Chapter

Cerebral Vasospasm: Mechanisms, Pathomorphology, Diagnostics, Treatment

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Abstract

Cerebral vessels constriction is one of the leading causes of mortality and disability in patients with acute cerebral circulatory disorders. The most dangerous type of acute cerebrovascular disease accompanied by high mortality is ruptured cerebral aneurysms with subarachnoidal hemorrhage (SAH). Following a constriction of the cerebral vessels on the background of SAH is the reason for brain ischemia. This chapter will focus on the mechanisms of formation of cerebral vascular spasm, pathomorphological aspects of the cerebral vessels constriction, and the stages of vascular spasm—the development of constrictive-stenotic arteriopathy, contractural degeneration of smooth muscle cells, and endothelial damage. We will cover classifications of cerebral vessels constriction by prevalence and severity, modern methods of clinical and instrumental diagnostics and treatment including paroxysmal sympathetic hyperactivity syndrome associated with the development of secondary complications, a longer stay of the patients in the ICU, higher disability and mortality.

Keywords: cerebral vessels constriction, SAH, arteriopathy, cerebral angiography, transcranial Dopplerography, paroxysmal sympathetic hyperactivity syndrome

1. Introduction

This chapter focuses on the problem of cerebral vessels spasm as the reason for brain ischemia. Vessel spastic constriction is one of the leading causes of mortality and disability in patients with ruptured cerebral aneurysms as the most dangerous type of acute cerebral circulatory disorders accompanied by high mortality. In this chapter, we describe the mechanisms of formation of cerebral vessels constriction, including on the background of subarachnoidal hemorrhage and various pathological conditions—migraine, traumatic brain injury, ischemia or hypoxia, and arterial hypertension. Pathomorphological picture of cerebral vessels constriction is described here, smooth muscle role in the constriction of cerebral blood vessels, stages of cerebral blood vessels spasm, the development of constrictive-stenotic arteriopathy, endothelial damage. Diagnostics of cerebral vessels constriction include neurological assessment and data of cerebral angiography, transcranial Dopplerography with quantitative assessment of blood flow. Here is described

the classification of cerebral vasospasm by prevalence and severity and its treatment including paroxysmal sympathetic hyperactivity syndrome, neurovegetative stabilization method, and therapeutic hypothermia.

1.1 Determination of cerebral vasospasm

Cerebral vasospasm is understood as a local or diffuse persistent spastic constriction of the smooth muscle elements of the vascular wall of the cerebral arteries, which is accompanied by a decrease in their lumen, that leads to a decrease in blood supply to the brain [1].

1.2 Background of the vasospastic theory of cerebral ischemia

The role of cerebral vasospasm in the genesis of cerebral ischemic disorders is currently the subject of discussion. At the end of the nineteenth century and in the first half of the twentieth century, cerebral vasospasm was considered as one of the leading causes of the development of ischemic stroke. As the methods of in vivo diagnosis of cerebrovascular pathology improved, the vasospastic theory gradually lost its significance. In addition, it was found that the cerebral arteries are one of the least reactive in the body [2]. It is assumed that only under strictly defined conditions, cerebral vasospasm can be the cause of cerebral ischemia, namely, in subarachnoid hemorrhage and, probably, in migraines [1, 3, 4]. At the same time, cerebral vasospasm has recently been considered again as a possible cause of the development of cerebral ischemic disorders during endovascular neurosurgical interventions [5].

2. The mechanisms of formation of cerebral vessels constriction

Until now, it is not completely clear what is the result of cerebral vascular spasm—an increase in the sensitivity of vascular smooth muscle cells to vasoconstrictor effects, an increase in the content of vasoconstrictors in the blood, a violation of the processes of postconstrictor relaxation of blood vessels, or morphological changes in the walls of blood vessels. The cause of vascular spasm can be the direct effect of oxyhemoglobin on the vascular wall, the breakdown products of red blood cells, endothelin, and many other factors [6]. The action of oxyhemoglobin may include direct vasoconstriction, the release of arachidonic metabolites and endothelin from the arterial wall, inhibition of endothelium-dependent vasodilation by removing nitric oxide, damage to perivascular nerves, and stimulation of free radical reactions [7].

2.1 Subarachnoidal hemorrhage and cerebral vessels constriction

Based on the results of the numerous studies, Towart R. identified three groups of factors that affect vascular tone in SAH [8]:

Group 1—Substances that cause vascular spasm (serotonin and its metabolites, catecholamines, histamine, angiotensin, vasopressin, prostaglandins, in particular, prostaglandin F2a, thromboxane A2);

Group 2—Substances that can contribute to the development of arterial spasm (red blood cell breakdown products, thrombin, fibrinogen breakdown products, prostaglandins, histamine, serotonin, and potassium);

Group 3—Factors that increase spasm due to increased sensitivity of vascular constrictors due to activation of the sympathetic nervous system (increased potassium content in the cerebrospinal fluid, the presence of blood components in the cerebrospinal fluid, fibrinogen breakdown products, angiotensin, platelet growth factor, endothelin).

It is known that when the endothelium is damaged against the background of SAH, activation of phospholipid peroxidation of the plasma membrane of a smooth muscle cell occurs, which leads to the accumulation of diacylglycerol, activation of protein kinase C, and prolonged constriction of the vessel wall [9–11]. On the other hand, it is suggested that reactive oxygen species are involved in the activation of protein tyrosine kinase and mitogen-activating protein kinase [12–14]. Against this background, various biological processes are induced—cell proliferation and migration, apoptosis.

Arterial vessels in the area of hemorrhage (directly in the hematoma or washed with bloody liquor) are exposed to biologically active compounds aggressive to the vascular wall—products of blood breakdown and inflammatory reactions [6].

Sympathetic activation after SAH can stimulate inflammatory reactions [7, 15].

Spasm of the cerebral vessels on the background of SAH exists for quite a long time (up to several weeks). It is obvious that the pathophysiological mechanisms of spasms in large cerebral arteries do not exhaust the problems of brain ischemia. Over time, there are ultrastructural changes in the large vessels of the brain (intima compaction, destruction of the endothelium), which leads to its chronic ischemia [4, 5].

Many vasoconstrictor substances (catecholamines, serotonin, prostaglandins, thromboxane A2, hemoglobin, and products of destruction of red blood cells) cause vasospasm through various mechanisms, but the common thing is that they increase the intracellular concentration of free calcium. These processes are controlled by cAMP and cGMP. Therefore, one of the ways to prevent vasospasm is to increase the concentration of cAMP and cGMP, which increase the calcium uptake by the sarcoplasmic reticulum, which, theoretically, should lead to vascular relaxation.

Thus, the pathophysiological mechanisms that lead to cerebral vasoconstriction are complex.

2.2 Mechanisms of formation of cerebral vessels spasm in various pathological conditions

Figure 1 shows the mechanisms of formation of cerebral vascular spasm in various pathological conditions (migraine, traumatic brain injury, ischemia or hypoxia, SAH, arterial hypertension) [2].

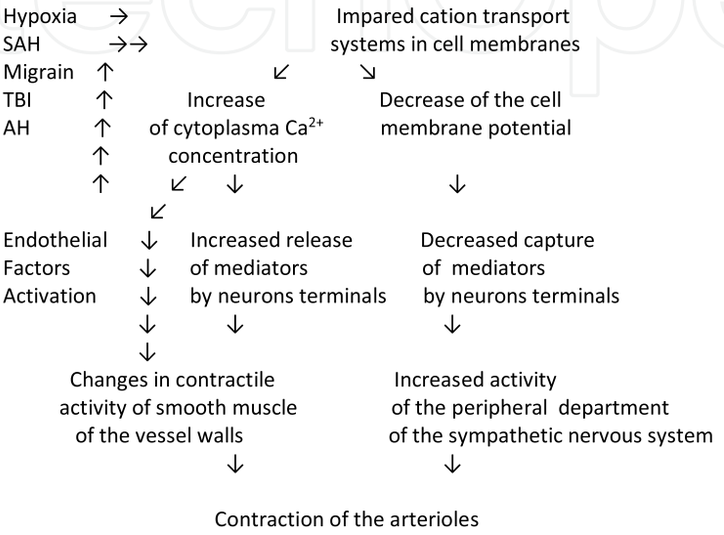

Figure 1.
Formation of cerebral vascular spasm [2].

3. Pathomorphology of cerebral vessels constriction

3.1 Smooth muscle role in the constriction of cerebral blood vessels

Smooth muscle in the cerebral blood vessels is involuntary. It is considered that normally the muscular apparatus of the arteries remains partially reduced and this "basal tone" ensures the maintenance of the necessary level of blood pressure. Increased tone (and pressure) is a result of constriction of the smooth muscle apparatus and narrowing of the artery lumen. Electron microscopic studies have established that three varieties of filaments are involved in the constriction of smooth muscle cells—thin (7 nm), thick (17 nm), and intermediate (continuous). The latter play a leading role in the constriction. They form a continuous system, a kind of network, inside each cell.

There are also so-called dense corpuscles, which act as reference points during the act of constriction. These formations contain a protein (α-actin), which allows us to consider them analogs of Z-plates of striated musculature. The reduction of intermediate filaments leads to the dislocation of thin (actin) and thick (myosin) filaments, their sliding along with each other leads to cell deformation. In the intervals between dense parts, the cytoplasmic membrane bulges outwards. A shrunken cell in a scanning microscope has a "bumpy" surface [16].

3.2 Stages of cerebral blood vessels spasm

Like any pathological process, vasospasm passes through three stages in its development—normal vessel tone → spasm (reversible constriction of the vessel lumen) → irreversible spasm.

The irreversible phase of the pathological spasm is accompanied by damage to the structural elements of the artery wall with the development of contractural degeneration of myocytes, subsequent cell death, and endotheliosis.

Developing arteriopathy is the result of a spasm (constriction) and is manifested by a hemodynamically significant narrowing (stenosis) of the lumen due to intussusceptions (indentation) of the intima and internal parts of the t. media and edema into it [17].

The development of constrictive stenotic arteriopathy against the background of prolonged or chronic vasospasm can be divided into two phases:

- functional spasm and stenosing spasm (contracture).

3.2.1 Arterial spasm (reversible functional state)

Morphological manifestations of spasm of the arteries of the base of the brain (**Figure 2**):

- narrowing of the vessel lumen;
- thickening of the artery wall with the formation of protrusions into the lumen;
- wavy ("corrugated") the stroke of the internal elastic membrane (data);
- change of the horizontal (planar) orientation of the endothelium to the vertical;
- shortening and thickening of myocytes;
- stellate configuration of the myocyte nucleus;
- the wavy course of collagen fibers in adventitia [17–22].

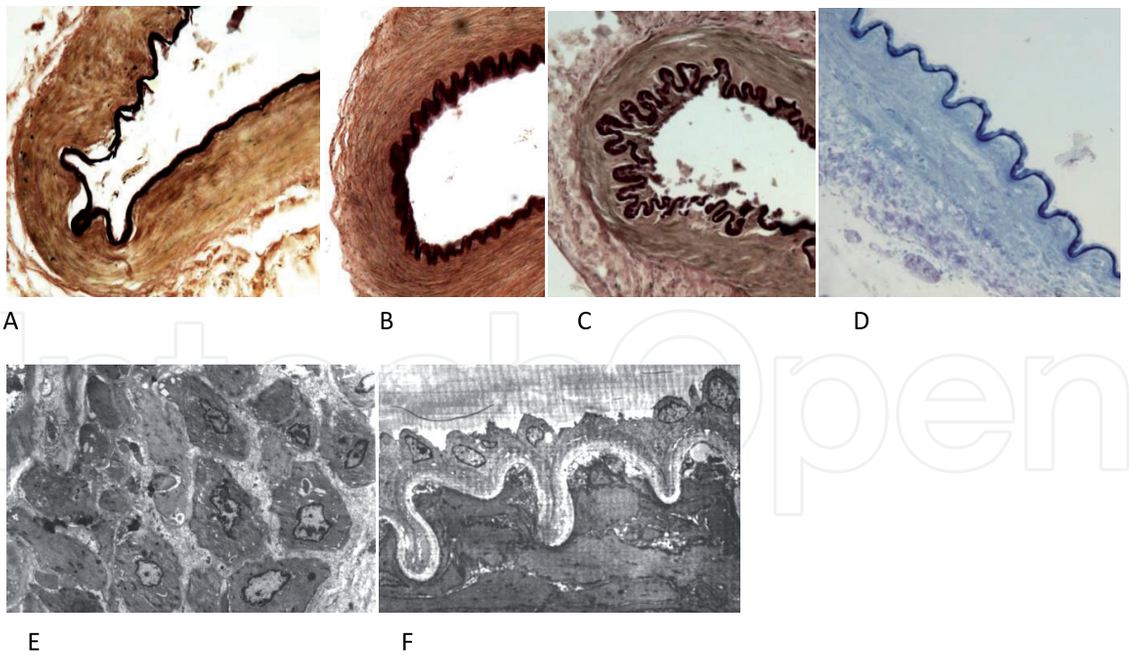

Figure 2.
Morphology of different arterial tones and spasms. A. Atonic state of the artery. Straightened internal elastic membrane, segmentally weakly pronounced folds on the inner surface of the artery. Coloring with orsein on elastic. Magnification 200. B. Increased arterial tone. A corrugated internal elastic membrane without the formation of muscle folds. Coloring with orsein on elastic. Magnification 200. C. Mild spasm. Small folds of the internal elastic membrane with muscle invaginations. Coloring with orsein on elastic. Magnification of 200. D. Moderate spasm. Uniform internal folds of the artery. The color is toluidine blue. Magnification 200. E. Stellate configuration of myocytes and nuclei, the appearance of electron-dense particles in the cytoplasm during constriction. Electronogram.Magnification 200. F. On the surface of the folds of the intima of the spastic artery, the" bulging "endothelium is rounded on the surface and compressed in the depth of the folds. Electronogram.Magnification 750.

3.2.2 Stenosing spasm (contracture)

With prolonged spasm, the following changes in the artery wall are added to the above-listed manifestations of ordinary spasm, leading to additional narrowing of the lumen:

- the formation of large longitudinal folds of the intima, formed due to a sharp reduction in the internal bundles of smooth muscle cells and significantly protruding into the lumen of the vessel;

- hyperhydration of the walls with the accumulation of edematous fluid under the IEM on the tops of the intima folds and aggravation of lumen stenosis. The formation of large folds carries the effect of stenosis—an additional volume appears in the maximally narrowed lumen of the artery, due to which not only the internal relief of the vessel changes but even more its throughput for blood decreases, which is recorded by radiopaque methods of examination and is designated as a vascular spasm (**Figure 3**).

3.2.3 Contractural degeneration (destruction) of smooth muscle cells

A material substrate of irreversible changes in smooth muscle cells with spasm, which are the final of a long stay of the vessel (arteries) in an aggressive environment, contractural degeneration appeared—a variant of irreversible dystrophy, which was not previously listed in the list of such processes in relation to smooth muscle cells. Irreversible damage to the cell myofibrils with the subsequent development of dystrophic changes, colliquation and coagulation necrosis of the nuclei and cytoplasm of the

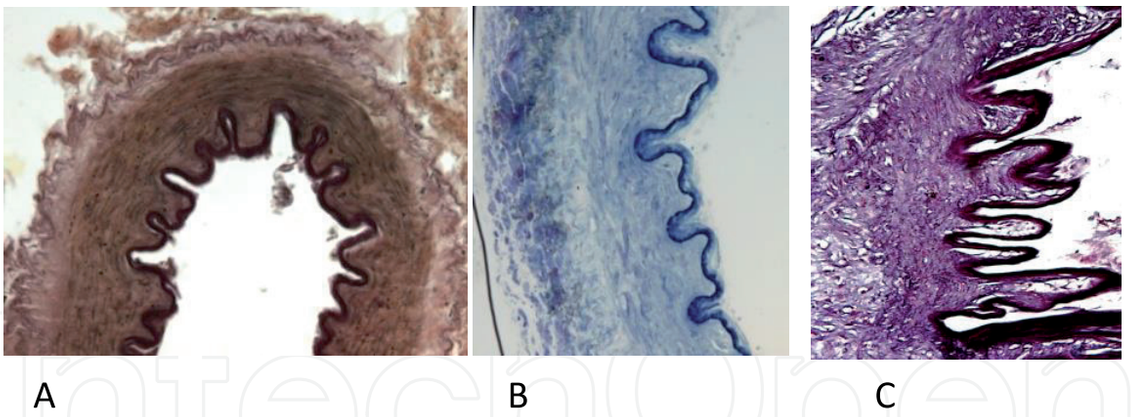

Figure 3.
Constrictive-stenotic arteriopathy ("vasospasm"). A. Deep muscle invaginates forming deep folds stenosing the lumen of the artery. Coloring with orsein on elastic. Increase 200. B. Double-humped invaginates of the muscular membrane, rough deep folds. The color is toluidine blue. Magnification 200. C. There is an accumulation of edematous fluid in the invaginate zone under the internal elastic membrane. Staining with thionine. Magnification of 200.

cell elements of the middle shell, is the result of mechanical rupture of the cell myofibrils with prolonged spasm, developing at 2–4 weeks under the influence of biologically aggressive substances of the spilled blood. The morphogenesis of contractural degeneration, as a special case of myocyte damage, is demonstrated in **Figure 4** [23].

Stages of destructive changes in the contractile apparatus of smooth muscle cells of the arteries of the base of the human brain in constrictive-stenotic arteriopathy [24].

At the top, the smooth muscle cell is in a relaxed state (nucleus, contractile myofibrils: thin, thick, intermediate);

1. A contracted smooth muscle cell. The shape of the cell and the nucleus are changed, actin and myosin contractile fibrils have come into contact (in accordance with the principle of "sliding mechanism");

2. Prolonged spasm (contracture). Destruction of myofilaments;

3. Impregnation of the dead cell with plasma and tissue fluid;

4. Forming layered corpuscles in the dead smooth muscle cells;

5. Formed layered corpuscles;

6. The remains of a cell in the interstitial tissue (**Figure** 5).

3.2.4 Endotheliosis and desquamation of the endothelium

Against the background of prolonged spasm, dystrophic changes in the endothelium are recorded with vacuolization of the cytoplasm and a violation of the connection of endotheliocytes with the basement membrane. The endothelium is "squeezed" into the lumen from the depth of the folds formed during a stenotic spasm. Changes in the endothelium during a spasm and the development of constrictive-stenotic arteriopathy (**Figure 6**):

- endothelial damage (endotheliosis);
- desquamation of the endothelium;
- formation of surface erosions of the intima.

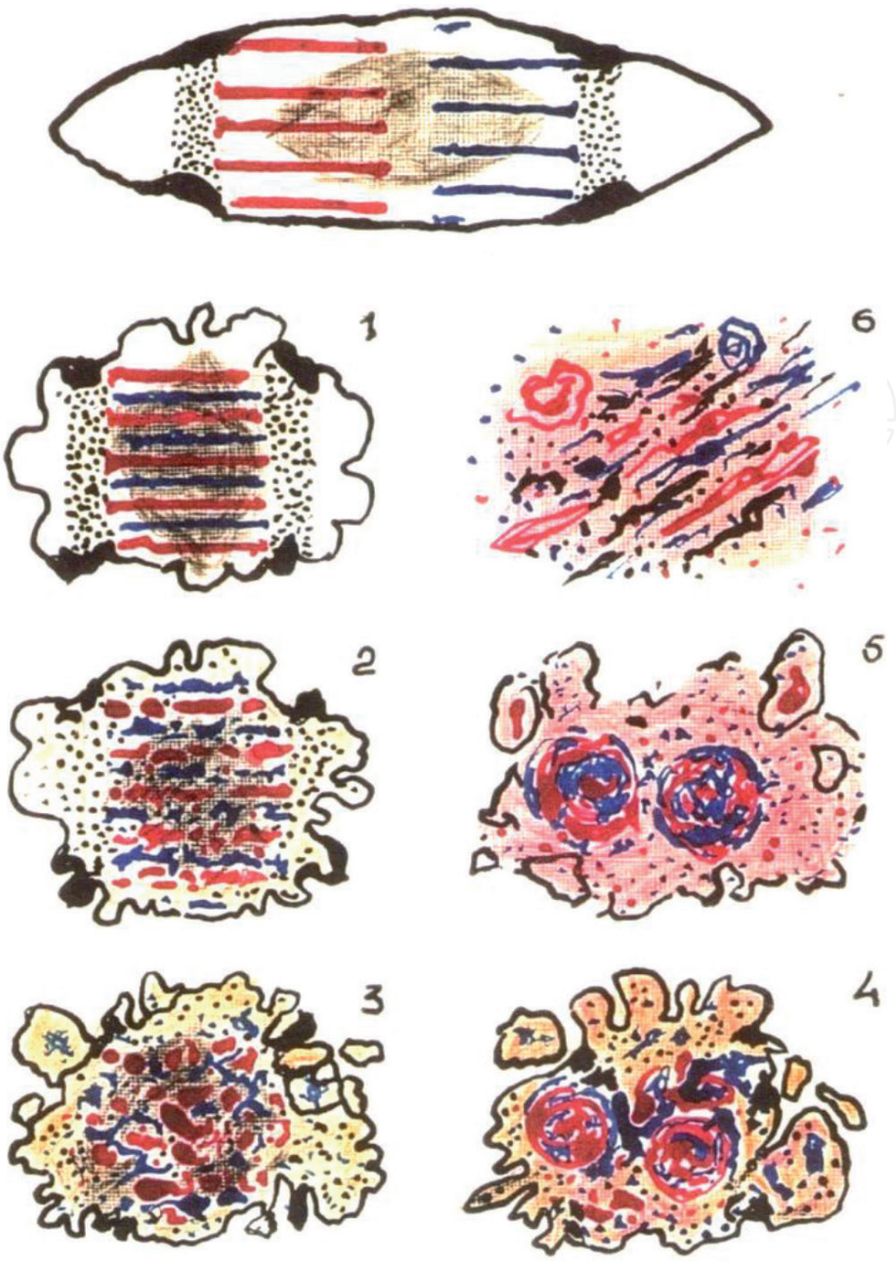

Figure 4.
Damage to smooth muscle cells during prolonged vasospasm (author's drawing of Professor Medvedev Yu.A., 2001).

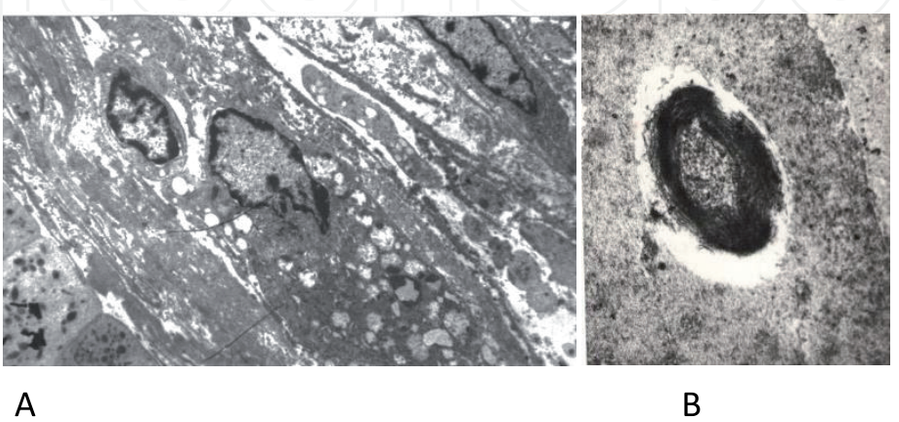

Figure 5.
Damage to smooth muscle cells in contracture degeneration. A. Vacuole dystrophy and myocytolysis. Electronogram.Mag. 2000. B. a layered body made of fragments of fused myofibrils destruction of the functional substrate of the artery wall (smooth muscle it explains the tolerance of blood vessels to drug dilation therapy in constrictive-stenotic arteriopathy Electronogram.Mag. 20000 [24].

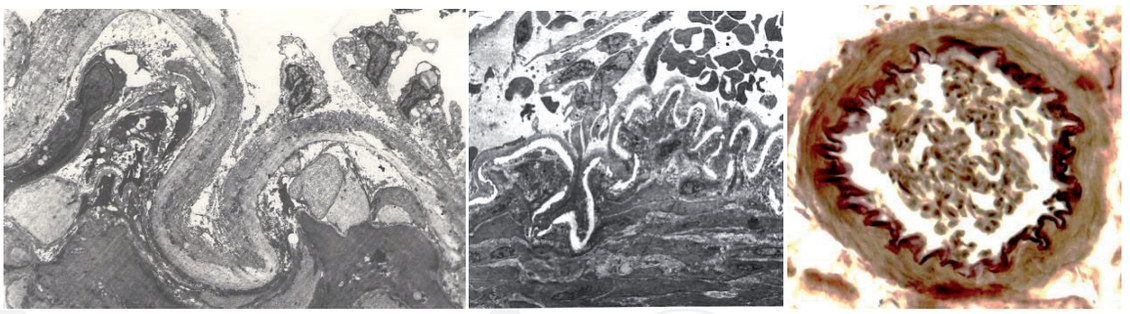

Figure 6.
Constrictive-stenotic arteriopathy ("vasospasm"). Endotheliosis. A. on the surface of the intimate fold, on the right, there is an endothelium with degenerative changes (vacuolized cytoplasm and deformed nucleus), cell decomplexation, and loss of connection with the basement membrane, on the left—the inner surface is devoid of an endothelial layer, in the roughness of the folds there is cellular detritus of a necrotized endotheliocyte, under the inner elastic membrane there is an accumulation of fluid and dystrophically altered myocytes. Electronogram.mag. 2000. B. Desquamation of the endothelium in the zone of pronounced folding of the wall with the erosion of the inner circumference of the artery. There is a desquamated endothelium in the lumen of the spasmed artery. Electronogram.mag. 750. C. Cellular embolus of desquamated endothelium in the lumen of a spasmodic small artery. Coloring with orsein on elastic. mag. 200.

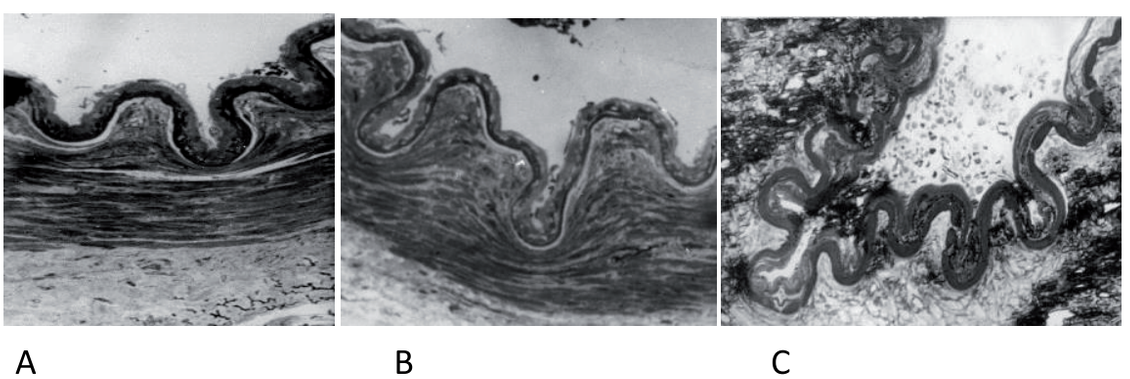

Figure 7.
Stages of constrictive-stenotic arteriopathy. A. Stage of reactive spasm. Reversible phase. B. Stage of stenosing spasm (contracture). C. Stage of edema and destructive changes. The irreversible phase.

Endothelial damage explains the observed endothelial dysfunction. The loss of the endothelium does not yet lead to thrombosis, a violation of the parietal membrane can affect the rheology of the blood.

Thus, vasospasm after intracranial hemorrhages should be considered as a pathological process that develops as a result of prolonged reactive spasm with the development of arteriopathy, consisting in contractural degeneration of myocytes, endotheliosis, and desquamation of the endothelium with the formation of surface erosions (**Figure 7**).

Contractural degeneration occurs not only in aneurismal hemorrhages. It occurs in all those situations when it comes to hemorrhages in the substance of the brain and its membranes. This is a wide range of diseases, including, first of all, hypertension, as well as other diseases accompanied by arterial hypertension (kidney diseases, endocrinopathy, hemorrhagic diathesis of various nature, traumatic brain injury, surgical brain injury, etc.) [4].

4. Diagnostics of cerebral vessels constriction

4.1 Neurological assessment

Neurological examination is the main clinical tool for the diagnosis of stroke and cerebral vasospasm in particular. The diagnosis of symptomatic vasospasm is based

on the appearance of focal or global neurological deterioration. Fluctuation of the level of consciousness, negative dynamics in the form of an increase in the focal neurological deficit, and deprivation of the level of consciousness to stun, sopor up to coma require immediate CT scan of the brain with cerebral angiography. In patients with verified SAH, the condition at admission is assessed on the Hunt-Hess scale [25]. The state at discharge—according to the Glasgow outcome scale [26].

The stimulation of the higher cortical center of the sympathetic nervous system — the insular cortex—with blood spilled due to SAH is realized in a sympathetic "storm" or paroxysmal sympathetic hyperactivity syndrome (PSH). PSH is associated with the development of secondary complications, a longer stay of the patient in the ICU, higher disability, and mortality [27, 28].

Timely and adequate prevention and therapy of the syndrome improves the functional result [29, 30]. Criteria for PSH syndrome and differential criteria are present in **Tables 1** and **2**.

Indicators/points	**0**	**1**	**2**	**3**
Main criteria				
Pulse rate	<100	110–119	120–139	>140
BP syst	<140	140–159	160–179	>180
Breath rate	<18	18–23	24–29	>30
Kerdo index	0	+1 – +10	+10 – +20	>+21
T C	<37	37–37.9	38–38.9	>40
Increased muscle tone (points)	0	1–2	3	4–5
Frequency of episodes of vegetative instability (in 24 h)	No	3	6	>6
Additional criteria				
Level of consciousness (points) (GCS)	15–14	14–13	12–10	<10
Hyperhydros	No	+	++	+++
Skin hyperemia	no	+	++	+++
Albumin g/l	34–48	28–34	22–28	<22
EEG signs of irrigation of diencephalic structures	no	+	++	+++

Interpretation of results:
0—no; 1–7 p according to the main criteria, no more than 5p according to additional criteria—weakly expressed PSH syndrome; 8–14 p according to the main criteria, no more than 10 p according to additional criteria—moderate PSH syndrome; 15–21 p-according to the main criteria, 10–15 p according to additional criteria- pronounced PSH syndrome.

Table 1.
Criteria for PSH syndrome.

Indicators/points	**1**	**2**	**3**
ΔT C	>0.5	>0.7	>1
Procalcitonin test (qualitative method)	>0.5	>2	>10
Pain	+	++	+++
Pulse rate	80–99	60–79	<60
BP syst	90–100	80–90	<80
T	<36	<35.5	<35

Interpretation of the results: 1–5 p—possible combination with other conditions that require additional diagnosis and treatment; 5–11 p—PSH syndrome is doubtful or is not leading; 11–18 p—PSH syndrome is excluded.
Notes: The assessment is carried out only under the condition of normovolemia, pO2 > 60 mmHg or SpO2 > 85%, pCO2 < 50 mmHg, glycemia > 3.5 mmol/L. DT C - the difference between rectal and axial temperatures; Kerdo index = 100× (1-ADdiast/HR); + weak severity of the sign +. ++ moderate severity of the sign ++. +++ strong severity of the sign +++. The level of consciousness is assessed according to the Glasgow Coma Scale. The assessment of muscle tone is made according to the Ashworth spasticity scale.

Table 2.
Differential criteria.

Pain syndrome assessment in patients with preserved consciousness can be performed according to a 5-point verbal pain assessment scale [31], where 1 point = +; 2–3 points = ++; and 4 points = +++.

The assessment of the level of sympathetic hyperactivity is made at least once a day. The use of differential criteria for the initial and each subsequent assessment is mandatory.

4.2 Instrumental diagnostics of cerebral vasospasm

Instrumental diagnosis of vascular diseases of the brain and cerebral vasospasm, in particular, is based on the joint use of methods of radiation and ultrasound diagnostics.

4.2.1 Cerebral angiography

The "gold standard" for the diagnosis of cerebral vasospasm remains cerebral angiography. The angiographic diagnosis of cerebral vasospasm is established by the presence of local or diffuse narrowing of the cerebral arteries (**Figures 8** and **9**).

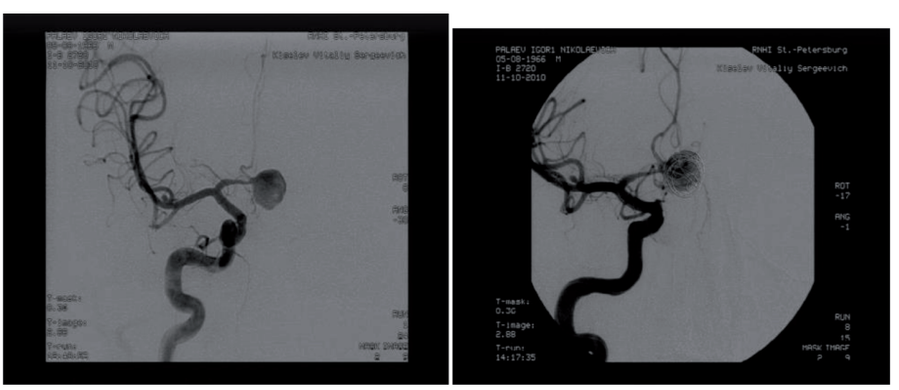

Figure 8.
Cerebral angiography. Multiple cerebral aneurysms: ACA, right MCA in patient P., 45 years old. Cerebral vasospasm detected in the A1 segment right ACA.

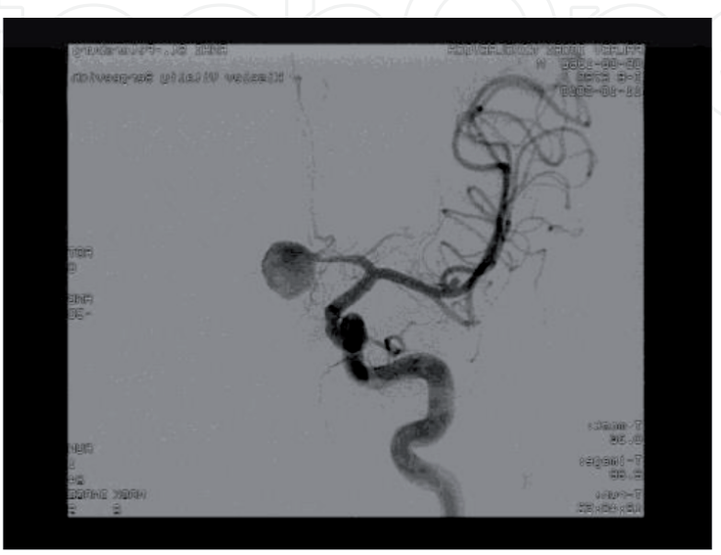

Figure 9.
Local cerebral vasospasm of the A1 segment of the left ACA developed during embolization of the left ACA sac aneurysm (9, 1 × 7, 8 × 6, 1 mm).

4.2.2 Transcranial dopplerography

The possibilities of diagnosing cerebral vasospasm, including its initial stages, have expanded after the introduction of the transcranial Dopplerography method into clinical practice [3].

Ultrasound assessment of blood flow in the cerebral arteries is the most mobile method of screening, dynamic observation, and monitoring of the condition of patients with acute cerebral circulatory insufficiency. In acute cerebral ischemia due to the development of cerebral vasospasm, the prognostic marker and the purpose of monitoring are universal and reproducible characteristics—the flow direction, the type of spectrum, the value of the cerebral blood flow velocity, and the autoregulatory reserve [3, 32–34].

In cerebral vasospasm, an increase in linear blood flow velocities and, above all, the maximum systolic velocity (or frequency), as well as a violation of cerebrovascular reactivity, is recorded. Thus, in cerebral vasospasm, the Doppler picture is similar to stenosis and is usually observed in several cerebral arteries [3]. The initial stage of angiospasm is diagnosed when the peak systolic blood flow rate in the middle cerebral artery (MCA) increases to 120 cm/s. With a moderate degree of vasospasm, its value varies from 120 to 200 cm/s, and with severe vasospasm, it exceeds 200 cm/s [34, 35].

With all the variety of pathogenetic variants of damage to the cerebral vascular bed, there are several diagnostically important parameters of the Doppler signal, the changes of which are universal and reproducible, such as the direction of flow relative to the source of ultrasound radiation, the type of spectrum, and the value of the maximum systolic and minimum diastolic velocity [3, 33].

4.2.3 The quantitative assessment of blood flow

The quantitative assessment of blood flow in the arteries of the brain is based both on the directly measured parameters of the Dopplerogram (amplitude, frequency distribution, pulse variations) and on various calculated indices.

The most popular measured Doppler parameter is the flow rate:

- Maximum systolic blood flow velocity (Vsist);
- End diastolic blood flow velocity (Vdiast);
- Average rate per cardiac cycle (MenV);
- Average speed per systole (Vms).

The flow rate is a reference value for arterial vessels with certain characteristics that are close to constant (diameter, depth). Initially, it is assumed that in the absence of structural anomalies and vascular diseases that form the cerebral arterial system, the absolute values of blood flow parameters at rest are constant for a particular person, and their deviations during functional loads (hypoxia, physical exertion, etc.) correspond to the range of the autoregulation reserve.

Based on the indicated parameters characterizing the spectral curves, calculated coefficients have been developed that allow us to quantitatively describe the normal and pathological features of the received signal. The most common methods used for the clinical assessment of blood flow parameters are as follows:

- Circulatory resistance index (RI);

- Pulsatility index (PI);
- Systolic-diastolic index (ISD);
- Spectral Expansion Index (SBI);
- Coefficient of asymmetry (KA);
- Pulse wave rise index (PPI).

Absolute values of blood flow velocity play an important role in assessing the reserve of collateral circulation or calculating the transmission pulsation index (the ratio of velocities in the extra-and intracranial segments of the carotid basin arteries) in cerebral vasospasm.

In addition, all judgments about the quantitative values of the tonic component of the dislocated vessel, the state of the resistive segment of the cerebral arterial pool, and reactive changes during the period of functional stress are also derived from the analysis of the velocity parameters [35].

Turning to the absolute values, it is necessary to take into account some features of the distribution of speed parameters along with the cerebral arteries, due to a combination of physiological and instrumental reasons. These features are manifested by the physiological hierarchy of values of the linear velocity of blood flow in the cerebral and precerebral arteries. At the extracranial level—internal carotid artery > external carotid artery > vertebral artery. At the intracranial level—middle cerebral artery > anterior cerebral artery > internal carotid artery > posterior cerebral artery > main artery > vertebral artery [32].

Between the arteries of the large anastomosis of the base of the brain (Willis circle), the predominance of speed in the middle cerebral artery over the speed in the anterior cerebral artery and posterior cerebral arteries fits into the 20% range [34]. The flow along the main artery is usually always higher than in the best of the vertebral arteries. The normative value of the coefficient of asymmetry between the same carotid arteries of the different sides should not exceed 20%, a 30% difference in speed indicators is permissible for vertebral arteries. Taking into account the anatomical features (the formation of the right arterial sections from the brachiocephalic trunk), lower values are more often recorded in the right vertebral arteries and the internal carotid artery.

Thus, the diagnosis of cerebral vasospasm is based on the data of neurological symptoms, data of cerebral angiography, and the results of transcranial Dopplerography. When comparing instrumental and clinical data, reversible neurological symptoms are usually registered in patients with moderate vessels constriction, and persistent neurological deficit—in severe vasospasm.

5. Classification of cerebral vasospasm

According to transcranial Dopplerography of brain vessels angiospasm is assessed by three degrees of severity: at a blood flow rate of <120 cm/s- I degree, 120–200 cm/s - II degree, >200 cm/s- III degree; by prevalence—vascular spasm of one carotid area-local (segmental), vascular spasm in both carotid areas—widespread (multisegmental), spasm of carotid and vertebrobasilar areas-total (diffuse).

The severity of cerebral vasospasm during endovascular neurosurgery is assessed according to Atkinson P. classification [32].

6. Treatment of cerebral vessels constriction

Treatment of patients with acute disorders of cerebral circulation requires early determination of the causes of acute cerebrovascular accidents, as well as a dynamic assessment of pathogenetic processes.

Previous studies have shown that 13–30% of patients with SAH suffered clinical deterioration due to an ischemic event secondary to cerebral vasospasm, and approximately 50% of these patients either had a long-term pathology or died as a result of such an event [7, 36–39]. Angiographic vasospasm has been reported to occur in 50–70% of patients with SAH [38–40]. A number of researches aimed to identify early predictors of vasospasm after SAH, since such identification could provide more effective prevention of vasospasm and subsequently lead to better neurological outcomes [41].

Vasospasm, which develops in a number of cases during endovascular neurosurgical interventions, is considered a possible cause of perioperative cerebral ischemia [5]. The frequency of subarachnoid hemorrhage (SAH) is 15–18 per 100 thousand people per year [42]. The main causes of death in patients with a ruptured cerebral aneurysm are the direct influence of spilled blood, hydrocephalus and ischemic complications resulting from vasospasm. If the first two causes are coped with more successfully due to the improvement of microsurgical neurosurgical techniques of aneurysm operations and methods of hydrocephalus treatment, then vasospasm and related ischemic complications occupy a leading place among the complications [5, 42].

It was revealed that vasospasm of the I and II degrees is effectively treated conservatively and has no significant effect on the clinical outcome, and diffuse vasospasm of the III degree negatively affects the outcomes and requires the use of endovascular angioplasty and intraarterial pharm angioplasty [43, 44].

It is known that vasospasm appears on the fourth day, increases to 14–17 days, and gradually decreases to 21–30 days.

Figure 10 shows a Dopplerographic picture of cerebral vasospasm of the III degree on the 16th day from the rupture of the ACA aneurysm.

Dopplerography is performed in dynamics in all patients with detected vasospasm in order to determine the effectiveness of treatment. Against the background of positive neurological dynamics, by the end of the fourth week of the disease, most patients have both a general and regional decrease in speed indicators, which is associated with overcoming edema, reducing the volume of brain tissue in the affected pool, restoring the compliance of perfusion capabilities with the metabolic and functional needs of the preserved areas of the brain.

The lengthening of the period of instability of speed parameters or significant fluctuations in absolute values can serve as a marker of an unfavorable prognosis of the deepening of the ischemia process (progredient course), which undoubtedly serves as a basis for clarifying the etiological and/or pathogenetic factor, searching for errors in the choice of therapeutic tactics.

The Fisher CT scale, which evaluates the amount of blood in any cracks or tanks, as well as the presence of intraventricular hemorrhage or intracerebral hemorrhage, is widely used to identify patients with a high risk of developing cerebral vasospasm after SAH [45, 46]. The Fisher CT scale is widely used to identify patients with a high risk of developing cerebral vasospasm after SAH [45, 46]. Vasospasm, according to Fischer's classification, is directly proportional to the outpouring of blood in the basal cisterns (**Figure 11**).

According to this classification, patients with intracerebral hematomas (ICH) and intraventricular hemorrhages (IVH) are at high risk of developing vasospasm [47]. Despite the widespread protocols for the prevention and treatment of vasospasm in recent years, the introduction of endovascular technologies (balloon angioplasty, pharm angioplasty), the results are still unsatisfactory.

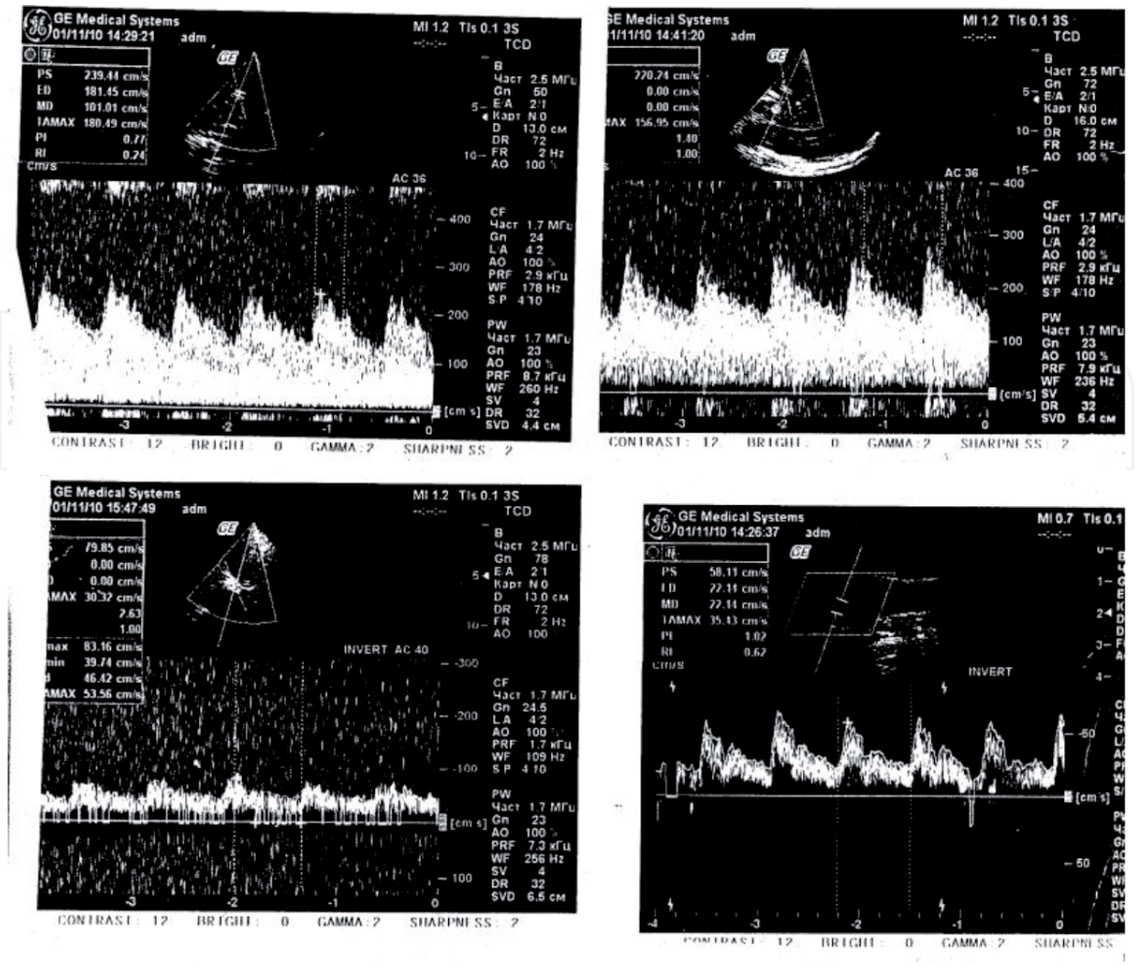

Figure 10.
Cerebral vasospasm of the III st. in both MCA (D < S) in patient M. on the 16th day from a rupture of the ACA aneurysm. Doppler study data.

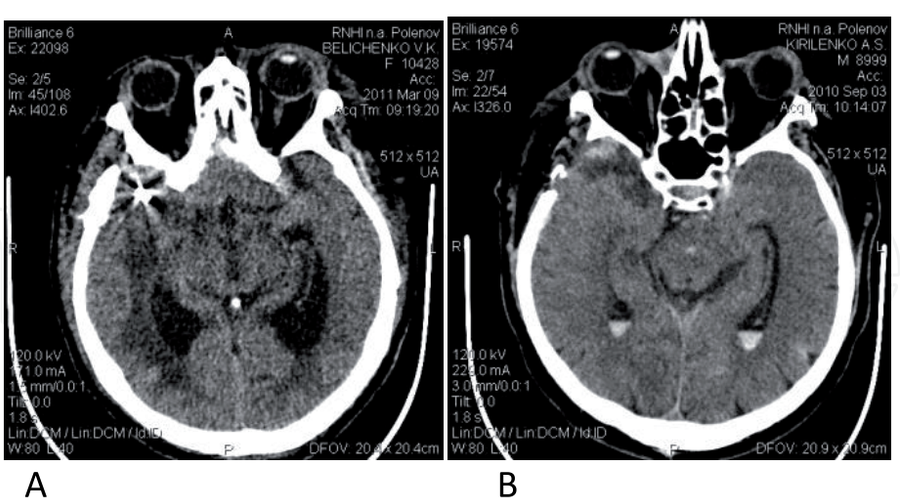

Figure 11.
Fisher CT III-IY in patients with a cerebral aneurysm, right ACA-ACA (A), left ACA-ACA (B).

Japanese researchers have shown that the amount of blood on computed tomography (CT) is a predictor of cerebral vasospasm after SAH [48]. However, the influence of the location of blood on the frequency of vasospasm remains unclear. The authors retrospectively evaluated the relationship of blood volumes in individual components (tanks and slits) of computed tomography with angiographic vascular spasm after SAH [49–51]. The study included 149 patients with SAH who

were scheduled for clipping of a cerebral aneurysm. The amount of subarachnoid blood was classified according to the Fisher CT scale. The amount of subarachnoid blood in five tanks or three slits was also estimated on the SAH scale from 0 to 3 (0 - no blood, 3 - completely filled with blood) [52, 53]. Spasm of the cerebral vessels was diagnosed according to the results of angiography. The researchers obtained the results according to which angiographic vasospasm developed in 51 of 149 patients (34%). Of these, 26 patients had neurological symptoms. The Fisher CT and SAH scores in the right and left Sylvian fissures and suprasellar cisterns were significantly higher in patients with angiographic vasospasm than in patients without it. One-dimensional logistic regression analysis showed that a high level of Fisher CT and high SAH scores in the right and left Sylvian fissure and suprasellar cisterns were predictors of angiographic vasospasm. Multivariate analysis showed that the SAH score in the right Sylvian fissure was an independent predictor of angiographic vasospasm (odds ratio, 3.6; 95% confidence interval (CI), 1.7–7.7; $P = 0.01$) [48].

Activation of the sympathetic nervous system is associated with the development of vasospasm [54–58]. Peerless et al. [54] indicated that vessels removed from direct contact with blood showed reactive narrowing 1 week after SAH, suggesting that cerebral vasospasm may be mediated by a central control mechanism acting through the sympathetic nervous system. Bunc et al. in an experiment on rabbits [55] demonstrated that the influence of the noradrenergic blockade of cerebral noradrenergic areas of the hypothalamus and brain stem prevents vasospasm in circumstances similar to SAH by way of exclusion of the activity of the sympathetic nervous system.

It is well known that the cardiovascular centers of the brain stem are involved in the regulation of cardiac function through sympathetic and parasympathetic efferents [2]. However, recent data have shown that supratentorial centers can also participate in the regulation of the cardiovascular system. Hirashima et al. [59] showed that the amount of SAH in the right Sylvian fissure was independently associated with abnormal ECG changes in patients with SAH, and the degree of the amount of SAH in the right Sylvian fissure was a better predictor of ECG changes than the degree of Fisher CT. These authors suggested that, since the insula cortex is an important site for controlling autonomic function with a right-sided predominance of sympathetic cardiovascular effects, blood in the right Sylvian fissure may stimulate the insula cortex, which leads to sympathetic cardiovascular effects, such as ECG changes. Sympathetic activation can activate inflammatory reactions [7, 15]. Yoshimoto et al. [15] reported that patients with SAC with systemic inflammatory response syndrome had a higher probability of cerebral vasospasm upon admission. Recently, Kato et al. [60] demonstrated that inhibition of sympathetic activation by beta-adrenergic receptor antagonists reduces the levels of proinflammatory cytokines in the cerebrospinal fluid in a rat model of SAH.

Usually, vasospasm is more pronounced on the side of the aneurysm and in the vessels carrying the aneurysm. All patients receive infusion therapy with the calcium channel blocker nimodipine (60 mg every 4 hours). As the degree and prevalence of vasospasm increases, the outcomes worsen, but this does not reach a significant degree, since the cause of fatal and unsatisfactory outcomes in patients with ICH is mainly the volume effect of hematoma, edema, and dislocation of the brain.

Prophylaxis of local cerebral ischemia and cerebral vasospasm following temporary occlusion of the afferent artery during surgical clipping cerebral aneurysm was proposed with short intervals of vessels occlusion in combination with intraoperative intravenous administration of Inosine+Nicotinamide+Riboflavin+Succinic Acid (20,0 ml). Such tactics expands the tolerability to artery occlusion in patients operated in the “cold” period, reduces the possibility of neurological deficit, reduces

the recovery period and resuscitation bed-day after neurosurgery [61]. Outcomes in patients with IVH and ICH + IVH were also analyzed depending on the degree and prevalence of vasospasm [1]. According to the data of a number of authors, starting from the second degree of widespread vasospasm, the share of unsatisfactory outcomes and mortality increases sharply [42].

According to the data available in the literature, angiospasm of the I and II degrees did not have a significant effect on the condition and outcome of the disease, but diffuse vasospasm was an independent factor aggravating both the condition and the outcome of the disease [1].

Angiospasm is often observed in patients with ICH and IVH due to the rupture of aneurysms. Taking into account the occurrence and increase of vessels construction, starting from 4 days after hemorrhage, early diagnosis of patients with SAH and hospitalization in specialized vascular neurosurgical centers will allow, along with the shutdown of the aneurysm from the bloodstream, also on the first–fourth day to sanitize the basal cisterns, which largely prevents the occurrence of vasospasm. Conservative treatment with modern drugs is quite effective in patients with angiospasm of I and II degrees. Such an angiospasm has no significant effect on the condition of patients and the outcome of the disease.

Diffuse angiospasm of the III degree is an independent factor that worsens the outcome in patients with aneurysmal ICH and IVH, conservative treatment is ineffective in most cases, therefore, it requires more active treatment in the form of balloon angioplasty and intraarterial pharm angioplasty.

In the diagnosis of cerebral vasospasm of II–III degree and PSH syndrome in patients with SAH, conservative treatment is carried out:

Mild PSH syndrome (1–7 points) - pharmacotherapy—beta-blockers, phenytoin, NSAIDs; physical methods-therapeutic hypothermia.

Moderate PSH syndrome (8–14 points) - pharmacotherapy—beta-blockers, phenytoin, alpha-2 adrenoagonist, NSAIDs; physical methods - therapeutic hypothermia.

Severe PSH syndrome (14–21 points) - neurovegetative stabilization (opioid analgesic, alpha-2 adrenoagonist, hypnotics); physical methods—therapeutic hypothermia (craniocerebral hypothermia).

The duration of therapy is determined individually, after a repeated assessment of the patient's condition.

6.1 Neurovegetative stabilization

Neurovegetative stabilization in the intensive care program for cerebral vasospasm and acute cerebral injury implies the creation of conditions for the absence of debilitating sympathicotonia and the implementation of long-term economical adaptation associated with the predominance of the parasympathetic tone of the autonomic nervous system. It includes intravenous administration of the opioid analgesic fentanyl 0.5–1 mcg/kg/h, alpha-2 adrenoagonists (clonidine 0.2–0.7 mcg/kg/h or dexmedetomidine 0.2–0.5 mcg/kg/h), sodium thiopental 2–4 mg/kg/h [62].

6.2 Therapeutic hypothermia

Apply physical cooling methods to maintain normothermy—craniocerebral hypothermia, which consists in lowering the temperature of the scalp to 5–8°C with the help of helmets cooled by circulating fluid, to maintain the skin temperature at a constant level during the entire cooling session. The cooling duration is from 12 hours to 7 days, with an increase in temperature after the cooling is stopped repeat the procedure, carry out until a stable normothermy is achieved, do not allow

the body temperature to drop below 35.5°C; it is permissible to use other cooling methods to maintain normothermy [63].

7. Conclusion

The understanding of the nature of cerebral vessels constriction is not clear thoroughly. To ensure adequate treatment, a rapid diagnostics of cerebral vessels constriction and its nature and cause is necessary. The development of secondary complications, a longer stay of the patients in the ICU, higher disability, and mortality are associated with cerebral vessels constriction. In our opinion, it is necessary to start treatment of cerebral vessels spasm of II–III degree and PSH syndrome in patients with SAH, aneurysmal ICH, and IVH after its verification as soon as possible. Specialized neurosurgical and neurological departments (ICU) allow for modern dynamic neurological and instrumental assessment and specific therapy and surgical intervention.

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Conflict of interest

There is no conflict of interest.

Abbreviations

AH	arterial hypertention
cAMP	cyclical adenosine-monophosphate
cGMP	cyclical guanosine-monophosphate
CT	computer tomography
ACA	anterior cerebral arteria, anterior communicante arteria
MCA	middle cerebral arteria
SAH	subarachnoidal hemorrhage
TBI	traumatic brain injury
PSH	paroxysmal sympathetic hyperactivity
IVH	intraventricular hemorrhage
ICH	intracerebral hemorrhage
ICU	intensive care unite

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