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Improving diagnostic approaches to cerebrovascular disorders in patients with hypertensive encephalopathy

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Abstract:

BACKGROUND: Modern research today proves an increase in the incidence of ischemic stroke. Risk factors for vascular disease have become more common among young people. Clinical studies have shown that hypertension, dyslipidemia, and diabetes are traditional risk factors among the elderly. The aim of the study was to improve diagnostic approaches to cerebrovascular disorders in patients with hypertensive encephalopathy (HE) by clarifying the development of pathogenesis mechanisms, based on a comprehensive clinical study.

MATERIALS AND METHODS: This qualitative study was carried by clinical and neurological examination; neuropsychological examination (Mini-Mental State Examination, abbreviated multifactorial personality questionnaire, Beck depression scale, Spielberger scale).

RESULTS: The study was examined 351 patients (150 men, 201 women) with HE in hypertension of 2 degrees. The clinical examination was performed according to a two-stage method, which involves the establishment or exclusion of symptomatic hypertension. The study did not include patients with secondary hypertension, diabetes mellitus, cardiac arrhythmias, and conduction disorders, heart failure who suffered from acute cerebrovascular accident and myocardial infarction.

CONCLUSION: The necessity of obligatory examination by a neurologist of patients with arterial hypertension for detection of manifestations of HE with the use of modern research methods, which allows to prevent damage to target organs, and first of all – brain damage, has been proved.

Keywords:

Cerebrovascular disorders, comprehensive research, diagnosis of hypertensive encephalopathy, hypertensive encephalopathy, stroke risk factors

Introduction

Recent studies have shown an increase in the incidence of ischemic stroke, and risk factors for vascular disease are becoming more common among young people and accumulate in some people at high risk of stroke.^[1,2] Stroke is characterized by a high rate of morbidity, mortality, and disability; therefore, it is associated with a serious social and economic burden.^[2]

Analysis of the relationship between vascular risk factors and early onset of stroke made it possible to screen between

risk factors and assess the effectiveness of primary disease prevention. Studies have shown that ischemic stroke in young people grow with increasing risk factors for stroke: hypertension, dyslipidemia, diabetes, smoking, and obesity.^[3]

Hypertension can exist for a long time without clinical manifestations, have a detrimental effect on blood vessels and brain matter, and form hypertensive encephalopathy (HE). The disease of hypertension is heterogeneous and multifactorial in origin, so early diagnosis of target organs is important. Today, it is proven that almost 50% of patients with asymptomatic carotid artery stenosis

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have cognitive impairment. Recent data suggest that hypoperfusion of the brain is an important cause of cognitive impairment. It has been shown that carotid artery stenosis was associated with decreased ipsilateral perfusion of the brain compared with the opposite hemisphere in more than 80% of patients.^[4]

Risk factors for stroke include antithrombin deficiency as an inherited genetic disease with an autosomal dominant type that leads to the formation of a venous thrombus. It is estimated that antithrombin deficiency is present in 5%–8% of young patients who have suffered a stroke.^[5]

Mitchell *et al.* in a study of young patients with ischemic stroke in the United States found high rates of hypertension (42%), diabetes (17%), and obesity (40%) were found among young patients with ischemic stroke.^[6,7]

Over the past two decades, researchers have pinned their hopes on a new era of combining reperfusion and neuroprotection for stroke treatment. Today, the results obtained in preclinical studies reflect an incomplete picture of the pathophysiology of stroke and require further research.^[8]

The aim of the study was to improve diagnostic approaches to cerebrovascular disorders in patients with HE by clarifying the development of pathogenesis mechanisms based on a comprehensive clinical study.

Materials and Methods

Analysis of the results of modern highly informative methods of examination of patients with HE requires a comprehensive approach to diagnosis and treatment with analysis of structural changes to assess the degree of brain tissue damage.

Study design and setting

The study was conducted in the neurological departments of the Kyiv Regional Clinical Hospital in Ukraine and was examined 351 patients (150 men, 201 women) with HE with hypertension of 2°.

Study participants and sampling

The clinical examination was performed in two-stage method. This involves the establishment or exclusion of symptomatic hypertension. The mean age in the group was 50.7 + 11.5 years, the duration of hypertension was 9.44 + 5.64 years. Depending on the stage of encephalopathy, patients have been divided into two groups:

- First group – 100 patients with HE stage I
- Second group – 251 patients with HE stage II (51 patients – a subgroup with mixed atherosclerotic and HE).

Data collection tool and technique

A set of diagnostic methods was used to solve the set tasks. During daily blood pressure (BP) monitoring, mean BP, systolic BP (SBP) and diastolic BP (DBP), pulse BP, BP variability, degree of night BP decrease, time and area index, morning BP rise rate were analyzed. Daily monitoring of BP was performed on a device type AVRМ-04 (firm “Meditech,” Hungary). To assess the state of the autonomic nervous system, we used the analysis of spectral indicators of heart rate variability based on the results of electrocardiography monitoring. The analysis of cardiovascular risk factors was performed with the calculation of body mass index, office BP, detection of changes in the electrocardiogram, and the condition of the vessels of the fundus. The study used the normative values of BP recommended by the European Society of Cardiology.

Duplex scanning of common and internal carotid arteries was performed on an ultrasound machine “Sonoline omnia” (“Siemens,” Germany) according to standard methods.

Single-photon emission computed tomography (SPECT) was performed on a two-detector gamma camera “ECam” (Siemens) with a low-energy high-distribution collimator (LEHDC). In clinical practice, the indicator Tc-99 m hexamethylpropyleneaminooxime is used to visualize SPECT.^[9]

We identified areas or foci of low radioactivity due to decreased perfusion. We also performed a quantitative assessment of the volume of cerebral blood flow in the hemispheres of the brain mathematically by the method of N. Lassen, the results of which can be presented in absolute terms (mL/100 g/min).^[8]

Laboratory tests included conventional blood and urine tests, biochemical blood tests, determination of total cholesterol, triglycerides. The method of immunological phenotyping of peripheral blood cells by laser flow cytometry was used to assess apoptosis. The analysis was performed on a FACScan laser flow cytometer from Becton Dickinson (BD, USA). Determination of homocysteine in serum was performed by enzyme-linked immunosorbent assay using a standard set of “Axis-Shield,” UK.

Ethical consideration

This article is integral part of the planned research work of the Department of Neurology and Reflexology of the National Medical Academy of Postgraduate Education named after P. L. Shupyka, state registration №0105V002320, rubricator of the National Library of Ukraine Name V. I. Vernadsky: NBUV P627.703+P410.030; NBUV code: RA365728 (Kyiv, Ukraine).

Results

Patients' characteristics

We have analyzed the patient's group with HE in several parameters. It can be concluded, patients with HE have a fairly high frequency of overweight – $29.02 \pm 2.15 \text{ kg/m}^2$ and abdominal obesity (57%), in the formation of which a low level of physical activity (44%) plays a role. The above risk factors for cardiovascular complications were more observed in women. Men were characterized by: burdened heredity (32%) and smoking (24%), which is an independent risk factor for the development of GE ($r = 0.542$). The control group included 90 people (45 men and 45 women) with normal BP, the average age was $49.86 + 10.14$ years.

Complaints of general malaise of varying severity were filed by 154 (44%) patients, headache – 312 (89%) patients, dizziness – 224 (64%). Noise in the head bothered 196 (56%) patients, pain in the heart area was noted by 210 (60%), palpitations – 143 (41%) patients. Disorders of the psycho-emotional sphere were characterized by complaints of mostly anxious and depressive nature, and disorders of the cognitive sphere were in the form of complaints of decreased memory and attention.

The characteristics of the signs' flowing

In the early stages of the disease, when the signs of damage to the nervous system did not allow to consider them in the presence of the syndrome, diffuse neurological symptoms were observed in 12.6%. Signs of amyostatic (40.2%), pyramidal (34.6%), vestibulo-cerebellar (9.4%) syndromes were found quite often in patients with stage II HE. In 64.7% of patients, it was found that amyostatic and pyramidal syndromes were combined.

A detailed analysis of the risk factors present in the examined patients depending on the stage of HE showed that excess body weight was determined with the same frequency in patients with HE I and II stages. In stage II HE, hypercholesterolemia was registered more often than in stage I HE (51% and 42.9%, respectively).

The results of comparative analysis showed that retinal vascular lesions, signs of left ventricular hypertrophy, and hypercholesterolemia were more common in stage II HE than in stage I HE. It was found that the normal level of homocysteine was in most patients with HE (64.7%), a moderate increase in HC was observed in 5.9% of cases, the average degree of increase in homocysteine was found in 26.5% of patients, and a significant degree – only in 2.9% of patients. Elevated levels of homocysteine in HE increase the risk of vascular complications.

The stage I HE neurological symptoms and disease progression increased gradually.

Along with the pronounced cephalic syndrome of polymorphic nature, in 91.5% of cases revealed nonsystemic dizziness with shaking when walking (67%), nausea (68%), and vasomotor disorders (80%). Cardialgia was observed in 80% of patients, palpitations – in 89%. In stage II HE, testing revealed cognitive impairment (74.1%) with a decrease in verbal memory (61.1%), sleep disorders (90%). Neurological syndromes prevailed over subjective manifestations. In patients with stage II HE, the leading neurological syndromes were vestibulo-atactic syndrome (84%), pyramidal insufficiency syndrome (76.5%), early sensory disturbances (80%), early mnemonic disorders (94.5%) with decreased memory on current events and a decrease in professional memory. Autonomic dysfunction was characterized by polymorphism, polysymptomatic with the involvement of two or more functional systems. It was found that there is a positive relationship between the subjective manifestations characteristic of HE and the severity of depressive and anxiety states.

Studies have shown that the daily BP profile in patients with stage I and II GE is characterized by a consistently high level of systolic, diastolic, and pulse BP compared with the control group. Significantly exceeded the normative level of "pressure load," especially for SBP at night. An increase in the value of the morning rise of DBP was also established. The results were consistent with the Ohasama study, which found that morning and evening BP levels provide sufficient information to determine the risk of stroke.^[10]

Arterial hypertension at night was registered only among patients with stage II HE (2%), and excessive decrease in SBP at night was observed in patients almost equally – 48.9% in stage I HE and 51.1% in stage II HE.

The conducted multifactor correlation analysis revealed the presence of associations of diurnal SBP variability with disease duration and age of patients ($r = 0.34$ and $r = 0.30$; $P < 0.05$), which indicates the influence of age on the growth of variability BP in normotensive patients. Spectral analysis of heart rate variability in patients with HE showed a decrease in the value of generally accepted indicators of general heart rate variability due to the weakening of parasympathetic and increased sympathetic effects on the cardiovascular system.

Analysis of velocity parameters of blood flow according to duplex scanning revealed a marked decrease in the level of the common carotid artery in patients with stage II HE. As the weight of the HE increased, a significant increase in the thickness of the intima media of the common carotid artery ($1.09 \pm 0.03 \text{ mm}$ and $1.18 \pm 0.05 \text{ mm}$) and the speed of the pulse wave of the aorta was found – a significant increase in the speed

of the pulse wave of the aorta. A significant increase in the thickness of the intima media (1.14 ± 0.06 mm) in patients with insufficient BP at night (nondipper) compared with patients in whom the circadian rhythm of BP was physiological (dipper). Due to the comparison of radionuclide study data and duplex scanning, there is a correlation between the increase of the intima media of the common carotid artery and the severity of foci of hypoperfusion according to SPECT.

When evaluating SPECT data, the level of brain perfusion in patients with GE was in the right hemisphere – 36.9 ± 2.5 mL/100 g/minute, in the left hemisphere is 36.7 ± 4.7 mL/100 g/minute, which indicates a significant decrease relative to the control group (respectively — 41.1 ± 3.0 mL/100 g/min, and 41.6 ± 2.8 mL/100 g/min). According to SPECT, in 41 patients (52%), visually clear changes in cerebral perfusion were observed, which did not correspond to the indicators of the unaffected brain in emission tomography. In these patients, a clear asymmetry of radioactivity was observed in the cerebral hemispheres, due to a decrease in perfusion in the pools of the internal carotid arteries in 43.9%, and in the projection of the semioval centers in 36.6%.

The identified changes are the result of cumulative and mutually reinforcing effects of processes occurring in the walls of blood vessels: remodeling, age involution, and the development of atherosclerosis. It was found that the development of HE in hypertension of 2 degrees is accompanied by an increase in the intensity of free radical reactions according to the activity of neutrophils, an increase in reserve capacity and a decrease in the NO-synthetic function of neutrophils. Thus, neutrophils achieve a state of priming, with the activation of free radical reactions, which has a cytotoxic effect by initiating the processes of peroxidation of lipids of cell membranes. The study of the marker CD95+ provided additional information on the total population of blood cells capable of developing apoptosis in chronic cerebral ischemia.

Discussion

At the present stage, combination therapy occupies a priority position in the tactics of stroke treatment and includes the impact on pathogenetic mechanisms, taking into account risk factors, potentiation of organ protective effects, summation of antihypertensive effect, and minimization of side effects.

We have obtained that there was a significant predominance of the frequency of lesions of the internal carotid arteries in patients with HE, compared with normotensive patients ($P < 0.01$). Decreased blood flow velocities, increased peripheral resistance indices

reflect a progressive decrease in the elastic properties of the vascular wall, increased rigidity and tortuosity of the carotid arteries in the combination of hypertension and atherosclerotic lesions. Prolonged hypertension in the walls of large, medium, and small arteries leads to smooth muscle hypertrophy and accumulation of elastic fibers, which is a manifestation of compensatory-adaptive changes in the arteries of the brain in conditions of prolonged increase in BP.

There is little data on the risk of stroke after HE diagnosis, as most reports focus on the increased risk of stroke when handling HE.^[9,11]

Our study has proved that HE has a heterogeneous condition. Diffuse damage to small vessels with the development of their stenosis and reactivity leads to impaired autoregulation of cerebral circulation, depletion of hemodynamic reserve, and narrowing of the range of allowable changes in perfusion. Due to endothelial dysfunction, and later sclerosis, small vessels lose the ability to dilate, which makes it impossible to redistribute perfusion in favor of active brain and leads to their functional inactivation, and then to irreversible damage.

Furthermore, it was found changes in BP profile according to the results of daily BP monitoring in patients with stage I HE in comparison with stage II should be considered as predictors of a high risk of cardiovascular complications. Excessive lowering of BP at night indicates the progression of HE. The fluctuating nature of the BP can also contribute to the development of HE.^[12]

High pulse pressure is accompanied by impaired brain perfusion (according to SPECT) and is an independent risk factor for the development of HE. A correlation was found between the variability of SBP and the thickness of the intima-media complex of the common carotid artery ($P < 0.05$). Thus, the proposed diagnosis is more suitable for assessing changes in brain diffusion.^[13]

In HE, informative signs of changes in the elastic properties of arteries are increase in pulse aortic wave velocity and thickness of the intima-media complex of the common carotid artery. Increased pulse BP in patients with HE is associated with changes in the elastic properties of the vascular wall. A correlation was found between the variability of SBP and the thickness of the intima-media complex of the common carotid artery ($P < 0.05$).

Careful examination, including testing for the causes of hypercoagulation, vascular imaging, and echocardiography, can often identify or narrow the list of potential risk factors for stroke, which is crucial

to prevent recurrent strokes to reduce the risk of brain damage in the long term. It is advisable to introduce a mandatory examination by a neurologist of patients with hypertension to detect the manifestations of HE using modern research methods, which can prevent damage to target organs, and in the first place there is brain damage.

Limitation and recommendation

The study did not include patients with secondary hypertension, diabetes mellitus, arrhythmias and conduction disorders, heart failure who suffered from acute cerebrovascular accident, and myocardial infarction.

Conclusion

Based on a comprehensive study of clinical and neurological data, the results of biochemical, instrumental, and neuroimaging research methods of HE in patients with grade 2 hypertension, the presented assessment of the diagnosis can greatly contribute to the correct diagnosis. The developed system of complex diagnostics of HE makes it possible to assess the stages of HE, the degree of cerebral hemodynamic impairment and prescribe combined therapy.

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Conflicts of interest

There are no conflicts of interest.

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