

Plasma homocysteine level and the course of ischemic stroke

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Abstract. Increased level of homocysteine (Hcy) in blood seems to influence negatively the course of ischemic stroke (IS), the possible mechanism of this action could be acceleration of oxidative stress. The aim of this study is to assess the influence of Hcy level in patients with IS on the prognosis 3 months after the stroke onset. 75 patients aged 68.27 ± 12.62 years, with the diagnosis of first ever IS were examined. Patients with the symptoms corresponding with TACS at the beginning of stroke and with diminished level of consciousness were not included. The level of Hcy over $15 \mu\text{mol/l}$ was assessed as mild hiperhomocysteinemia (MHcy). 74 (98.7%) patients were assessed 3 months after IS onset in the Rankin scale. Recovery was assessed, according to Rankin Scale: good recovery (GR) 0-2, bad recovery (BR) 3-5 and death. MHcy was seen in 9 (14.5%) with GR and in 8 (66.7%) with BR ($P=0.0005$). MHcy increases the risk of BR 11.78 times (95%CI 2.93-47.42).

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Homocysteine (Hcy) is the product of dietary amino acid methionine metabolism. Its plasma level depends both: on dietary and hereditary factors (Hankey and Eikelboom 1999). The correlation between cardiovascular diseases and mild elevation of Hcy level in blood is widely discussed in the literature (Hankey and Eikelboom 1999, McCully 1969, Wald et al. 2002). Usually the level of Hcy over 15 $\mu\text{mol/l}$ is regarded as mild hiperhomocysteinemia (Hankey and Eikelboom 1999). Many authors claim that homocysteine is an independent risk factor for developing of atherothrombotic vascular disease (Bautista et al. 2002, Schnyder et al. 2002, Wald et al. 1998) among them stroke (Bostom et al. 1999, Hankey and Eikelboom 2001). It is also suggested, that increased level of homocysteine is found in patients with more severe course of the cardiovascular disease (Al-Obaidi et al. 2000, Omland et al. 2000, Malinow et al. 1996) being the causative factor of this bad outcome. Nygard et al. (1997) found that increased level of homocysteine increased the probability of death in patients with coronary artery disease. One of the possible mechanisms of action of homocysteine on the course of the disease could be activation of oxidative stress which could be one of the mechanisms involved in neuronal damage induced by ischemia (El Kossi and Zakhary 2000, Leinonen et al. 2000, Lipton et al. 2000).

Poland belongs to the countries with relatively high stroke mortality (Sarti et al. 2000). At the same time the incidence of stroke is comparable with this found in Western Europe. Massing et al. (1998) found the existence of different stroke mortality trends in Poland and USA (decreased in USA and increased in Poland). All above-mentioned facts implies that prognosis in patients with stroke in Poland is worse in comparison with the western countries. Probably there is no simple factor responsible for that. It is probably truth, that management of stroke in Poland is generally beyond the western standards, but probably this fact couldn't be responsible for the whole difference.

In the present work, we wanted to test the hypothesis that increased level of homocysteine is associated with more serious course of the ischemic stroke.

Our material consists of 75 patients with first ever ischemic stroke (demographic data and risk factors are shown in Table I). The patients with the signs corresponding with Total Anterior Circulation Stroke (TACS) at the beginning, as well as the patients with disturbances of consciousness were not included into

Table I

Characteristic of the patients (<i>n</i> = 75)	
Age (mean \pm SD)	68.27 \pm 12.62
Males/Females	42/33
Hypertension	48 (64%)
Diabetes Mellitus	12 (16%)
Coronary Artery Disease	31 (41%)
Myocardial Infarction in history	11 (15%)

the study. Detailed medical history based on the standard questionnaire was obtained from the patients and their relatives. In accordance with the obtained data prestroke handicap of the patients was assessed in the Modified Rankin Scale (Warlow 1991) which assessed whole patient handicap – both due to neurological and non-neurological impairments. Patients who were assessed as more than 1 in Rankin scale before the stroke and with any suspicion of prestroke dementia were excluded from the study. In all the patients CT scan was performed in order to exclude the other possible cause of the disease. At the time of inclusion neurological deficit must be present.

All the patients were treated and diagnosed within the Stroke Unit according to the local protocol and recommendation of European Stroke Initiative (2000). The stroke cause was then established according to the TOAST criteria for probable cause of stroke (Adams et al. 1993).

In all the patients the venous blood (3 ml in EDTA) was drawn within 24 hours from the stroke onset after 8 hours fasting. The blood was centrifuged within 1 hour, and plasma separated and aliquoted into a plastic tube and frozen at -70°C . Homocysteine level was then measured using immunoassay method (Shipchandler and Moore 1995). The level over 15 $\mu\text{mol/l}$ was regarded as mild hiperhomocysteinemia.

The physician (blind to the result of homocysteine assessment) observed all the patients for three months from the stroke onset. All of them obtained appropriate secondary prevention for stroke (aspirin, ticlopidin or oral anticoagulation). Three months after stroke onset they were assessed in the Modified Rankin Scale. In accordance with these results they were arbitrary divided into two groups: patients with good recovery (GR - Rankin 0-2), and patients with bad recovery (BR - Rankin 3-5, death) after 3 months.

Table II

Homocysteine level in different patients groups				
	All patients <i>n</i> = 75	Good Recovery (GR) <i>n</i> = 62	Bad Recovery (BR) <i>n</i> = 12	<i>P</i> (between GR and BR)
Hcy level \pm SD	12.57 \pm 4.47	11.64 \pm 3.49	16.8 \pm 6.15	0.01
	mmol/l	mmol/l	mmol/l	
No of patients with Hcy > 15 mmol/l	18 (24%)	9 (14.5%)	8 (66.7%)	0.0005

The local ethics committee approved the study.

Among the 75 patients we diagnosed (using TOAST criteria) large artery atherosclerosis in 9 (12.0%), cardioembolism in 10 (13.3%), lacunar stroke in 10 (13.3%), other cause 1 (1.4%) and in 45 (60%) stroke of undetermined etiology. The mean Hcy level was 12.57 \pm 4.47 μ mol/l in our patients group. In 18 (24%) patients we found mild hiperhomocysteinemia.

We got follow up in 74 out of 75 patients (98.7%). Within three months 3 patients died (4.1%). In 62 patients (83.8%) there was GR and in 12 (16.2%) BR, in accordance to the distinction described above. Detailed results of Hcy level in the studied groups are shown in the Table II. The relative risk of bad prognosis of stroke in patients with mild hiperhomocysteinemia increased among our patients 11.78 times (95%CI 2.93-47.42). Using stepwise logistic regression we found, that only mild hiperhomocysteinemia was associated with bad outcome, other tested variables: age, sex, hypertension, diabetes mellitus, myocardial infarction and coronary artery disease had no influence on the stroke outcome.

In our group of patients mild hiperhomocysteinemia was found statistically more often in patients with bad stroke recovery. Only 4.1% of our patients died. It was because we deliberately didn't include into the study patients with the most severe stroke (TACS at the beginning, disturbances of consciousness), as in this group the burden caused by stroke at the beginning is so big, that there is no place for future fluctuation of the patients condition. There is very probably, that this is also the cause for the under representation of atherosclerosis as a stroke etiology, (which has usually more serious course). But the main aim of this study was to evaluate the impact of hiperhomocysteinemia on the stroke

course and not to test otherwise well-documented hypothesis, that Hcy is a risk factor for atherosclerosis and stroke (Eikelboom et al. 2000, Shimizu et al. 2002).

Our results may suggest that a mild hiperhomocysteinemia could be connected with bad stroke outcome. Similar results with the respect to the coronary artery disease were also found by Nygard et al. (1997). In this work the authors found that the increased level of homocysteine increased the risk of death in patients with coronary artery disease. Omland et al. (2000) found similarly, that serum Hcy concentration could be regarded as an indicator of survival in patients with acute coronary syndrome. Other authors draw similar conclusion in the patients with coronary artery disease (Al-Obaidi et al. 2000, Schnyder et al. 2002). Malinow et al. (1996) documented the difference between the homocysteine level in different populations (higher in Ireland and lower in France). According to the results this difference could be partially responsible for the different mortality from coronary artery disease in these two populations (much higher in Ireland). The mechanism by which Hcy could influence the severity of tissue damage caused by ischemia is not clear. El Kossi and Zakhary (2000) proposed that homocysteine could be responsible for free radical generation and this way lead to the injury during acute phase of stroke. Similar conclusion was formed by Al-Obaidi et al. (2000) in the work dealing with patients with acute coronary syndrome.

All those data could suggest, that mild hiperhomocysteinemia could influence negatively the course of ischemia. Taking into consideration the fact, that homocysteine level is at least partially dietary dependent, these results (if confirmed in the future) could explain (of course partially) the difference in the stroke course between the populations with different Hcy levels).

CONCLUSION

Mild hiperhomocysteinemia influenced negatively the course of stroke increasing the risk of bad outcome 11.78 times (95%CI 2.93-47.42).

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