RELATED HYPERHOMOCYSTEINEMIA AS A CAUSE OF SECONDARY HIGH RISK OF CEREBROVASCULAR EVENTS IN PATIENTS HAVING IN THE ANAMNESIS CEREBROVASCULAR DISORDERS. THE CLINICAL ANALYSIS

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Annotaiton. This paper discusses the patients with stroke in case history, high blood pressure and high level of homocysteine. Will these events contribute to the high probability of the risk of secondary cerebrovascular disease and how these cerebrovascular risks depend on the relations between the levels homocysteine and high blood pressure.

Our results indicate that elevated levels of plasma homocysteine level of above 10.0 μmol/L and the presence of hypertension are associated with increased risk of secondary cerebrovascular disease patients after the first stroke.

Cerebrovascular risks are gendered nature: Research homocysteine level of the adult population of six Chinese cities showed that 75% of subjects have elevated levels homocysteine (> 10 μmol/L). Among adults with elevated levels homocysteine men was 91% and the women's — 60%.

The study also found that patients with a high risk of secondary cerebrovascular diseases were two major risk factors — high blood pressure and elevated levels of homocysteine.

Thus, according carried out the clinical analysis the main cause of secondary cerebrovascular risk is closely associated with high blood pressure and elevated levels of homocysteine concentration in primary anamnesis with the presence of a stroke. These two factors potentiated each other and increase the risk of secondary cerebrovascular events.

Key words: hypertension; homocysteine; stroke; recurrence; risk factor, stroke relapse.

Introduction. Cerebrovascular disease (CVD) is one of the leading causes of morbidity and mortality worldwide and places a huge burden on the health care system. The most common forms of CVD are ischemic cerebrovascular disease (ICVD) and hemorrhagic cerebrovascular disease (HCVD). Since, the treatment, prognosis and rehabilitation of CVD is frustrating, prevention of CVD by properly addressing its modifiable risk factors might be the spearhead to combat the burden. There are several established risk factors associated with CVD, but a newer modifi-
able risk factor, hyperhomocysteinemia has created a new window for limiting the occurrence of CVD. Homocysteine is potentially vasculotoxic because of its association with endothelial dysfunction and impairment of fibrinolytic system.

**Objective.** Examine does increased homocysteine levels in patients with high blood pressure and the carry-forward of the primary stroke history at high risk of secondary stroke.

**OBJECTS AND METHODS**

1. **Object:** in patients with cerebral apoplexy studies began in June 2007 and June 2011, 200 stroke patients were selected for the survey in our hospital. Men were analyzed according to the international classification 9(ICD9) standard version, the presence of high levels of homocysteine, the presence of stroke, high blood pressure cerebral infarction (cerebral infarction, 90 cases), lacunar cerebral infarction (62 cases) and cerebral hemorrhage (48 cases). The central nervous system is examined using computer tomography (CT) or magnetic resonance imaging (MRI) in diagnosis. A neurologist based on the basic clinical material was evaluated by a special manifestation of stroke scale. Dynamic control was carried out using a special questionnaire or by phone.

In patients with a high risk of recurrent stroke, cerebrovascular events were repeated in 95% of cases.

Follow-up included: the level of mortality, the presence of a new stroke and new cardiovascular events, etc.

2.1. **Assessment of the patient:**

Observation of recurrence of stroke and cerebrovascular death of various etiologies. Fourth National Conference were developed diagnostic standards disorders secondary cerebrovascular strokes: (1) accounting neurological symptoms, such as variables and constants; (2) dynamic control by CT or MRI in order to control for the discovery of new cerebrovascular damage; (3) it is necessary to predict the possible worsening of cerebrovascular disease and stroke with a mandatory recording of events in the history of the disease to family history and analysis of the causes of death.

2.2. All patients with hypertension from 8-10 a.m.: the study on the standard operation protocol (SOP). Blood pressure was measured at least three times. By average indicator measures the quality of the therapeutic effect. For 30 minutes before the study was prohibited smoking, drinking coffee, controlled emptying of the bladder and the implementation of the five-minute rest before the test.

2.3. Undertake certain concentration of homocysteine in plasma:

2.3.1. Blood samples: morning venous blood sampling was performed volume of 2 ml of 5% EDTA anticoagulated with cooling in an ice bath, followed by centrifugation at 3000 rev/min for 10 minutes,

2.3.2. Determining the level homocysteine produced in the plasma.

2.3.3. To determine the level of homocysteine in plasma, we used high-performance liquid Frick fluorescence analysis, [8], etc. Krijt [9]. As a standard control homocysteine into the serum used Instruments and reagents in US Sigma company Agilent LC-1100 highly effective liquid phase color spectrometer, ultraviolet detector and Ying attached Light detector; Using C18 (250 mm × 4.6 mm, 5 mm), protect column on C18 column and core.

3. Statistical processing was carried out from the beginning of the emergence of a new stroke during a relapse and in the final stage of observation. To study the role of homocysteine on the flow of secondary events and cerebrovascular stroke all the subjects were divided into four groups depending on the concentration of homocysteine in plasma (< 11.4, 11.5—14.6, 14.7—19.7, 19.8 µmol frequency/L).
In the statistical analysis of patient survival, depending on the level of homocysteine used Cox regression model that allows us to study the factors of cerebrovascular risk correction of data, taking into account gender, age, body mass index, smoking, alcohol consumption, lipid profile, glucose and family history of diabetes and cerebrovascular disorders and stroke.

As a statistical software for analysis of the resulting material was used statistical software package SPSS 10.0.

**Results 1**

After Cox regression analysis, the survival of 200 patients with high homocysteine had a stroke and underwent a high degree of risk. New patients with high levels of homocysteine were again at a high level of risk. After 4 years of follow up were identified 200 cases of cerebrovascular events, including 50 recurrent strokes. In addition to traditional risk factors such as age, alcohol, smoking cysteine levels in plasma with low level of risk of cerebrovascular events was less pronounced. In groups with higher levels of homocysteine risk of recurrent cerebrovascular events was significantly higher ($P < 0.05$) compared with groups with low homocysteine after adjustment for age, sex, smoking, alcohol consumption, etc.

2. Comparative analysis of the risk of cerebrovascular events depending on the levels of homocysteine in plasma is presented in Table 1.

### Table 1

#### Plasma homocysteine comparison between different groups

<table>
<thead>
<tr>
<th>Group</th>
<th>I ($&lt; 11.4 \mu$mol/L)</th>
<th>II (11.4—14.5 \mu$mol/L)</th>
<th>III (14.6—19.6 \mu$mol/L)</th>
<th>IV (&gt; 19.7 \mu$mol/L)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke corpus column</strong></td>
<td></td>
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</tr>
<tr>
<td>Recurrence rate</td>
<td>8.1 (95/459)</td>
<td>10.1 (103/450)</td>
<td>10.7 (94/456)</td>
<td>18.3 (130/458)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>After correction risk</td>
<td>1.0 (0.85—1.51)</td>
<td>0.98 (0.71—1.31)</td>
<td>1.53 (1.17—2.20)</td>
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<tr>
<td><strong>Thrombosis of cerebral infarction</strong></td>
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<tr>
<td>Recurrence rate</td>
<td>18.2 (39/213)</td>
<td>24.1 (44/185)</td>
<td>17.9 (37/210)</td>
<td>26.7 (52/197)</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>After correction risk</td>
<td>1.0 (0.96—2.26)</td>
<td>1.15 (0.73—1.81)</td>
<td>1.88 (1.23—2.86)</td>
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<tr>
<td><strong>Thrombosis of cerebral infarction</strong></td>
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</tr>
<tr>
<td>Recurrence rate</td>
<td>23.9 (31/129)</td>
<td>21.2 (26/126)</td>
<td>19.3 (23/124)</td>
<td>26.2 (34/132)</td>
<td>&lt; 0.59</td>
</tr>
<tr>
<td>After correction risk</td>
<td>1.0 (0.47—1.35)</td>
<td>0.78 (0.45—1.31)</td>
<td>1.039 (0.63—1.68)</td>
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<tr>
<td><strong>Cerebral hemorrhage group</strong></td>
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<tr>
<td>Recurrence rate</td>
<td>18.7 (21/116)</td>
<td>21.8 (29/136)</td>
<td>22.2 (26/120)</td>
<td>31.9 (40/126)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>After correction risk</td>
<td>1.0 (0.83—1.45)</td>
<td>0.98 (0.73—1.31)</td>
<td>1.48 (1.13—1.93)</td>
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</tbody>
</table>

Note: the recurrence rate: to recur cases/total number [% (number)]. After correction risk ratio is 95% CI, representing 95% confidence interval. The same below.
The group of patients with low homocysteine amy in plasma and the subjects with a high level homocysteine have different risk of cerebrovascular events. The risk increases in proportion to the level of homocysteine in plasma. Increased risk of cerebrovascular events in total amounted to 18.3% and 10% after adjusting for age, gender and traditional cardiovascular risk factors (P < 0.05).

3. The ratio of the level of homocysteine in plasma and the risk of stroke number is listed in Table 2. Low cerebrovascular events, it has been detected in patients with low levels of plasma homocysteine and vice versa. The recurrence rate of stroke in the group with a high level homocysteine was at 16.4% higher compared to the group with low plasma homocysteine (P < 0.05). A subgroup analysis of patients also It shows that high levels of homocysteine and a new beginning of cerebral infarction and the risk of recurrence of cerebral hemorrhage stroke are significantly related.

### Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>I (11.4 µmol/L)</th>
<th>II (11.4—14.5 µmol/L)</th>
<th>III (14.6—19.6 µmol/L)</th>
<th>IV (&gt; 19.7 µmol/L)</th>
<th>p</th>
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<tbody>
<tr>
<td><strong>Stroke corps column</strong></td>
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<tr>
<td>Recurrence rate</td>
<td>6.8 (76/458)</td>
<td>8.1 (80/449)</td>
<td>8.6 (73/455)</td>
<td>16.3 (114/457)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>After correction than risk</td>
<td>1.0 (0.7—1.4)</td>
<td>1.19 (0.8—1.6)</td>
<td>1.75 (1.2—2.3)</td>
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<tr>
<td><strong>Thrombosis of cerebral infarction</strong></td>
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</tr>
<tr>
<td>Recurrence rate</td>
<td>15.4 (32/212)</td>
<td>18.7 (34/185)</td>
<td>13.6 (28/210)</td>
<td>22.6 (44/197)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>After correction than risk</td>
<td>1.0 (0.8—2.2)</td>
<td>1.13 (0.5—1.6)</td>
<td>2.06 (1.2—3.2)</td>
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<tr>
<td><strong>Lacunar cerebral infarction group</strong></td>
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<tr>
<td>Recurrence rate</td>
<td>17.0 (21/128)</td>
<td>18.8 (23/126)</td>
<td>16.0 (19/123)</td>
<td>23.2 (30/132)</td>
<td>&lt; 0.85</td>
</tr>
<tr>
<td>After correction than risk</td>
<td>1.0 (0.4—1.6)</td>
<td>0.80 (0.3—1.5)</td>
<td>1.00 (0.5—1.8)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Cerebral hemorrhage group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence rate</td>
<td>18.7 (21/116)</td>
<td>16.0 (21/136)</td>
<td>20.6 (24/1200)</td>
<td>30.4 (38/126)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>After correction than risk</td>
<td>1.0 (0.3—1.3)</td>
<td>0.94 (0.4—1.6)</td>
<td>1.78 (1.0—2.99)</td>
<td></td>
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</table>
DISCUSSION

A study of 200 cases of patients with cerebral apoplexy and long-term follow-up study showed that patients with high blood pressure and high levels of homocysteine have a statistically significant correlation with relapse of cerebrovascular events.

Patients with low plasma concentration homocysteine compared with patients in which the levels of homocysteine in the plasma is higher than 19.8 μmol/L. Risk of recurrence of cerebrovascular disease increases 1.54 times, and in some cases 1.74 times [9].

Control of blood pressure is an important component of a comprehensive prevention and to reduce the high incidence of stroke, since high blood pressure is a major risk factor for stroke.

Experience in treating most patients with high blood pressure and one or more other risk factors in China in 2005 showed that for the successful treatment of high blood pressure and need to control other risk factors [10]. The rate of progression of recurrent stroke increases significantly as the population ages. Differential approach will take into account new risk factors, which significantly increases the effectiveness of prevention and treatment of strokes. Experimental research and epidemiologic studies have shown that plasma homocysteine increase the risk of cerebrovascular diseases, regardless of other risk factors [9].

It was found that the China’s population with high blood pressure leading to stroke 1.5 times compared to the other countries. Four clinical trials in this country and comprehensive analysis shows that the reduction in systolic pressure at 9 mm Hg and diastolic pressure by 4 mm Hg reduces the risk of stroke by 36% and the risk of coronary heart disease to 3% [11].

Long-term use of folic acid reduces the level of homocysteine, is used in the primary prevention can reduce by 25% the risk of stroke and coronary heart [12]. The combination of the results for the prevention of stroke, blood pressure at the same time fully to consider lowering homocysteine levels. At the same time, effective control of the risks of cerebrovascular events is more important to control high blood pressure [13].

The results show that with the increase in plasma homocysteine levels are increased significantly the risk of recurrence of cerebrovascular events.

The results of the meta-analysis suggest that folic acid supplements can reduce plasma homocysteine levels and reduce the risk of stroke [14]. The recent use of vitamin B6, B12 and folic acid significantly improved the efficiency of the treatment of vascular diseases.

Albert, etc. [15] large clinical studies have shown that folic acid reduces the risk of cardiovascular disease (p = 0.03) [13]. Disease risk of stroke was reduced to 25% [14].

Li Jian Ping [16] observation Enalaprilat treatment of folic acid hypertension, confirmed the results of the control of high blood pressure and high homocysteine levels significantly better effect than pure use Enalaprilat.

Risk factors for stroke and high blood pressure, along with high levels of homocysteine increase the risk of cerebrovascular events due to a synergistic interaction.

Understanding the mechanism of risk of cerebrovascular events in China will allow to take important measures to adopt the international standard for optimal correction and prevention of high risk of cerebrovascular events.

REFERENCES


ГИПЕРГОМОЦИСТЕМИЯ
КАК ПРИЧИНА ВЫСОКИХ ВТОРИЧНЫХ РИСКОВ
РАЗВИТИЯ ЦЕРЕБРОВАСКУЛЯРНЫХ СОБЫТИЙ
У ПАЦИЕНТОВ, ИМЕЮЩИХ В АНАМНЕЗЕ
ЦЕРЕБРОВАСКУЛЯРНЫЕ ЗАБОЛЕВАНИЯ.
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Аннотация. В этой статье анализируются пациенты с наличием инсульта, высокого кровяного давления и высокого уровня гомоцистеина в анамнезе. Будет ли в этом случае высокий уровень гомоцистеина предиктором высокой вероятности риска вторичного цереброваскулярного события и как эти нарушения
мозгового кровообращения зависят от отношений между уровнями гомоцистеина и высокого кровяного давления.

В клиническом исследовании было показано, что повышенные уровни гомоцистеина в плазме выше 10,0 мкмоль/л и наличие гипертонии, связанно с повышенным риском цереброваскулярного заболевания после первого инсульта.

Сосудистые риски имеют гендерный характер: исследование уровня гомоцистеина взрослого населения шести городов Китая показали, что 75% испытуемых имеют повышенные уровни гомоцистеина (> 10 мкмоль/л). Среди взрослых с повышенным уровнем гомоцистеина мужчин было 91%, а женщин — 60%.

Исследование также показало, что у пациентов с высоким риском вторичных цереброваскулярных заболеваний были два основных фактора риска — высокое кровяное давление и повышенный уровень гомоцистеина.

Таким образом, в соответствии с проведенным клиническим анализом основная причина вторичного цереброваскулярного риска тесно связана с высоким кровяным давлением и повышенным уровнем концентрации гомоцистеина в первичном и вторичном анамнезе с наличием инсульта. Эти два фактора потенцируют друг друга и увеличивают риск вторичных нарушений мозгового кровообращения.

Ключевые слова: артериальная гипертензия; гомоцистеин; инсульт; рецидивы цереброваскулярных событий; факторы риска; рецидив инсульта.

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