Mild Hyperhomocyst(e)inemia
A Possible Risk Factor for Cervical Artery Dissection

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Background and Purpose—The pathogenesis of cervical artery dissection (CAD) remains unknown in most cases. Hyperhomocyst(e)inemia [hyperH(e)], an independent risk factor for cerebrovascular disease, induces damage in endothelial cells in animal cell culture. Consecutive patients with CAD and age-matched control subjects have been studied by serum levels of homocyst(e)ine and the genotype of 5,10-methylenetetrahydrofolate reductase (*MTHFR*).

Methods—Twenty-six patients with CAD, admitted to our Stroke Unit (15 men and 11 women; 16 vertebral arteries, 10 internal carotid arteries), were compared with age-matched control subjects. All patients underwent duplex ultrasound, MR angiography, and/or conventional angiography.

Results—Mean plasma homocyst(e)ine level was 17.88 μmol/L (range 5.95 to 40.0 μmol/L) for patients with CAD and 6.0±0.99 μmol/L for controls ($P<0.001$). The genetic analysis for the thermolabile form of *MTHFR* in CAD patients showed heterozygosity in 54% and homozygosity in 27%; comparable figures for controls were 40% ($P=0.4$) and 10% ($P=0.1$), respectively.

Conclusions—Mild hyperH(e) might represent a risk factor for cervical artery dissection. The *MTHFR* mutation is not significantly associated with CAD. An interaction between different genetic and environmental factors probably takes place in the cascade of pathogenetic events leading to arterial wall damage. **(*Stroke*. 2001;32:714-718.)**

Key Words: amine oxidoreductases ■ dissection ■ homocyst(e)ine ■ stroke ■ ultrasonography

In young adults, cervical artery dissection (CAD) is recognized as the second most frequent cause of stroke,[1–3] associated with approximately 10% to 20% of acute cerebrovascular events.[4–7] The pathogenesis of CAD is unknown. Trauma and primary disease of the arterial wall are the main recognized predisposing factors.[8]

In 1969 McCully[9] hypothesized a possible link between increased plasma level of H(e) and vascular disease. In 1974 Harker and associates[10] induced vascular injury and thrombosis by producing experimental hyperH(e) in baboons. Recently, mild hyperH(e) (ie, 12 to 40 μmol/L) was identified as an independent risk factor for vascular disease[11–13]; values even >10.2 μmol/L are associated with a doubling of vascular risk,[12] and the slope of the H(e)/risk relationship is steep.[14]

Among factors contributing to hyperH(e), the thermolabile form of the enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR) is a genetic abnormality that occurs in 4% to 10% of the general population as a homozygous form.[15–17] The genetic base of thermolability has been detected as the substitution of C to T at nucleotide 677 of the *MTHFR* gene.[13,17] Homozygotes for the thermolabile form have a specific activity of ≈50% of normal, while heterozygotes involve ≈75% of normal subjects. In the present study we measured serum levels of H(e) and assessed genotype for *MTHFR* in consecutive patients with CAD compared with age-matched controls.

Subjects and Methods

All consecutive patients with acute stroke in whom spontaneous CAD was first suspected by duplex ultrasound[18] and then confirmed by MR angiography[19,20] and/or conventional angiography[21,22] were included in the study. Only 2 patients refused to undergo conventional angiography.

The control group consisted of 30 age-matched subjects (15 men and 15 women) with a clinical history negative for cerebrovascular disease. The controls were recruited among outpatients referring to the Headache Center of our department; they were screened before starting any medication.

In both patients and controls, the genetic analysis was carried out after written informed consent was obtained. The definitions of risk factors were the following: hypertension if the blood pressure was >160/90 mm Hg in at least 2 measurements or if the subject was under treatment with antihypertensive drugs, diabetes mellitus if the fasting blood glucose was >110 mg/dL, and smoke habit if the patient was a current smoker. None of the subjects enrolled were treated with drugs that influenced homocyst(e)inemia.

Venous blood of patients and controls was collected into EDTA tubes after an overnight (12-hour) fast. Plasma was immediately

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TABLE 1. Baseline Characteristics of Patients With CAD and Control Subjects

Characteristic	Patients (n=26)	Controls (n=30)
Mean±SD age, y	51.6±15.4	50.6±11.5
Sex (M/F)	15/11	15/15
Caucasian, n (%)	25 (96.1%)	30 (100%)
Hypertension, n (%)	10 (38.5%)	9 (30.0%)
Diabetes, n (%)	3 (11.5%)	4 (13.3%)
Smoking habit, n (%)	2 (7.7%)	4 (13.3%)

prepared at 4°C and snap frozen and kept at −20°C until analyzed. In CAD patients, blood samples were obtained the morning after diagnosis of CAD, within 3 days from stroke onset, and were repeated after 1 week. Vitamin supplementation was started upon discharge of patients.

Plasma total H(e) was measured by using a high-performance liquid chromatography (HPLC) method coupled to fluorescence detection.[23] Briefly, the method consists of reduction of the sample with tri-n-butylphosphine, precipitation of proteins, and derivatization with 7-fluorobenzo-2-oxa-1,3-diazole-4-sulfonate, followed by HPLC separation and fluorescence detection. Quantitation was performed with use of an internal calibrator, mercaptopropionylglycine, and H(e) external calibration standards. The within-day and between-day coefficients of variation were found to be 6.2% and 6.5%, respectively.

DNA isolation was performed on 200 μL of whole blood with the QIAamp DNA Blood Mini Kit (Qiagen). Genotyping for *MTHFR* C677T (Ala-Val) polymorphism was carried out on the basis of the method by Frosst et al.[17]

In brief, primers with the sequences 5′-TGAAGGAGAAGGTGTCTGCGGGA-3′ and 5′-AGGACGGTGCGGTCAGAGTG-3′ were used in polymerase chain reactions. Amplification was performed using initial denaturation at 95°C for 2 minutes, followed by 29 cycles of 94°C for 30 seconds, 60°C for 30 seconds, and 72°C for 30 seconds, with a final extension at 72°C for 10 minutes. The C677T mutation creates a *Hin*fI recognition site so digestion of the polymerase chain reaction product generates 2 fragments (175bp and 23bp) that were size fractionated on 2% agarose gels.

For statistical analysis, we used the χ^2 test, with the Yates correction or Fisher exact test when appropriate.

Results

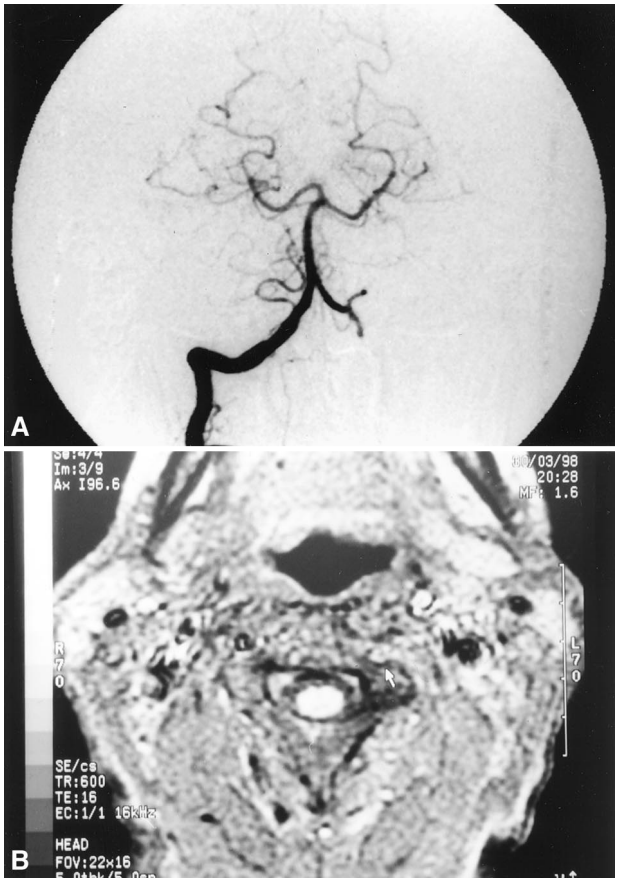
Twenty-six patients with stroke and CAD were included. Baseline characteristics of patients and controls are summarized in Table 1.

Of 26 patients, 10 showed internal carotid artery dissection and 16 vertebral artery dissection (Table 2). Twenty-five

TABLE 2. Characteristics of Patients With Cervical Arteries Dissection (CAD)

Patient No./Sex/Age, y	Dissected Artery	Vascular Risk Factors	Mechanical Stress	Territory	FMD
1/M/43	VA	None	No	PICA	No
2/F/77	VA	BP, D	No	PICA	No
3/F/50	ICA	None	No	MCA	No
4/M/53	ICA	BP	No	MCA	No
5/F/47	VA	None	No	PICA	Yes
6/F/72	VA	BP, D	No	PICA	No
7/M/57	VA	BP, S, D	Coughing	PICA	No
8/M/28	VA	None	Vomiting	PICA	Yes
9/M/50	VA	None	No	SAH	Yes
10/M/51	ICA	None	No	MCA	No
11/F/51	ICA	None	Stretching	. . .	No
12/M/52	VA	BP	No	PICA	No
13/F/82	VA	None	No	. . .	No
14/M/16	VA	None	Soccer playing	PICA, AICA	No
15/M/40	VA	Poss. Behçet	No	No	No
16/F/51	ICA	None	Coughing	MCA	No
17/M/49	ICA	None	Coughing	MCA	Yes
18/M/67	VA	BP	No	Pons	No
19/M/35	ICA	None	Minor trauma	No	No
20/F/40	ICA	None	Coughing	MCA	Yes
21/M/49	VA	BP	No	. . .	No
22/M/56	ICA	S	No	. . .	No
23/F/63	VA	BP	No	PICA	Yes
24/F/30	ICA	None	Coughing	MCA	Yes
25/M/57	VA	BP	No	PICA	No
26/F/71	VA	BP	No	. . .	No

ICA indicates internal carotid artery; MCA, middle cerebral artery; PICA, posterior inferior cerebellar artery; VA, vertebral artery; . . ., no infarct visible; BP, blood pressure; S, smoking habit; D, diabetes; and SAH, subarachnoid hemorrhage.



A, Occlusion at origin of left vertebral artery visualized only in V4 tract injected into the contralateral artery; atherosclerosis is evident in the right vertebral artery and at origin of the basilar artery. B, In MR angiography of the same vessel, subintimal hematoma was evident (white arrow).

patients had ischemic events, and 1 suffered subarachnoid hemorrhage from the rupture of a vertebral pseudoaneurysm into the space surrounding the artery (due to partial localized dissection causing a pseudoaneurysm). This patient also had signs of fibromuscular dysplasia at angiography.

None of the patients had a history of severe recent trauma; 4 patients reported minor trauma (sudden head movements during stretching, football playing, and vomiting) and 5 had severe coughing spells some days before CAD. No patient underwent chiropractic or other forms of manipulative neck treatment. Vascular risk factors were present in 10 patients: hypertension was present in all, diabetes in 3, and cigarette smoking in 2. Fibromuscular dysplasia was reported in 7 patients, 1 patient was affected by possible Behçet's disease (Table 2), fitting 2 (oral aphthous ulcers and skin lesions) of the 3 diagnostic criteria of the International Study Group for Behçet's Disease[24]; pathergy test was negative and there was no genital ulceration or typical eye lesions. Five of 26 CAD patients were older than 65 years of age; 4 disclosed an overt atherosclerosis, and 1 presented with fibromuscular dysplasia. No patients aged <65 years had signs of atherosclerosis. The Figure demonstrates a typical vertebral artery dissection taking place in a patient with atherosclerosis.

Twenty-four patients presented increased H(e) level (Table 2). There were only 2 patients who had normal H(e) levels,

TABLE 3. Values of H(e), Folate, and Vitamin B12 in CAD Patients

Patient No.	H(e), μmol/L	Folate, ng/mL	Vit. B12, pg/mL	C677T *MTHFR*
1	38.0	2.51	172.0	+/+
2	18.0	4.42	341.4	−/+
3	25.0	21.52	267.8	−/+
4	18.0	5.83	159.8	−/−
5	12.0	8.98	451.8	−/−
6	19.2	4.41	338.9	−/+
7	13.0	4.12	333.2	−/−
8	7.8	46.36	246.8	−/+
9	19.7	7.74	166.4	−/+
10	13.5	4.15	420.0	−/+
11	15.1	15.26	200.0	+/+
12	22.0	4.59	125.3	−/+
13	13.5	3.60	361.7	+/+
14	15.6	4.10	333.3	−/+
15	16.9	5.99	444.7	−/−
16	13.9	5.69	246.4	−/−
17	16.3	4.84	384.2	+/+
18	20	4.32	320.0	−/+
19	17.56	4.86	260.6	−/+
20	5.94	6.76	290.8	−/+
21	12.66	7.00	319.1	−/+
22	40.0	2.93	236.4	+/+
23	16.65	3.40	250.0	+/+
24	22	3.50	272.0	+/+
25	19.6	2.93	155.9	−/+
26	12.5	6.21	299.0	−/+
Mean values	17.88±7.53	7.52±8.91	285±92.53	

and 1 was under folate supplementation; both of them had fibromuscular dysplasia. Five patients were aged >65 years; 4 had atherosclerotic disease and 1 fibromuscular dysplasia, and all had abnormal H(e) values (12.5 to 20 μmol/L).

The mean fasting total plasma H(e) level of CAD patients (17.88±7.53 μmol/L) was significantly higher than that in control subjects (6.0±0.99 μmol/L, $P<001$). Values obtained at the first assessment, either within 24 hours or 3 days, and after 1 week were most similar. None of the patients or controls had impaired renal function or evidence of folate or vitamin B12 deficiency, and they were free from concomitant medications that could alter H(e) levels. The vascular risk factors were equally distributed between controls and patients (Table 1).

The distribution of genotype for the thermolabile form of *MTHFR* was different in the 2 groups (Table 3). The genetic analysis showed heterozygosity in 54% of CAD patients and 40% of controls ($P=0.4$), and homozygosity in 23% ($P=0.1$) of CAD patients versus 10% of controls. Allele frequency in the 2 groups is reported in Table 4.

TABLE 4. MTHFR Genotype in CAD Patients and in Control Subjects

	Patients (n=26)	Controls (n=30)
Allele frequency	54%	30%
+/+	7 (27%)	3
+/−	14 (54%)	12
−/−	5 (19%)	15

Discussion

In this series of CAD, there was an association between increased total plasma H(e) levels and CAD. The high values of H(e) persisted during the period of hospitalization.

Although it has been implicated as a pathogenetic factor in the development of vascular disease,[12,13–25] no previous report describes mild hyperH(e) as a risk factor for patients with CAD. In a series of patients with CAD, Brandt et al[6] excluded the presence of homocystinuria, a rare, genetically determined condition that is completely different from the condition of mild hyperhomocysteinemia.[13]

In our series, the mean age of patients was 8 to 10 years higher than described in most studies,[4] with a relative overrepresentation of vertebral dissection.[1] These findings might result from the improvement over the past years of ultrasound methodologies as the first step of the diagnostic workup.[26] Furthermore, the availability of noninvasive artery visualization by means of MR angiography allowed us to perform reliable examinations of the occluded vessel in older stroke patients, being thus possible to visualize specific details, such as subintimal hematoma in patient with diffuse atherosclerosis. Most probably, the incidence of CAD as described in previous reports is underevaluated.[5]

The exact pathomechanism of arterial dissection is not fully understood. Two main possibilities can be mentioned: a rupture of the intimal layer of the arterial wall with penetration of intraluminal blood into the wall[27] or a rupture within the connective tissue of the intramedial layer (including vasa vasorum) resulting in dissection of the wall.[6] Independent of the type of dissection mechanism, the endothelial damage appears to be an important step. The importance of hyperH(e) in inducing endothelial damage is well documented by both in vitro and in vivo studies.[10,28–31] In cell culture experiments, addition of H(e) into the cell medium induces cell detachment from the endothelial cell monolayer[29] and functional abnormalities in the release of endothelium-derived nitric oxide.[30]

As first shown by Harker in 1974[10] in nonhuman primates, a continuous H(e) infusion induces endothelial damage. He showed that a 3-month infusion of H(e) resulted in patchy endothelial desquamation amounting to 10% of the aortic surface. Moderate hyperH(e) induced by methionine feeding led to abnormal arterial vasomotor activity.[32] This suggests that the endothelial damage could be the first step of a process that results in endothelial dysfunction.[29,33] Woo et al[33] have demonstrated that in subjects with hyperH(e), there is an impaired reaction of endothelium-dependent and flow-mediated dilation. The pathophysiological mechanism has not been elucidated until now; there is probably a physical injury with cell desquamation,[28,29] abnormal interaction between nitric oxide–[34] and H(e)-related generation of reactive oxygen species.[35] Endothelial dysfunction can be a key for the early events of atherogenesis[36]; we propose that in addition it could be responsible for a weakness of the arterial wall (ie, "vascular stress" in minor trauma) in patients who experience CAD. However, it cannot be ruled out that hyperH(e) may contribute to thrombogenesis after the damage of the intimal layer and penetration of blood through intimal tear,[1,27] leading to a reduction or occlusion of the arterial lumen.

Mild hyperH(e) can result from a genetic alteration responsible for the thermolabile form of *MTHFR*[15–17]; in a previous observation,[37] we found a link between H(e), homozygosity for the thermolabile form of *MTHFR*, and CAD in a young patient without any other vascular risk factor. This result was not confirmed by the present study, which shows no correlation between the thermolabile form and CAD. Different studies have indicated that 677C-T mutation can be linked to vascular disease, such as coronary artery disease,[38] carotid atherosclerosis,[39] and silent brain infarction.[40] This genetic mutation may contribute to hyperH(e), leading to endothelial damage and CAD, although many other factors contribute to the increase of H(e). Spence and coworkers[41] have pointed out that the presence of a carotid plaque per se justifies the measurement of H(e), independent of the *MTHFR* genotype. Hassan and Marcus,[42] in a recent review of all genetic studies on stroke, did not found any correlation between the thermolabile form of *MTHFR* and stroke.

In conclusion, mild hyperH(e), as opposed to *MTHFR* mutation, seems to represent a risk factor for CAD.

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