Which Ischemic Stroke Subtype Is Associated with Hyperhomocysteinemia?

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Background: Stroke is still a major global health problem in both developed and developing countries. Defining stroke subtype and underlying etiologies is a major step to choose the best method for prophylaxis. Homocysteine is an endothelial toxin and elevated levels have been associated with stroke risk. In this study, we hypothesized that serum total homocysteine level may be related with specific atherothrombotic ischemic stroke subtypes and aimed to find if high serum homocysteine levels are correlated with any specific ischemic stroke subtype. *Methods:* Patients with ischemic stroke and aged between 18 and 65 are included. Ischemic stroke subtype is defined according to Causative Classification System. Hospital records are examined retrospectively to define patient demographics, ischemic stroke subtype, vascular risk factors, serum homocysteine, B12, and folic acid levels. *Results:* A total of 262 patients were included. Serum homocysteine level was elevated (≥16 μmol/L) in 99 patients (37.79%). The rate of patients with hyperhomocysteinemia was significantly more common in strokes due to intracranial stenosis (72.41%) (odds ratio 8.138; 95% confidence interval 2.366-27.989; $P < .01$) than extracranial large artery stenosis (52.00%), craniocervical arterial dissections (35.71%), cardioembolic strokes (27.87%), and lacunar infarctions (25.00%) after adjustment for other risk factors. High homocysteine levels were significantly more common in men and smokers ($P < .05$). *Conclusions:* Elevated levels of serum homocysteine are correlated with ischemic strokes due to intracranial large artery stenosis in young and middle-aged patients. This association may have an implication in stroke prophylaxis for intracranial atherosclerosis by using homocysteine-lowering therapies.
Key Words: Ischemic stroke—subtype—homocysteine—intracranial stenosis.

Introduction

Homocysteine is a sulfhydryl-containing amino acid derived from the essential amino acid methionine, which is abundant in animal sources of protein. Its serum level can increase in specific conditions such as congenital enzyme defects, chronic renal and liver dysfunction, and treatment with several drugs. Hyperhomocysteinemia can sometimes occur only with nutritional habits and insufficiencies in the absence of any specific disease.[1,2]

Increased serum homocysteine levels is accepted as a risk factor for cardiovascular diseases, including myocardial infarction,[3-5] peripheral arterial occlusive disease,[4,6,7] venous thrombosis,[4,8,9] and ischemic stroke.[10-15] The most

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The study protocol has been approved by the local institute's committee.

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likely underlying mechanism is the prothrombotic and atherogenic effects of elevated homocysteine levels, via vascular endothelial damage.[2,16,17]

The evidence of homocysteinemia to be a risk factor for stroke in adults comes from different geographic and ethnic populations.[18-21] However, regardless of the pathologic mechanism of homocysteine toxicity, different studies revealed that high homocysteine levels were associated with thrombotic, embolic, lacunar, or even hemorrhagic strokes.[22-27] The objective of this study is to assess the correlation between hyperhomocysteinemia and ischemic stroke subtypes defined according to a clear Causative Classification System together with a review of the existing scientific data.

Methods

Patients between 18 and 65 years who admitted to our clinic between January 2006 and December 2016 and had the diagnosis of ischemic stroke are included in the study. Hospital records are examined retrospectively to define patient demographics, ischemic stroke subtype, vascular risk factors, serum homocysteine, B12, and folic acid levels. The study is approved by the local institutional ethics committee.

Patient Selection and Stroke Subtype

Based on the World Health Organization criteria, ischemic stroke is defined as "a clinical syndrome consisting of rapidly developing clinical signs of focal (or global in case of coma) disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than a vascular origin."[28] Ischemic stroke subtype is defined according to Causative Classification System for acute ischemic stroke.[29] The subtype is retrospectively determined by 2 separate investigators considering clinical findings, the neuroimaging data including brain magnetic resonance imaging (diffusion-weighted images [DWI], apparent diffusion coefficient [ADC] maps) and computed tomography (CT) scans, angiography of cranial vessels in neck and brain (magnetic resonance [MR], CT angiograms, or digital subtraction angiography), cardiac investigations (electrocardiography, transthoracic echocardiography, and 24-hour rhythm Holter monitoring, or transesophageal echocardiography if needed), and blood tests for other rare causes of ischemic stroke. DWI was available in all patients within 72 hours after stroke onset, except 2 patients who had only CT scans because of their cardiac pacemakers. A CT or MR angiogram at the arterial phase was used to determine the presence of extracranial or intracranial stenosis or dissection. Six ischemic stroke subtypes were defined: extracranial large artery atherosclerosis (E-LAA), intracranial large artery atherosclerosis (I-LAA), cardioembolic stroke, stroke due to small artery disease (lacunar infarction), extra or intracranial dissections, and strokes due to other rare causes.

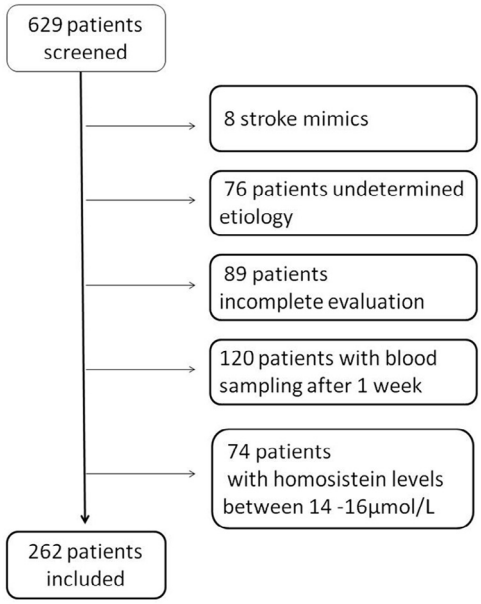

Figure 1. *The flowchart diagram for the included and excluded patients.*

Patients with undetermined cause of stroke were not included in the study.

Transient ischemic attacks without an acute cerebral infarction in DWI or CT, patients with venous thrombosis and venous infarction, strokes due to undetermined etiology, and with incomplete investigation are excluded. Only patients whose blood samples were collected within 7 days after index event are included. Homocysteine levels below 14 µmol/L are accepted to be normal, whereas homocysteine levels over 16 µmol/L are accepted to be high.[30] Homocystein levels between 14 and 16 µmol/L are accepted to be gray zone, neither elevated nor low, and not included in the statistical analysis.

Patients who received any kind of vitamin supplementation previous to ischemic stroke are excluded. Patients with known genetic defects in the enzymes involved in metabolism, pernicious anemia, chronic kidney disease and hepatic failure, gastrointestinal malabsorption of vitamins, and on drugs reducing vitamin B levels are not included in the study.

The flowchart diagram of outlined patients is given in Figure 1.

Blood Analysis

Blood analyses for serum homocysteine, B12, and folate levels are evaluated. According to the standard protocol of our institute, nonfasting blood samples are drawn from a peripheral vein, immediately brought to the biochemistry laboratory and centrifuged at $3000 \times g$, and the remaining serum samples are stored at –80C° before calculation. On evaluation day, the samples were melted at room temperature. The concentrations of total homocysteine in the serum were analyzed by a ThermoFisher Ultimate