Association between plasma homocysteine concentrations and extracranial carotid stenosis

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BACKGROUND: Increasing epidemiologic data support a relationship between elevated plasma total homocysteine levels and an increased risk for vascular disease. Higher plasma total homocysteine (tHcy) levels have been associated with extracranial carotid atherosclerosis and cerebral infarction in whites. However, data regarding such associations are limited for Asians. This study examined the association between tHcy level and carotid stenosis in Iranian subjects.

PATIENTS AND METHODS: In this retrospective study, the subjects were 158 patients with ischemic stroke, including 105 with a normal tHcy level and 53 with a high tHcy level. We investigated the extracranial carotid arteries by ultrasonography and measured serum tHcy by the ELISA method in these two groups.

RESULTS: We found no meaningful association between a high tHcy level and carotid stenosis.

DISCUSSION: The lack of any meaningful difference in carotid stenosis between patients with normal and elevated tHcy levels is probably due to the low frequency of extracranial disease in the Asian population and to the nature of homocysteine atherosclerosis.

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Increasing epidemiologic data support a relationship between elevated plasma total homocysteine levels and an increased risk for vascular disease.^{1,2,3} Homocysteine is a highly reactive amino acid.⁴ A severe elevation of serum homocysteine, a rare disease seen in homozygous homocystinuria and caused by an inborn error of homocysteine metabolism, is associated with premature cardiovascular complications induced by accelerated atherosclerosis and/or thromboembolism.^{5,6}

The toxic effects of homocysteine on the vasculature have been well documented in experimental studies. These effects consist, in particular, of endothelial cell injury and smooth muscle cell proliferation, which are two prominent features of atherogenesis.^{7,8} In contrast, the *in vivo* contribution of hyperhomocysteinemia to atherosclerosis in humans has been less fully investigated.

Diagnosis and management of carotid arterial occlusive disease and its comorbid illness have been the focus of extensive debate during the past two decades. The development of sophisticated ultrasound technology has enabled us to objectively define the severity of carotid stenosis. This study examined the association between carotid stenosis and total homocysteine (tHcy) levels in Iranian subjects.

Patients and Methods

We retrospectively studied 158 patients with ischemic stroke based on clinical and paraclinical findings (brain CT and MRI) that were

consecutively admitted to the Al Zahra Hospital (Isfahan, Iran) between September 2002 and July 2004. Exclusion criteria were malignant disease, hypothyroidism, chronic renal failure, recent myocardial infarction, major surgery, and the use of anticonvulsants, multivitamins or methotrexate.

Extracranial carotid arteries were evaluated ultrasonographically through Doppler examination with a high-resolution real time scanner equipped with a 5-MHz transducer by GE Logic 500 equipment. The patient lay briefly in the supine position in a dark room, and the examinations were done with the head held in the midline position or slightly tilted to either side initially. The common and internal carotid arteries were scanned crosssectionally and longitudinally. Carotid stenosis was measured based on flow velocity criteria for grading carotid stenosis used in the neurosonology laboratory of Wake Forest University Baptist Medical Center.¹⁵ The bilateral common and internal carotid arteries were examined by the same procedure.

For evaluation of plasma tHcy levels, blood was drawn from fasting subjects more than 2 weeks after the stroke because the levels can temporally elevate after stroke. Venous blood samples were collected in tubes containing EDTA, centrifuged within 60 minutes, and stored at -20° to avoid a false elevation in tHcy concentration as a result of its release from red blood cells. Homocysteine levels were then measured by the ELISA method.

The difference in carotid stenosis between the two groups (normal and high tHcy) was examined by the chi-square test with $P=0.05$ considered statistically significant. SPSS 9.0 statistical software was used for all analyses.

Results

The age and sex distribution of the 158 patients at baseline is shown in Figure 1. Ninety-two of the 158 patients were men and 66 were women. Patients were between 40 and 80 years old. Seventy-two men (45.5%) and 4 women (26%) had normal tHcy levels while 22 men (13.9%) and 23 women (14.6%) had abnormal tHcy levels (Figure 2). Increased levels of serum homocysteine were present in 38 patients (28.5%) (Table 1). Nineteen patients (18.1%) with normal serum tHcy levels and 17 patients (32.1%) with elevated serum tHcy had carotid stenosis (Table 2). We found no meaningful difference in the presence of carotid stenosis between patients with high and normal tHcy levels ($P=0.05$, $df=1$) (Table 2).

Figure 1. Age and sex distribution of the 158 patients with ischemic stroke.

Figure 2. Sex distribution and serum total homocysteine (tHcy) concentrations by age.

Discussion

Stroke places a tremendous burden on health resources throughout the world. Improved detection and modification of risk factors could reduce the impact of this disease. Ultrasonography of the carotid arteries is the modality of choice for triage, diagnosis, and monitoring of cases of atheromatous disease.¹⁰ Duplex ultrasonography is an accurate, noninvasive method for diagnosing, characterizing, and classifying atherosclerotic stenoses of the extracranial carotid artery system.¹¹ Carotid ultrasonographic methods capable of visualizing the arterial wall have

been used to obtain measures of intima-media thickness (IMT).¹² Plaque in the common carotid artery and internal carotid artery should be documented with gray-scale imaging.¹⁰

Elevated tHcy levels have attracted much attention in recent years as a potential risk factor for cardiovascular disease and for atherosclerotic lesions in the area around the carotid bulb and bifurcation that are responsible for cerebral ischemia and stroke.^{11,12} High tHcy levels have been linked to carotid atherosclerosis as assessed by IMT measurement.^{13,14} However, controversies still exist regarding whether a slight increase in IMT represents focal atherosclerosis.

In the present study, despite elevated tHcy levels, which were found rather frequently in patients with ischemic stroke, we found no meaningful difference in carotid stenosis between patients with a high tHcy level and a normal tHcy level ($P=0.05$, $df=1$). The finding that tHcy levels were often elevated in patients with ischemic stroke may be important in the planning for stroke prevention in our patients.

Table 1. Number of patients with normal and abnormal serum homocysteine (tHcy) concentrations for different stroke types.

		Thrombotic	Embolic	Lacunar	%
Normal tHcy	M	62	2	8	71.5%
	F	36	3	2	
Abnormal tHcy	M	20	-	2	28.5%
	F	18	-	5	

Table 2. Relationship between carotid stenosis and serum homocysteine (tHcy) concentration.

	Total n	Normal n (%)	Carotid stenosis n (%)
Normal tHcy	105	86 (81.9%)	19 (18.1%)
High tHcy	53	36 (67.9%)	17 (32.1%)

$P=0.05$, chi-square test

The lack of any meaningful difference in carotid stenosis between patients with normal and elevated tHcy levels is probably due to the low frequency of extracranial carotid disease in the Asian population¹⁵ and to the nature of homocysteine arteriosclerosis, which can lead to intima hyperplasia in the absence of lipid-laden atheroma and induce medial thinning.

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