also recruited in this study. Blood samples were collected for detecting plasma concentrations of ADMA and homocysteine and other biochemical parameters. *Results:* Plasma concentrations of ADMA and homocysteine were significantly higher in patients with ACI compared with healthy control ($P < .05$) and varied among the different subsets of patients. Both the levels were significantly different between the primary group and recurrent group. Age, systolic pressure, blood glucose, total cholesterol, body mass index, ADMA, and homocysteine were significant risk factors for ACI in Chinese population. Correlation analysis showed that plasma ADMA level was positively correlated with the plasma level of homocysteine in patients with ACI, and each of them was positively correlated with age, systolic pressure, diastolic pressure, and total cholesterol, whereas homocysteine level was also found to be positively correlated with smoking. *Conclusions:* The current results indicated that ADMA and homocysteine were important contributors to the development of ACI among Chinese population, and plasma concentrations of ADMA and homocysteine were positively correlated with one another and other risk factors. Our study also suggested close-response relationships of plasma concentrations of ADMA and homocysteine to recurrent ACI. **Key Words:** Acute cerebral infarction—asymmetrical dimethylarginine—homocysteine—risk factors.

Introduction

As the leading cause of disability worldwide, cerebral stroke is the second most common cause of death in China,[1] and patients with acute cerebral infarction (ACI) have been reported to account for 60%-80% of all the cerebral stroke patients.[2] Various mechanisms involved in the pathogenesis of atherothrombotic stroke include atherosclerotic processes and thrombophilic conditions, which may be linked to L-arginine–nitric oxide (NO) pathway.[3] Endothelial-derived NO, a potent vasodilator, has been reported to play a role as an endogenous anti-atherosclerotic molecule[4] and was synthesized from L-arginine by a

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family NO synthase. Reduction in NO bioavailability was suggested to be responsible for the biologic association of endothelial dysfunction with atherosclerotic vascular disease and inhibition of endogenous NO synthesis associated with the development of atherosclerosis.[5]

Asymmetrical dimethylarginine (ADMA), a circulating endogenous inhibitor of endothelial NO synthase, was a marker for endothelial dysfunction[6] and has been associated with the pathogenesis of atherosclerosis.[7] ADMA inhibited the production of NO in cultured endothelial cells and isolated blood vessels,[8] and increased plasma concentrations of ADMA was detected in vascular disease and vascular risk factors.[9,10] Kielstein et al[11] reported that plasma ADMA level in hemodialysis-treated patients exhibited a negative correlation to nitrate excretion. Previous study on Swedish population indicated that ADMA was a weak independent marker for acute stroke,[12] and elevated ADMA levels were significantly associated with an increased predicted risk for future development of ischemic stroke in the Japanese[13,14] and in Indian population.[7]

In addition to ADMA, increased circulating homocysteine was also suggested to be associated with vascular disease and vascular risk factors.[15,16] There was evidence that increased plasma concentrations of homocysteine impaired endothelial function by increasing the plasma concentration of ADMA.[17] The increased concentrations of homocysteine in the plasma of patients with Alzheimer disease were associated with an increase in the plasma concentrations of ADMA and a decrease in the plasma concentrations of NO. Homocysteine has been reported to inhibit the activity of endothelial dimethylaminohydrolase, which in turn cause the accumulation of ADMA and the inhibition of NO synthesis.[18] Previous studies on 52 South Korean patients with ischemic stroke showed that plasma homocysteine was a significant predictor of elevated ADMA level and was positively correlated to ADMA plasma level in elderly ischemic stroke patients.[3] However, some study also reported that homocysteine concentration was not elevated after recent atherothrombotic stroke,[19] and the clinical interpretation of homocysteine after stroke and the eligibility for clinical trials assessing treatment for elevated homocysteine levels have been suggested to require an adjustment in time since stroke to properly interpret the observed homocysteine levels.[20]

The findings of previous studies showed that ADMA and homocysteine levels in plasma of stroke patients were significantly higher than those in control subjects.[13] However, little has been published about possible variations of plasma concentrations of ADMA and homocysteine in the acute phase of ACI among Chinese population. The present case–control study aimed to investigate the distribution of plasma concentration of ADMA and homocysteine in Chinese population within the first 72 hours of ACI and to identify the potential risk factors for ACI and their correlations with plasma concentrations of ADMA and homocysteine.

Materials and Methods

Subjects

A total of 178 patients who had ACI within 72 hours were recruited from the neurology inpatient department of the Second Hospital of Tianjin Medical University in China during May 2008 to June 2011. Healthy controls were recruited from health checkup and volunteers of the hospital involving a total of 52 participants.

Written informed consent was obtained from all study subjects, and this study was approved by the ethics committees of the Second Hospital of Tianjin Medical University. All the cases were diagnosed with ACI according to the criteria of the Chinese Medical Association in 1995 and the criteria amended in the Fourth National Cerebrovascular Disease Conference. Diagnoses were further confirmed by computerized tomography or magnetic resonance imaging.

The exclusion criteria were as follows: (1) individuals with incidence of infection, thyroid disorders, liver or kidney dysfunction, autoimmune disease, cancer, Parkinson disease, and other neurologic diseases; (2) individuals were known to be taking drugs containing methotrexate, antiepileptic, or multivitamins that may affect detection results; (3) 1 year before the onset of drinking and consumed more than 300 g of alcohol weekly; and (4) smoking more than 10 cigarettes per day or less than 5 years before smoking cessation.

Grouping

According to the Trial of Org 10172 in Acute Stroke Treatment classification,[21] 178 patients with ACI were further assigned to 5 groups: large-artery atherosclerosis (LAA) group (n = 40), small-artery occlusion (SAO) group (n = 56), cardiac embolism (CE) group (n = 19), other certain (OC) group (n = 15), and undetermined etiology (UE) group (n = 48). On the other hand, patients were subdivided into the primary group and relapse group according to their morbidities.

Blood Sample Collection

Blood samples of 3 mL were collected by venipuncture into heparin anticoagulant tubes after an overnight fast (>12 hours) and the plasma separated by centrifugation at 3000 rpm for 10 minutes. The plasma was then stored at −70°C for further detection.

Determination of Homocysteine

Plasma concentration of homocysteine was determined by high-performance liquid chromatography (Waters 600E chromatograph; Waters Corporation, Milford, MA) equipped with a Kromasil column as described previously.[22]