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Increased Prevalence of Hyperhomocysteinemia in Cervical Artery Dissection Causing Stroke

A Case-Control Study

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Key Words
Cerebrovascular disease · Stroke · Cervical artery dissection · Homocysteine

Abstract
Background: Spontaneous cervical artery dissection (sCAD) is a nonatherosclerotic vascular disease of unknown etiology. Mild elevation of total plasma homocysteine (tHcy) levels may be a risk factor for sCAD, but the precise mechanism remains unknown. On the other hand, mild hyperhomocysteinemia is also associated with ischemic stroke related to atherothrombotic or small artery disease. We undertook a case-control study to compare the prevalence of mild hyperhomocysteinemia and tHcy levels between patients with a first ischemic stroke due to sCAD and healthy volunteers, as well as patients with a first ischemic stroke due to atherothrombotic or small artery disease. ***Methods:*** Fasting tHcy levels were determined in 346 consecutive patients with a first ischemic stroke due to sCAD (n = 86) and atherothrombotic or small artery disease (n = 260) within 24 h after the onset of symptoms, and in 100 healthy volunteers. ***Results:*** Mild hyperhomocysteinemia was more prevalent in patients with sCAD causing ischemic stroke (n = 33, 38%) than in healthy volunteers (n = 23, 23%; p = 0.034), and less prevalent than in patients with ischemic stroke due to atherothrombotic or small artery disease (n = 149, 57%; p = 0.001). Mean fasting tHcy levels of patients with ischemic stroke caused by sCAD showed a trend to be higher (11.4 ± 3.8 μmol/l) than those of healthy volunteers (10.2 ± 3.0 μmol/l, p = 0.61), but were lower than those of patients with stroke due to atherothrombotic or small artery disease (13.6 ± 6.6 μmol/l, p = 0.002). ***Conclusion:*** Our results suggest that mild hyperhomocysteinemia may be a risk factor for sCAD causing ischemic stroke, but further studies are needed to identify a possible mechanism. This study confirms the association of hyperhomocysteinemia with ischemic stroke due to atherothrombotic or small artery disease.

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Introduction

Spontaneous cervical artery dissection (sCAD) is a major cause of ischemic stroke in young adults [1, 2], but the pathogenesis of this disease remains poorly under-

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stood. Case-control studies reported a significant association of sCAD with total plasma homocysteine (tHcy) [3–5] and the TT methylenetetrahydrofolate reductase genotype, which predisposes to hyperhomocysteinemia [5, 6]. Mild hyperhomocysteinemia is also a risk factor for ischemic stroke [7], probably by enhancing the development of atherosclerosis in large [8] and small [9, 10] cerebral arteries. In contrast, patients with sCAD typically have no or minimal atherosclerosis, and are not known to have small artery disease [11, 12]. Therefore, these findings suggest that mild hyperhomocysteinemia may predispose to sCAD and also to ischemic stroke due to atherothrombotic or small artery disease.

We undertook this case-control study to compare the prevalence of mild hyperhomocysteinemia and tHcy levels between patients with sCAD causing a first ischemic stroke and: (1) healthy volunteers, and (2) patients with a first ischemic stroke due to atherothrombotic or small artery disease.

Methods

Patients and Healthy Volunteers

Patients were taken from the Zürich Stroke Data Bank [13], and the recruitment period lasted from January 1999 until December 2004. Patients were included if: (1) they had had a first ischemic stroke due to sCAD, or due to atherothrombotic or small artery disease according to the criteria of TOAST [14], and (2) tHcy levels had been determined within 24 h after the onset of stroke symptoms as levels progressively increase in the acute phase of stroke [15]. The local ethics committee approved the protocol. All patients underwent a thorough evaluation, which included the assessment of medical history, medical and neurological examination, risk factors for ischemic stroke, routine blood examinations, 12-lead ECG, extracranial, transorbital and transcranial color duplex sonography, and brain CT or MRI, or both [13]. sCAD was detected using cervical MRI and magnetic resonance angiography or digital subtraction angiography, or both [16]. A sCAD was diagnosed when a string sign, an intimal flap or a pseudoaneurysm was identified by angiography, a wall hematoma by cervical or cerebral MRI, or both [16]. Echocardiography, 24-hour ECG and additional laboratory analyses were performed if the treating physician deemed them necessary.

The following stroke risk factors were differentiated: current cigarette smoking that included by definition cigarette smoking within the last 5 years [17]; former cigarette smoking defined as abstention from cigarette smoking that started more than 5 years ago [17]; arterial hypertension defined as a history of hypertension or the use of antihypertensive drugs, or both; diabetes mellitus defined as a history of diabetes mellitus, fasting venous plasma glucose concentration of ≥7.8 mmol/l on at least 2 separate occasions, or venous plasma glucose concentration following the ingestion of 75 g of glucose of ≥11.1 mmol/l at 2 h and at one other occasion during the 2-hour test; hypercholesterolemia defined as a total venous plasma cholesterol level above 5.0 mmol/l; abnormal high-density lipoprotein (HDL) cholesterol defined as values below 1.0 mmol/l, abnormal low-density lipoprotein (LDL) cholesterol defined as values above 3.0 mmol/l; abnormal total/HDL cholesterol ratio defined as values above 5, and abnormal triglyceride levels defined as values above 1.6 mmol/l; history of migraine with aura.

Healthy volunteers (n = 100, 50 men; mean age 43.6 ± 13.1 years, range 20–68) were blood donors who were selected after exclusion of a multitude of diseases precluding blood donation by rigorous screening according to the published standards of the Swiss Red Cross (www.zhbsd.ch), which also provided more recent reference values of homocysteine plasma levels for clinical purposes.

Determination of Fasting tHcy Levels

The fasting levels of tHcy were determined in stroke patients within 24 h after the onset of symptoms and in healthy volunteers with an immunoassay that uses sample pretreatment and monoclonal mouse antibodies (Immulite 2500, Abbott IMX, Abbot Park, Ill., USA). Hyperhomocysteinemia was defined as fasting tHcy levels above 12.0 μmol/l.

Statistics

Normality of data distribution was checked with skewness and kurtosis tests. Unpaired t tests were used to compare parametric data between: (1) patients with sCAD, and (2) patients with atherothrombotic or small artery disease; χ^2 tests or Fisher exact test were used to compare nominal data. Logistic regression models were performed to evaluate the association between tHcy levels and: (1) patients with sCAD, and (2) patients with atherothrombotic or small artery disease (considered either as a continuous or as a binary variable with an increased level defined at ≥12 μmol/l), while adjusting for 12 covariates (sex, age, current and past smoking, hypertension, diabetes mellitus, hypercholesterolemia, decreased HDL cholesterol levels, increased LDL cholesterol levels, increased total/HDL cholesterol ratio, increased triglyceride levels, migraine with aura). Current antiplatelet or anticoagulant therapy was not considered in the analysis, as no influence on tHcy levels has been proven [5]. Analysis of covariance was used to compare tHcy levels among: (1) patients with sCAD, (2) patients with atherothrombotic or small artery disease, and (3) healthy controls, while adjusting for age and gender. Bonferroni correction was applied in multiple group comparisons.

Sensitivity analysis was also applied to find the best discriminating threshold value of tHcy for predicting sCAD. Statistical analysis was carried out with Stata, release 9.2 (College Station, Tex., USA).

Results

Six hundred and sixty-eight consecutive patients (445 men; mean age 62.5 ± 13.6 years, range 20–90) had a first-ever ischemic stroke due to sCAD (n = 108) or atherothrombotic or small artery disease (n = 560). All 344 (52%) of the 668 patients who presented within 24 h after the onset of symptoms (235 men; mean age 60.5 ± 13.8

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Table 1. Presenting characteristics of patients with stroke due to sCAD (n = 86) and atherothrombotic or small artery disease (n = 260), and simple and multiple logistic regression models evaluating the association between sCAD and tHcy levels

	sCAD	Atherothrombotic or small artery disease	p	Crude models		Adjusted model	
				OR and 95% CI	p	OR and 95% CI	p
Male sex, n	58 (67)	177 (68)	0.913	0.97 (0.58–1.64)	0.913	1.63 (0.59–4.46)	0.344
Mean age, years	46.1 ± 10	65.3 ± 11.1	<0.0001	0.86 (0.84–0.89)	0.000	0.86 (0.83–0.90)	0.000
Smoking actual, n	30 (35)	91 (35)	0.984	0.99 (0.60–1.66)	0.984	0.37 (0.16–0.86)	0.020
Smoking past 5 years, n	10 (12)	59 (21)	0.026	0.45 (0.22–0.92)	0.029	0.80 (0.26–2.44)	0.696
Hypertension, n	22 (26)	190 (73)	<0.0001	0.13 (0.07–0.22)	0.000	0.30 (0.14–0.64)	0.002
Diabetes mellitus type II, n	1 (1)	38 (15)	0.001	0.07 (0.01–0.51)	0.009	0.10 (0.01–1.44)	0.090
Migraine with aura, n	10 (12)	8 (3)	0.002	4.14 (1.58–10.87)	0.004	1.18 (0.26–5.22)	0.832
Mean total cholesterol, mmol/l	5.51 ± 1.24	5.78 ± 1.31	0.092	0.84 (0.69–1.03)	0.100	1.08 (0.38–3.01)	0.890
Mean HDL cholesterol, mmol/l	1.40 ± 0.34	1.55 ± 0.89	0.019	0.71 (0.46–1.09)	0.122	0.11 (0.01–1.34)	0.084
Mean LDL cholesterol, mmol/l	3.56 ± 1.26	3.40 ± 1.16	0.326	1.11 (0.91–1.36)	0.305	2.61 (0.94–7.25)	0.065
Mean ratio total/HDL cholesterol	4.08 ± 1.49	4.31 ± 1.41	0.204	0.89 (0.74–1.06)	0.191	0.42 (0.20–0.89)	0.024
Mean triglyceride, mmol/l	1.59 ± 1.16	1.89 ± 1.24	0.043	0.79 (0.62–1.00)	0.052	1.38 (0.86–2.22)	0.185
Mean homocysteine, μmol/l	11.4 ± 3.8	13.6 ± 6.6	0.002	0.92 (0.87–0.97)	0.002	0.89 (0.81–0.98)	0.019

Figures in parentheses are percentages or 95% CI. Regression models were adjusted for 12 covariates (sex, age, current and past smoking, hypertension, diabetes mellitus, hypercholesterolemia, decreased HDL cholesterol levels, increased LDL cholesterol levels, increased total cholesterol/HDL cholesterol ratio, increased triglyceride levels, migraine with aura).

years, range 20–87; sCAD, n = 86, 80%; atherothrombotic or small artery disease, n = 260, 46%) were included in the study. The remaining 322 (48%) patients presented after 24 h. Their presenting characteristics (table 1) did not differ from those of the study population, with the exception of a higher mean age (64.6 ± 13.2 years, range 22–90; p = 0.0001) and frequency of diabetes mellitus (20.0 vs. 11.3%; p = 0.002), and a lower frequency of sCAD (6.8 vs. 24.9%; p < 0.001).

The 86 patients (58 men; mean age 46.1 ± 10.4 years, range 20–68) with stroke due to sCAD had 68 dissections of the internal carotid artery (sICAD) and 24 dissections of the vertebral artery (sVAD). sCAD included unilateral sICAD in 64 patients, unilateral recurrent sICAD in 1 patient, unilateral sVAD in 15 patients, bilateral sVAD in 3 patients, and both sICAD and sVAD in 3 patients. In the 260 patients (177 men; mean age 65 ± 11 years, range 35–90) with stroke due to atherothrombotic or small artery disease, the etiology of stroke was atherothrombotic artery disease in 158 (60.8%) and small artery disease in 102 (39.2%).

Compared to patients with atherothrombotic or small artery disease (table 1), those with sCAD were younger, had a higher prevalence of migraine with aura, a lower prevalence of former smokers, less hypertension and diabetes mellitus, lower triglyceride levels, and higher HDL cholesterol levels.

Hyperhomocysteinemia and tHcy Levels. Hyperhomocysteinemia was more prevalent in patients with sCAD (n = 33, 38%) than in healthy volunteers (n = 23, 23%; p = 0.034), and less prevalent than in patients with atherothrombotic or small artery disease (n = 149, 57%; p = 0.001). tHcy levels of patients with sCAD causing stroke (11.4 ± 3.8 μmol/l) were: (1) higher than in healthy volunteers (10.2 ± 3.0 μmol/l), but this difference was not significant (p = 0.61), and (2) lower than in patients with stroke due atherothrombotic or small artery disease (13.6 ± 6.6 μmol/l, p = 0.002; crude OR: 0.92, 95% CI: 0.87–0.97, p = 0.002) which remained significant after adjusting for age and sex (adjusted OR: 0.89, 95% CI: 0.81–0.98, p = 0.019; table 1).

Considering all patients, increasing tHcy levels showed a weak association with stroke due to atherothrombotic or small artery disease (R^2 = 0.029; p = 0.002), age (R^2 = 0.026; p = 0.003) and male gender (R^2 = 0.025; p < 0.004). In multiple regression analysis, just the weak association with sex remained significant (R^2 = 0.062; p = 0.0011).

Discussion

In the present case-control study, we found that patients with ischemic stroke due to sCAD had: (1) a higher prevalence of mild hyperhomocysteinemia, but similar

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Table 2. tHcy levels in healthy subjects, patients with sCAD with and without ischemic stroke, and patients with ischemic stroke due to a cause other than cervical artery dissection

First authors	Subjects and patients	Mean tHcy, μmol/l
Healthy subjects		
Gallai [3]	30	6.00 ± 0.99
Kelly [7]	2,554	11.1
Konrad [4]	95	10.7 ± 3.7
Pezzini [5]	36	8.9 (5–17.3)[2]
Soriente [33]	182	12.5 ± 7.8
Present study	100	10.2 ± 3.0
Patients with sCAD with/without stroke		
Konrad [4]	95	12.2 ± 4.0
Pezzini [5]	25	13.2 (7.0–32.8)[1]
Patients with sCAD and stroke		
Gallai [3]	26	17.88 ± 7.99 (5.94–40)
Present study	86	11.4 ± 3.8
Patients with stroke not due to sCAD		
Kelly [7]	1,487	13.5
Pezzini [5]	31	10.9 (6–30.2)[2]
Soriente [33]	60	15.8 ± 14.6
Present study	260	13.6 ± 6.6[2]

Figures in parentheses are ranges.
[1] Median.
[2] Ischemic stroke due to atherothrombotic or small artery disease.

tHcy levels compared to healthy volunteers, and (2) a lower prevalence of mild hyperhomocysteinemia and lower tHcy levels than patients with ischemic stroke caused by atherothrombotic or small artery disease, also after adjustment for age.

Prevalence of mild hyperhomocysteinemia was lower in the present patients with ischemic stroke due to sCAD (38%) compared to previous studies reporting values of 57–92% [3–5]. An explanation could be that the prevalence of mild hyperhomocysteinemia varies according to the geographical area and ethnic background of the population under investigation. However, a similar prevalence of mild hyperhomocysteinemia in the control groups of the present study (23%) and previous investigations (14–27%) [4, 5] counters this argument. Another explanation of those differences could be that tHcy levels have been shown to increase on the third and subsequent days after a stroke [15]. Blood samples for determining tHcy levels were obtained in the present study within 24 h after the onset of stroke symptoms – while in the 2 of 3 studies demonstrating higher tHcy levels [3, 5], they were taken within 3 [5] and 7 [3] days after the onset of the stroke. In the third study [4], blood samples were taken at a median delay of 833 days after the onset of sCAD symptoms. Lindgren et al. [18] reported an increase in the median tHcy level from 11.4 to 14.5 μmol/l from the acute (mean 2 days after stroke onset) to the chronic phase (median 583 days after stroke onset). Thus, the later blood sampling might explain the higher tHcy values and prevalence of mild hyperhomocysteinemia reported in previous studies [3–5]. Another cause of the difference in prevalence might be the low number of included patients with sCAD (table 2) [3–5].

tHcy levels were higher in patients with sCAD than in healthy volunteers, although the difference failed to reach statistical significance. In contrast, the difference between patients with sCAD and healthy volunteers was significant in previous studies [3–5] (table 2).

Total tHcy levels of the present patients with ischemic stroke due to atherothrombotic or small artery disease were similar compared to those of a meta-analysis including 1,487 patients with ischemic stroke (table 2) [7]. Thus, our findings underscore that patients with ischemic stroke have mild hyperhomocysteinemia [7].

In conclusion, this study suggest that patients with ischemic stroke due to sCAD have a small increase in prevalence of hyperhomocysteinemia compared to healthy volunteers, and the prevalence of hyperhomocysteinemia and tHcy levels are lower compared to patients with ischemic stroke due to atherothrombotic or small artery disease. The higher prevalence of hyperhomocysteinemia in stroke patients with atherothrombotic or small artery disease is evident, and explanations have been extensively discussed [7]. In contrast, the precise pathomechanism of tHcy levels slightly above normal values predisposing to the development of sCAD remains undetermined. The small difference in tHcy levels and prevalence of hyperhomocysteinemia between healthy volunteers and patients with sCAD might well be an artifact. This assumption is underscored by several findings: this study, like previous studies, does not have an assessment of tHcy levels before stroke onset. Even though the tHcy samples are collected soon after the event, there is still time for them to be affected by the stroke. Homocysteine has been suggested to be an acute-phase reactant [19, 20]. Therefore, elevated tHcy could be the consequence of cerebral ischemia or also an infection which has been shown to be associated with sCAD [21, 22] rather than a cause of the disease. Also, food deprivation increases the tHcy levels [18, 23, 24]. In acute stroke, patients are kept fasting, and tHcy may therefore increase independently of the ischemic process.

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The levels of tHcy increase with age and are higher in men than women [25–28], and latter has been reconfirmed in this study. Increasing tHcy levels are not associated with age, and, also after adjustment, the difference in age between patients with stroke due to sCAD and patients with stroke due to atherothrombotic or small artery disease does not account for the different tHcy levels observed between the 2 groups. These results are also in accordance with those of another study in patients with acute ischemic stroke [29], which found no association between tHcy levels and gender or age.

In the present study, patients with stroke due to sCAD were younger, had less vascular risk factors and lower tHcy levels compared to those with stroke due to atherothrombotic or small artery disease, and more often had a history of migraine with aura (table 1). The significantly higher age of patients with atherothrombotic or small artery disease is the most likely explanation of the observed differences in vascular risk factors [30]. The higher prevalence of migraine with aura in the sCAD patients reflects the observation in 3 case-control studies that migraine was an independent risk factor for sCAD [31].

In this study, total and LDL cholesterol levels as well as the ratio total/HDL-cholesterol were similar in patients with stroke caused by sCAD and atherothrombotic or small artery disease. Patients with sICAD causing ischemia have higher cholesterol levels than those without ischemia [32], which may explain the surprising lack of difference for cholesterol levels between both groups.

A limitation of the present and also previous studies is the fact that tHcy levels were obtained after and not before the onset of stroke or sCAD, which may explain the higher tHcy levels. Another limitation is the retrospective nature of the analysis, although the data have been collected prospectively. We had to exclude 20% of patients with stroke due to sCAD and 54% patients with stroke due to atherothrombotic or small artery disease. A possible explanation could be that the patients with sCAD are younger, and thus referred more rapidly. Another limitation is that the vascular risk factors, with the exception of tHcy, were determined by a comprehensive clinical screening procedure alone in the healthy subjects. Also, cofactors of the tHcy metabolism such as folate, vitamin B6 and B12, were not included in the routine investigation, and were just measured if the treating physician deemed it necessary. However, previous studies reported that the plasma levels of folate, vitamin B6 and B12 were in the normal range in patients with sCAD, and did not differ between patients with stroke due to sCAD and other causes [3, 4].

In conclusion, this case-control study suggests that patients with ischemic stroke caused by sCAD have an increased prevalence of hyperhomocysteinemia compared to healthy subjects, but a lower prevalence of hyperhomocysteinemia and lower tHcy levels compared to patients with stroke due to atherothrombotic or small artery disease. Mild hyperhomocysteinemia may be a risk factor for sCAD causing ischemic stroke, but further studies are needed to identify a possible pathomechanism. This study confirms the association of hyperhomocysteinemia with ischemic stroke due to atherothrombotic or small artery disease.

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