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The relation between hyperhomocysteinemia and the intima-media complex thickness in common carotid artery, as risk factors for ischemic stroke

Zależność między hiperhomocysteinemią a grubością kompleksu intima media tętnic szyjnych wspólnych jako czynniki ryzyka udaru niedokrwiennego mózgu

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Keywords

carotid IMT, risk factors, homocysteine, stroke

Słowa kluczowe

grubość błony wewnętrznej i środkowej tętnic szyjnych (KIM), czynniki ryzyka, homocysteina, udar

Summary

Introduction. Cerebrovascular events are the third most frequent cause of death globally and the most common cause of disability in the general population. There may be other, rarer disorders predisposing to cardiovascular complications, besides traditional risk factors of ischemic stroke, as the data prove, one of them is hyperhomocysteinemia.

Aim. Relation between intima-media complex thickness (IMT) and homocysteine level in patients with ischemic stroke.

Material and methods. The study group consisted of 32 patients with first-ever ischemic stroke diagnosed. The control group contained of 28 healthy people matched in terms of gender and age. The concentration of homocysteine was measured in the blood serum using the IMX immunoassay ABBOTT analyzer. Evaluation of intima-media thickness of carotid arteries was performed with Sonoline ELEGRA using a 7.5 L 40 line probe at 9 MHz.

Results. The average homocysteine concentration in patients with ischemic stroke was 16.55 umol/L. Elevated values of homocysteine were found in 20 patients. In Doppler examination of the carotid arteries, the mean IMT in patients with stroke was 0.88. The correlations between the homocysteine level and the IMT were evaluated- in the control group and in patients with stroke.

Conclusions. There is relationship between hyperhomocysteinemia and increased thickness IMT in young patient with ischemic stroke.

Streszczenie

Wstęp. W populacji ogólnej incydenty naczyniowo-mózgowe są trzecią najczęstszą przyczyną zgonów na świecie i najczęstszą przyczyną niepełnosprawności. Poza tradycyjnymi czynnikami ryzyka udaru niedokrwiennego mózgu, mogą występować inne, rzadsze zaburzenia, predysponujące do powikłań sercowo-naczyniowych, np. hiperhomocysteinemia.

Cel pracy. Określenie zależności między grubością KIM i poziomem homocysteiny u pacjentów z udarem niedokrwiennym mózgu.

Materiał i metody. Grupę badaną stanowiło 32 pacjentów z dokonanym, pierwszorazowym udarem niedokrwiennym mózgu. Grupę kontrolną stanowiło 28 osób zdrowych dobranych pod względem płci i wieku. Stężenie homocysteiny oznaczano w surowicy krwi za pomocą analizatora immunologicznego IMX firmy ABBOTT. Badanie grubości błony wewnętrznej i środkowej tętnic szyjnych (KIM) wykonano aparatem Sonoline ELEGRA z użyciem sondy liniowej 7,5 L 40 przy częstotliwości 9 MHz.

Wyniki. Średnie stężenie homocysteiny u pacjentów z udarem niedokrwiennym mózgu wyniosło 16,55 umol/L. Podwyższone wartości stwierdzono u 20 pacjentów z grupy badanej. W badaniu dopplerowskim tętnic szyjnych, średnia grubość KIM u chorych z udarem mózgu wynosiła 0,88. Następnie oceniono zależności między poziomem homocysteiny a grubością KIM – w grupie kontrolnej oraz u pacjentów z udarem mózgu.

Wnioski. Występuje zależność między współistnieniem hiperhomocysteinemii i zwiększoną grubością KIM u młodych pacjentów z udarem niedokrwiennym mózgu.

Conflict of interest
Konflikt interesów

None
Brak konfliktu interesów

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INTRODUCTION

Cerebrovascular events are the third most frequent cause of death globally and the most common cause of disability in the general population (1).

Ischemic stroke is a consequence of the coexistence of comorbidities and the presence of factors conducive to the development of changes in the vessels of micro- and macrocirculation. There may be other, rarer disorders predisposing to cardiovascular complications, besides traditional risk factors of ischemic stroke, as the data prove. One of them is hyperhomocysteinemia (2-4).

Even mild hyperhomocysteinemia (hHcy) may increase the risk of ischemic stroke, as has been confirmed in studies. The prevalence of hyperhomocysteinemia in people with stroke is 19-42% (4, 5).

Homocysteine is a sulfuric aminoacid, that is converted into cysteine or methionine under physiological conditions. Hyperhomocysteinemia is associated mainly with genetically determined deficiency of cystathionine β-synthase and deficiency of methylenetetrahydrofolate reductase (6, 7).

Hyperhomocysteinemia is more common in the elderly, male, those with folic acid, B_6 and B_{12} vitamins deficiency, alcohol and caffeine abusers, tobacco-smokers, those treated with certain drugs (methotrexate, phenytoin, carbamazepines, folic acid antagonists, levodopa) and suffering from certain diseases like malignant tumors, hypothyroidism, Alzheimer's disease or arterial hypertension (5-7).

High concentration of homocysteine activity damage of vascular endothelium (through cytotoxic activity) (5). In addition, homocysteine shows a pro-thrombotic effect by neutralizing vasodilatatory effect of NO through binding it – which leads to the vasoconstriction and increased platelet aggregation ability, may lead to the occurrence of arterial and venous thrombosis in organs (brain, myocardium, lungs and kidneys) (8). Also contributes to the modification of cholesterol fractions LDL and HDL, intensification of the inflammatory condition and disregulation of coagulation and fibrinolysis processes (6). Therefore, hyperhomocysteinemia has been recognized in recent years as a risk factor for ischemic strokes.

The thickness of the internal membrane and carotid median membrane (intima-media complex thickness – IMT) can be considered as a morphological exponent of the risk factors for atherosclerosis and ischemic stroke. It has been proved, that there is a clear, positive correlation between the thickness of intima-media complex and the risk of ischemic stroke (9-11). So far, many studies have been published, that show relationship between structural changes in the carotid vascular wall, expressed in IM thickening, presence of atherosclerotic plaques, and exposure to the basic risk factors for stroke. In addition, IMT (intima-media thickness) increases linearly with age (12), and therefore seems to be a good determinant of the biological age of vessels (9).

AIM

As a consequence of the above mentioned, the aim of the study was to determine relation between intima-media complex thickness (IMT) and homocysteine level in patients with ischemic stroke.

MATERIAL AND METHODS

The study group consisted of 32 patients with first-ever ischemic stroke diagnosed according to the criteria adopted in the Classification of Cerebrovascular Diseases III (13). In all of the patients examined, the diagnosis of ischemic stroke was confirmed by the computed tomography of the head, carried out within 24 hours of the onset of clinical symptoms of the disease. To eliminate patients with ischemic stroke resulting from cardiac embolism, in which the occurrence of stroke may be determined by valvular or arrhythmic disorders, those with permanent and paroxysmal atrial fibrillation, valvular defects and left ventricular hypertrophy were excluded from our study.

The control group contained of 28 healthy people matched in terms of gender and age. Examinations of persons from the control group were carried out after obtaining their written consent. The homocysteine concentration in the blood serum and the IMT were determined in all subjects.

The concentration of homocysteine was measured in the blood serum using the IMX immunoassay analyzer from ABBOTT. A type of FPIA (Fluorescent Polarization Immunoassay) reaction, i.e. an enzyme-based immunoenzymatic reaction based on fluorescence polarization, was used for this purpose.

Evaluation of intima-media thickness of carotid arteries was performed with Sonoline ELEGRA using a 7.5 L 40 line probe at 9 MHz. IMT was obtained using module for automated measurement.

The examination was performed with the patient in the supine position with the neck slightly extended and head turned away from the side being examined. Common carotid artery was exposed in longitudinal plane.

Measurements were made on the distal artery wall at a distance of 1-2 cm before the sinus at 3 points determined depending on the location of the probe relative to the sternocleidomastoid muscle (front, lateral, posterior). The thickness of the inner and middle membrane was assumed to be the distance between the first hyperechogenic structure constituting the border between the lumen of the vessel (hypoechogenic blood) and the inner layer of the vessel and the second hyperechogenic line corresponding to the reflection from the vessel's adventitia. The average of all measurements was considered as the result representing IMT of specific artery. We did not include atherosclerotic plaques (thickness > 1 mm or > 100 thickening of the complex in relation to the adjacent segment).

RESULTS

32 patients with diagnosed ischemic stroke were examined: 9 women and 23 men aged 38-57 years (mean

age 47 years) and 28 healthy volunteers from the control group. The homocysteine concentration in serum was determined in all subjects. The average homocysteine concentration in patients with ischemic stroke was 16.55 umol/L (minimum 7.18, max 19.5 umol/L) (fig. 1).

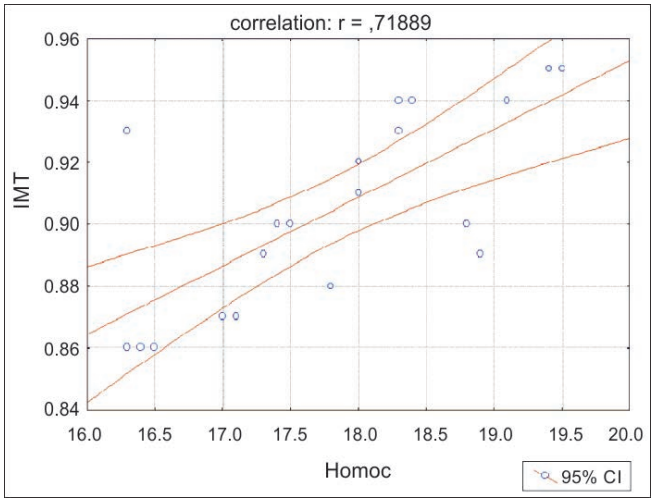

Fig. 1. Correlation between IMT and hyperhomocysteinemia

The following values were obtained in the control group: average 9.28 umol/L (minimum 6.9, max. 14.8 umol/L). While normal values for people under 60 are 5-15 umol/L, and above 60 years of age 5-20 umol/L.

Elevated values of homocysteine were found in 20 patients from the study group.

All patients also had Doppler examination of the carotid arteries. The mean IMT in patients with stroke was 0.88, including: IMT on the left side – 0.90 on average (min. 0.55, max. 0.95), on the right side – 0.86 on average (min. 39, max. 0.94, respectively in the control group: the average IMT was 0.69 IMT on the left in the control group – on average 0.66, on the right – on average 0.70.

Three groups of patients were distinguished:

- group I – patients with hyperhomocysteinemia and increased IMT (20 people – 62.5%),
- group II – patients with elevated IMT with normal homocysteine concentration (8 people – 25%),
- group III, in which high homocysteine concentration was found at the correct KIM thickness (4 – 12.5%).

Next, the correlations between the homocysteine level and the IMT were evaluated – in the control group and in patients with stroke.

In group I, a statistically significant linear correlation was found between hyperhomocysteinemia and IMT. Such correlations have not been demonstrated in the case of other groups of patients (fig. 1).

DISCUSSION

Results we received are consistent with observations made by other authors. Bos MJ and colleagues have shown that hyperhomocysteinemia is a risk factor for recurrent TIA episodes and ischemic stroke in patients aged 18-45, who were not burdened with other risk factors for stroke (14). Similar results were obtained by Toyoda et al. (15) and Boysen et al., investigating 1039 elderly patients with recurrent stroke (16).

Patients who were included in our study also had no other risk factors for stroke, while the vascular episode occurred for the first time in their lives.

Hyperhomocysteinemia, according to some authors is an independent risk factor for vascular diseases leading to atherosclerosis of large arteries. This was confirmed by Parnetti et al. who evaluated homocysteine concentration in the group of 161 patients with ischemic stroke (17).

Similar results were obtained by Tan NC by examining a group of 109 patients of Asian origin, who were under 50 (18). Eikelboom et al. stated, on the basis of research conducted in patients with the first in life ischemic stroke that elevation of homocysteine by 5 μmol/l may be a strong independent risk factor for stroke (3). Prevalence of hyperhomocysteinemia in stroke patients is determined depending on the source: from 19% (19) to 42% (20). Smaller part of patients, cause only 12.5% showed elevated homocysteine concentration in the examined group.

25% of patients with ischemic stroke had an increased IMT without additional risk factor in the form of hyperhomocysteinemia. There is a positive correlation between the IMT and the risk of ischemic stroke, as showed research published so far by other authors. Statistically significant relationship between IMT and the occurrence of stroke was found by Kazmierski et al., who investigated group of 47 people with ischemic stroke and 50 people from the control group (9). IMT was evaluated in group of 470 patients with ischemic stroke and 463 patients of control group by Touboul et al. Linear relationship between IMT and the occurence of stroke was shown by authors (21). Directly proportional dependence was found between IMT and the risk of ischemic stroke and myocardial infarction in older patients by Kitamura et al. in study on a group of more than 1129 people (22).

Our study concerned young patients. Patients with hyperhomocysteinemia, as well as with increased IMT were the largest group – 20 people (62.5%). Statistically significant relationship between hyperhomocysteinemia and IMT was shown in the study. Similar conclusions were drawn by Okamura et al., who examined group of 474 patients from Japanese population. Correlation was found by authors between high homocysteine levels and intensity of atherosclerotic lesions in precerebral arteries in older patients (60-74 years) (23). Correlation was also shown by Rahman et al. between homocysteine level and IMT (24). This suggests that increased IMT, in addition to hyperhomocysteinemia is another risk factor for ischemic stroke. There wasn't any relationship found between homocysteine level, IMT and the genomic MTHFR polymorphism in this study of 130 patients with type 2 diabetes. These

authors showed, that IMT was associated with other factors such as age, body mass index, systolic blood pressure, level of blood glucose and cholesterol (25). Similar conclusion was drawn by Linnebank et al. Dependence was found between IMT and age, gender, creatinine concentration, lipoprotein A level, smoking, hypertension and diabetes. There wasn't any correlation found between IMT and homocysteine level in their study of German population (26).

CONCLUSIONS

It can be concluded, based on our research, that important role plays concomitance of hyperhomocysteinemia and increased IMT in young people, apart from other known risk factors of ischemic stroke.

As we know, pathogenesis of homocysteine-induced vascular lesions is multifactorial. Among factors involved in this process are: direct damage of vascular endothelium by homocystein, stimulation of smooth muscle cells proliferation, increased peroxidation of LDL lipoprotein, increased platelet aggregation and direct effect on coagulation (8). These processes may also affect the thickness of infima-media complex, and thus induce predisposition to ischemic stroke.

BIBLIOGRAPHY

1. Ryglewicz D: Czynniki ryzyka w udarach mózgu. Post Psychiatr Neurol 1994; 5: 33-40.
2. Choy PC, Mymin D, Zhu Q et al.: Atherosclerosis risk factors: the possible role of homocysteine. Mol Cell Biochem 2000; 207(1-2): 143-148.
3. Eikelboom JW, Hankey GJ, Anand SS et al.: Association between high homocysteine and ischemic stroke due to large-and small-artery disease but not other etiologic subtypes of ischemic stroke. Stroke 2000; 31(5): 1069-1075.
4. Lehotsky J, Tothova B, Kovalska M et al.: Role of Homocysteine in the Ischemic Stroke and Development of Ischemic Tolerance. Front Neurosci Nov 2016; 10: 538.
5. Banecka-Majkutewicz Z, Gąsecki D, Jakóbkiewicz J et al.: Hiperhomocysteinemia – ważny czynnik ryzyka udaru mózgu. Udar mózgu 2005; 7: 61-65.
6. Baszczuk A, Kopczyński Z, Thielemann A: Dysfunkcja śródbłonka naczyniowego u chorych na pierwotne nadciśnienie tętnicze z hiperhomocysteinemią. Postępy Hig Med Dosw 2014; 68: 91-100.
7. Adamkiewicz B: Hyperhomocysteinemia a ryzyko udaru mózgu. Akualności Neurol 2002; 2(3): 236-244.
8. Fridman O: Hyperhomocysteinemia: atherotrombosis and neurotoxicity. Acta Physiol Pharmacol Ther Latinoam 1999; 49(1): 21-30.
9. Kaźmierski R, Kozubski W, Watała C: Grubość kompleksu intima-media tętnic szyjnych wspólnych oceniona metodą ultrasonografii jako czynnik ryzyka udaru niedokrwiennego mózgu. Neur Neurochir Pol 2000; 34(2): 243-253.
10. Mannami T, Konishi M, Baba S et al.: Prevalence of asymptomatic carotid atherosclerotic lesions detected by high-resolution ultrasonography and its relation to cardiovascular risk factors in the general population of a Japan city: the Suite study. Stroke 1997; 28: 518.
11. Polak J, Pencina M, O'Leary D et al.: Common carotid artery intima-media thickness (IMT) progression as a predictor of stroke in MESA (Multi-Ethnic Study of Atherosclerosis). Stroke 2011; 42(11): 3017-3021.
12. Veller MG, Fisher CM, Nicolaides A et al.: Measurement of the ultrasonic intima-media complex thickness in normal subjects. J Vasc Surg 1993; 17: 719.
13. Classification of Cerebrovascular Diseases III. Stroke 1990; 21: 637.
14. Bos MJ, van Goor ML, Koudstaal PJ et al.: Plasma homocysteine is a risk factor for recurrent vascular events in young patients with an ischaemic stroke or TIA. J Neurol 2005; 252(3): 332-337.
15. Toyoda K, Uwatoko T, Shimada T et al.: Recurrent small-artery disease in hyperhomocysteinemia: widowers' stroke syndrome? Intern Med 2004; 43(9): 869-872.
16. Boysen G, Brander T, Christensen H et al.: Homocysteine and risk of recurrent stroke. Stroke 2003; 34(5): 1258-1261.
17. Parnetti L, Caso V, Santucci A et al.: Mild hyperhomocysteinemia is a risk-factor in all etiological subtypes of stroke. Neurol Sci 2004; 25(1): 13-17.
18. Tan NC, Venketasubramanian N, Saw SM et al.: Hyperhomocysteinemia and risk of ischemic stroke among young Asian adults. Stroke 2002; 33(8): 1956-1962.
19. Lindgren A, Brattstrom L, Norrving B et al.: Plasma homocysteine in the acute and convalescent phases after stroke. Stroke 1995; 26: 795-800.
20. Clarke R, Frost C, Leroy V et al.: Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomized trials. Homocysteine Lowering Trialists' Collaboration. BMJ 1998; 316: 894-898.
21. Touboul PJ, Elbaz A, Koller C et al.: Common carotid artery intima-media thickness and brain infarction: the Etude du Profil Genetique de l'Infarctus Cerebral (GENIC) case control study. The GENIC Investigators. Circulation 2000; 102(3): 313-318.
22. Kitamura A, Iso H, Imano H et al.: Prevalence and correlates of carotid atherosclerosis among elderly Japanese men. Atherosclerosis 2004; 172(2): 353-359.
23. Okamura T, Kitamura A, Moriyama Y et al.: Plasma level of homocysteine is correlated to extracranial carotid-artery atherosclerosis in non-hypertensive Japanese. J Cardiovasc Risk 1999; 6: 371-377.
24. Rahman A, Quraishi F, Miah N et al.: Relationship between homocysteine and carotid artery stenosis in ischemic stroke. J Neurosci 2012; 28(1): 1-9.
25. Mazza A, Motti C, Nulli A et al.: Lack of association between carotid intima-media thickness and methylenetetrahydrofolate reductase gene polymorphism or serum homocysteine in non-insulin-dependent diabetes mellitus. Metabolism 2000; 49: 718-723.
26. Linnebank M, Moskau S, Farmand S et al.: Homocysteine and carotid intima-media thickness in a German population: lack of clinical relevance. Stroke 2006; 37: 2840-2842.

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