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The Role of Biomarkers by Age and Sex in Acute Ischemic Stroke

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Abstract In recent years, increasing attention has been paid to "novel" risk factors that promote the development of chronic dysmetabolic processes in the vascular walls and brain tissues. Among these, hyperhomocysteinemia (HHcy) holds a special place. According to several authors, HHcy is closely associated not only with damage to intracranial and visceral vessels but also plays a role in the pathogenesis of cerebral vascular accidents. HHcy adversely affects vascular autoregulation, lipid metabolism, and the blood's coagulation potential.

Keywords Acute ischemic stroke, Hyperhomocysteinemia, Endothelial dysfunction, Homocysteine, Thrombomodulin, Endothelin-1

1. Introduction

One of the key objectives faced by angioneurologists is to provide effective and appropriate care not only in the acute phase of ischemic stroke (IS) but also during the early recovery phase. This necessitates an in-depth study of the pathogenesis of brain structural damage occurring in the early post-stroke period [1]. According to some researchers, there is a rapid increase in endothelial dysfunction markers following acute IS. Endothelial dysfunction is often associated with increased total plasma homocysteine levels and may be partially related to oxidative stress. Other authors suggest that thrombomodulin is associated with cerebrovascular ischemic conditions and may serve as an important biomarker for the early onset of ischemic stroke. Our findings confirmed that thrombomodulin levels in AIS patients were significantly higher than in both the control group and CCI patients ($p<0.05$), indicating severe endothelial dysfunction in the acute phase [2].

2. Materials and Methods

A study of biochemical markers of endothelial dysfunction (homocysteine, thrombomodulin, and endothelin-1) was conducted in 165 patients with acute ischemic stroke (AIS), of whom 29 had chronic cerebral ischemia (CCI). The control group consisted of 30 practically healthy individuals without clinical signs of chronic cerebrovascular disorders. Among the 136 patients with AIS in the acute phase, 26.5% (36 patients) were of young age, 40.4% (55 patients) of middle age, and 33.1% (45 patients) of elderly and senile age.

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3. Results and Discussion

The analysis showed that thrombomodulin (TM) levels in AIS patients during the acute phase were significantly higher compared to those in the control group ($p<0.05$) and in patients with CCI ($p<0.05$), indicating a high degree of endothelial dysfunction. Moreover, an age-related increase in TM levels was observed. In young patients, TM levels averaged 58.9±5.6 µg/L, while in elderly and senile patients, the levels were 2.2 times higher ($p<0.05$).The level of endothelin-1 (ET-1) in AIS patients during the acute phase was on average 3.4 times higher than in the control group ($p<0.01$). In CCI patients, ET-1 levels were 1.7 times higher than in the control group ($p<0.05$). With advancing age, ET-1 levels increased from 8.6±0.12 pg/mL in young patients to 10.8±0.55 pg/mL in elderly and senile patients ($p<0.001$).Correlation analysis showed a moderate to strong direct correlation between age and levels of homocysteine ($r=0.568$; $p=0.002$), thrombomodulin ($r=0.732$; $p=0.003$), and endothelin-1 ($r=0.668$; $p=0.003$).

With aging, these indicators increased significantly: TM levels in elderly and senile patients were 2.2 times higher than in young individuals ($p<0.05$). Similarly, ET-1 levels were 3.4 times higher in AIS patients than in controls ($p<0.01$), and 1.7 times higher in CCI patients ($p<0.05$). In older patients, ET-1 levels reached up to 10.8±0.55 pg/mL,

compared to 8.6±0.12 pg/mL in younger patients (p<0.001). Homocysteine levels also rose with age: 2.6-fold increase in younger patients (p<0.05) and 4.8-fold in elderly patients compared to controls (p<0.001).

Compared to the control group, patients with chronic cerebral ischemia (CCI) showed a statistically significant increase in homocysteine levels (p<0.05). In patients in the acute phase of ischemic stroke (IS), this marker was 1.9 times higher in younger individuals and 3.5 times higher in elderly and senile patients (p<0.001).

The study also identified certain patterns in the relationship between biochemical markers of endothelial dysfunction (homocysteine, thrombomodulin, endothelin-1) and sex-related characteristics of the patients [3]. These patterns are presented in Table 1 and illustrate that the severity of endothelial dysfunction and its association with specific biochemical markers vary depending on the patient's sex [4]. This information is of practical importance for the further development of more precise approaches to the prevention and treatment of endothelial dysfunction.As shown in the data, male patients exhibited higher levels of both thrombomodulin and homocysteine across all age groups compared to female patients [5].

ET-1 levels were significantly higher in female patients compared to males (p<0.01), and this trend was observed across all age groups. We also assessed the relationship between neurological deficit severity and the concentrations of biochemical markers of endothelial dysfunction (homocysteine, thrombomodulin, endothelin-1) during the acute phase of ischemic stroke (IS). It was found that in patients with severe neurological deficit, there was a marked increase in homocysteine (from 10.5±1.2 µmol/L to 21.3±3.1 µmol/L; p<0.001), thrombomodulin (from 65.6±3.2 µg/L to 140.3±6.3 µg/L; p<0.01), and endothelin-1 (from 8.9±0.21 pg/mL to 12.5±0.27 pg/mL; p<0.01) — representing an approximate twofold rise in each marker (Table 3).

Table 1. Presents age-related quantitative changes in biochemical markers of endothelial dysfunction (homocysteine, thrombomodulin, endothelin-1) in the examined patients

Parameters	Control group, n = 16	Patients with chronic cerebral ischemia (CCI), n = 29	Patients with acute ischemic stroke (AIS), n = 136	Young age group, n = 36	Middle-aged group, n = 55	Elderly and senile age group, n = 45
TM (2.5–40 µg/L)	21,25±0,73	25,6±0,33	94,0±5,7***^^^	58,9±5,6**^	91,4±6,8***^^	131,75±9,7***^^^
ET (0.7–5 pg/mL)	2,85±0,09	4,92±0,07*	9,7±0,41***^^^	8,6±0,12**^	9,69±0,21***^^	10,8±0,55***^^^
Homocysteine (0.5–8.0 µmol/L)	4,25±0,41	5,84±0,29*	19,9±1,3***^^^	10,9±0,47*^	17,2±0,86***^^	20,6±2,2***^^^

Note: — statistically significant compared to the control group (*p<0.05; **p<0.01; ***p<0.001);
^ — statistically significant compared to patients with chronic cerebral ischemia (^p<0.05; ^^p<0.01; ^^^p<0.001).

Table 2. Sex- and age-related quantitative changes in biochemical markers of endothelial dysfunction (homocysteine, thrombomodulin, endothelin-1) in patients with acute ischemic stroke

Endothelin Markers	Among young patients (n = 36)			Among middle-aged patients (n = 55)			Among elderly and senile patients (n = 45)		
	In total	M., n=21	F., n=15	In total	M., n=34	F., n=21	In total	M., n=26	F., n=19
Homocysteine (0.5–8 µmol/L)	10,9±0,47	11,2±0,21	9,5±0,12^	17,2±0,86*	18,3±1,4*	12,4±1,2^*	20,6±2,2**#	22,3±1,5**#	13,9±1,1^***#
TM (2.5–40 µg/L)	58,9±5,6	62,3±5,1	46,6±4,8^	91,4±6,8*	98,3±5,3*	85,6±5,9^*	131,75±9,7*#	138,3±8,2*#	125,2±8,4^**#
ET-1 (0.7–5 pg/mL)	8,6±0,12	7,5±0,13	9,3±0,18^	9,69±0,21*	8,9±0,15*	10,4±0,17^*	10,8±0,55*#	9,6±0,24**#	11,3±0,31^**#

Note: — statistically significant compared to the values in younger patients (*p<0.05; **p<0.01; ***p<0.001);
^ — statistically significant difference between male and female patients (^p<0.05);
— statistically significant compared to the values in middle-aged patients (#p<0.05).

Table 3. Changes in biochemical markers of endothelial dysfunction (homocysteine, thrombomodulin, endothelin-1) according to the severity of neurological deficit in patients during the acute phase of ischemic stroke

Parametrs	Homocysteine(0.5–8 µmol/L)	TM (2.5–40 µg/L)	ET-1 (0,7-5 пг/мл)
Mild neurological deficit	10,5±1,2^#	65,6±3,2^^###	8,9±0,21^^#
Moderate neurological deficit	17,4±2,3*#	111,5±4,5*##	10,7±0,24*#
Severe neurological deficit	21,3±3,1**^	140,3±6,3**^^	12,5±0,27**^

Note:— statistically significant compared to patients with mild neurological deficit (*p<0.05; **p<0.01);
^ — statistically significant compared to patients with moderate neurological deficit (^p<0.05; ^^p<0.01);
— statistically significant compared to patients with severe neurological deficit (#p<0.05; ##p<0.01).

Furthermore, the predictive significance of elevated biomarker levels for the development of severe neurological deficit was identified. Specifically, a homocysteine level exceeding 16.59 µmol/L (AUC = 0.878, sensitivity – 77.3%, specificity – 89.2%; p<0.001), a thrombomodulin level above 70.0 µg/L (AUC = 0.869, sensitivity – 87%, specificity – 86.3%; p<0.001), and an endothelin-1 level greater than 9.2 pg/mL (AUC = 0.889, sensitivity – 86%, specificity – 84%; p<0.001) were identified as threshold values associated with poor neurological outcomes.

4. Conclusions

An age-dependent increase in the levels of homocysteine, thrombomodulin, and endothelin-1 was observed in patients during the acute phase of ischemic stroke, confirming the presence of pronounced endothelial dysfunction. These elevations, which intensified with age, reflect significant impairments in endothelial function and highlight its critical role in stroke pathogenesis.Sex-specific differences in the levels of endothelial dysfunction biomarkers were also observed: men exhibited higher levels of homocysteine and thrombomodulin, whereas women showed significantly elevated endothelin-1 levels.

The combined use of these biomarkers provides additional insight into the functional state of brain tissue during the hyperacute phase of ischemic stroke and may serve as an important tool for outcome prediction.

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