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DEVELOPMENT OF HEMORRHAGIC STROKE NEUROSURGERY AT THE PRESENT STAGE (REVIEW)

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The article analyzes the current trends in the development of hemorrhagic stroke (HS) neurosurgery. The studies were conducted using the Web of Science, Scopus, PubMed, CyberLeninka, eLibrary databases by searching/analyzing sources published over three years, as well as individual publications older than five years (2014 to 2022). A total of 50 literature sources were analyzed. The article considers neurosurgical approaches to the treatment of HS and current approaches to the study of pathological mechanisms, predictors, and risk factors. It was found that much attention is paid to a comparative study of the outcomes of classical and minimally invasive methods of treating the pathology. An increase in the proportion of the latter leads to a decrease in the mortality rate in HS. Arterial hypertension is an unambiguous risk factor in the development of pathology. Many studies are devoted to potential predictors of HS outcomes (prealbumin level, hyperuricemia, lymphocyte/neutrophil ratio). Particular attention is paid to the mechanisms of formation of programmed cell deaths in the postoperative period. A list of molecular-cellular predictors optimal for risk stratification in GI has not been formed. It is necessary to search for therapeutic targets through an in-depth study of the mechanisms of development/remission of pathology at the molecular-cellular level.

Key words: hemorrhagic stroke, hematomas, intraventricular hemorrhages, minimally invasive methods.

Introduction. Worldwide, stroke ranks 1-2 among all-cause mortality and is the leading cause of disability in adults. The prevalence of stroke is significantly (5 times) lower than that of the ischemic variety. At the same time, the mortality rate (up to 50% of patients) in the first case is much higher, and the acquisition of disability can reach 75% according to different registers [1]. Stroke is more common in people of working age and manifests itself in the form of spontaneous subarachnoid hemorrhages (SAH), intracerebral hematomas (ICH) and spontaneous extra-subdural hematomas. In 70-80% of cases, SAH is caused by cerebral arterial aneurysms (CA) [2]. Traditional risk factors for the development of hemorrhagic stroke are divided into modifiable (the presence of hypertension, diabetes mellitus, high blood cholesterol, cardiovascular disease, atrial fibrillation, sedentary lifestyle, smoking/alcohol consumption) and non-modifiable (age, gender) [3].

The aim of this review is to analyze the trends in the development of neurosurgery for hemorrhagic stroke at the present stage.

The localization of the IMH is most often found in the area of the subcortical nodes of the GM. These formations in relation to the internal capsule are classified as lateral (putamenal), medial (thalamic), subcortical (lobar). Their prevalence in the world in the specified groups among patients with GI is 55, 10 and 15%, respectively [4].

The research was conducted through searching and analyzing Russian and English language literature using Web databases. of Science , Scopus , PubMed , CyberLeninka , eLibrary . The search was conducted with the objective of identifying current trends in GI research. The data of some authors were presented schematically to improve the perception of the material. Several original articles were included in separate schemes. This made it possible to summarize the latest results of a number of aspects of GI research. The literature analysis was mainly carried out for 2021-2022, including some sources published within three years, as well as single publications older than five years . A total of 50 literary sources were reviewed.

Complications arising in hemorrhagic stroke. The most severe complications of HS are intraventricular hemorrhages (IVH) (Fig. 1), the outcome of which is diagnosed using several methods. Mortality in IVH is 50% and leads to serious disability of survivors [5]. IVH is mainly considered as an independent predictor of an unfavorable outcome [6]. Most often (77.8%) IVH develops with massive SAH, and sometimes with a median hematoma volume of 29.8 ± 5.6. The II degree of IVH severity is common, the prevalence of which is more than 60%, the rest falls on degrees I and III according to the criteria of blood filling and the characteristics of the clot density in the cerebral ventricles according to the Graeb and Hounsfield assessment scales [7]. Other complications of GI include the following: (1) dislocation syndrome of midline structures more than 5 mm, (2) signs of trunk compression, (3) deformation of cisterns.

Current standards for the treatment of patients with hemorrhagic stroke are based on the provisions reflected in the domestic clinical guidelines “Hemorrhagic stroke” developed in 2020 (URL: https://ruans.org/T ext/Guidelines/hemorrhagic_stroke-2020.pdf), which describe in detail the surgical options for the treatment of hemorrhagic stroke depending on the period of SAH: (1) acute (14 days), in which the most acute period is distinguished (0-72 hours, the period before the onset of vasospasm); (2)

pre-acute (15-31 days, regression of the main complications of SAH); (3) cold (>1 month, residual disorders). The indicated surgery on the aneurysm, according to the specified current Russian clinical guidelines, is allowed in the acute period if the severity of SAH is I-IV or V on the Hunt-Hess scale. The last degree of SAH severity should be in combination with data on the Glasgow Coma Scale (Glasgow Coma Scale) of 8 points, the

volume of cerebral hemispheres >30 ml. Postponement of surgical intervention is necessary in an extremely severe condition (>7 points on the Glasgow Coma Scale). It is important to note that the implementation of the vascular program in the Russian Federation contributed to a decrease in mortality from acute cerebrovascular accident in general, while the volume of surgical care for CI increased 7-fold from 2007 to 2016 [8].

Immediate and accurate detection of IVH is a key diagnostic component for the effectiveness of further treatment. The IVH detection algorithm "Canon AUTO Stroke" was developed using artificial intelligence to accurately identify patients with and without IVH and detect intraparenchymal, intraventricular, subdural and SAH. The application of the algorithm can significantly improve the treatment time of patients with IVH [9]. Expansion of IVH after its occurrence is an independent predictor of worse outcome. Severity (Graeb score >5) is associated with worse outcome at hospital discharge compared to lower severity (Graeb score 1-4) [10]. Approximately 30% of patients with IVH experience hematoma expansion within 6 h after the onset of neurological deficit [11]. The presence, extent, and distribution of IVH are associated with adverse outcomes in aneurysmal SAH, and ventricular radioactivity in patients with aneurysmal SAH and IVH, along with Glasgow Coma Scale score and age, may serve as a predictor of clinical outcome [12].

Problems of modern neurosurgery in hemorrhagic stroke. HS in general is characterized by a high percentage of complications (Fig. 2), which elevates this pathology to the rank of the most pressing problems in neurology [2]. The levels of unfavorable outcomes in HS at the current stage of medicine development remain very high: mortality in the first three days from its debut and after 30 days is 38-74 and 44-52%, respectively, disability is 70-80% [8, 13].

The first indicator for ischemic stroke is only 10-15%. Two main trends in the improvement of technologies for eliminating the consequences of HS can be identified: (1) there is a constant development/implementation of diagnostic/treatment methods; (2) as a result of expanding the possibilities of combating pathology and due to the ineffectiveness of conservative therapy, the percentage of surgical treatment of HS is steadily increasing. Before 2015, the range of application of surgical interventions varied from 0 to 20% in different medical institutions [14].

The main problem of HS treatment is the search for opportunities to improve surgical treatment, mainly through the development of minimally invasive neurosurgical technologies. The development of new approaches aimed at surgical intervention implies solving two problems: removing hematomas/ blood clots and minimizing damage to the brain parenchyma. The latter is necessary to reduce the number of complications and postoperative mortality [2]. Puncture aspiration and local fibrinolysis of deep parenchymal hemorrhages are the main modern minimally invasive methods of surgical treatment of HS

with improved outcomes compared to open types of surgical interventions [4]. In this regard, the analysis of the experience of surgical treatment and risk factors for potential complications, their frequency and outcomes is of great importance for improving the tactics of managing patients with HS [2]. It has been established that the risks of medical complications of HS include one specific provoking factor, which is often both arterial hypertension and diabetes mellitus. Complications in HS are observed in 75% of patients with risk factors. Mortality in women is higher than in men [15]. Stroke onset >3 h ago, gastrointestinal bleeding and urinary tract infection are independent predictors of poor prognosis in HS [16].

Modern methods of hemorrhagic stroke treatment. The main minimally invasive methods of HS treatment at the current stage of medical technology development include puncture aspiration, endoscopic removal of hematomas under the control of neuronavigation equipment, local fibrinolysis. These methods are recommended as the most effective [2]. The choice of intervention depends on the tasks and goals of neurosurgical treatment. Thus, the treatment of IVH is effective only by means of a surgical method, and a conservative approach is not effective. The choice of the intervention option depends on the degree of manifestation of the complication (Fig. 3). In the studies of M.S. Mustafin et al. [2], delayed operations are performed more often than interventions in the acute period, and minimally invasive methods are used in about half of patients with HS. According to the current clinical guidelines "Hemorrhagic stroke" in the acute period include the following surgical interventions: endovascular operations under general anesthesia, installation of external ventricular drainage in acute hydrocephalus and the need to relieve intracranial hypertension. Surgical treatment of patients with complicated SAH according to the Hunt-Hess scale IV and V is tactically difficult due to the fact that direct surgical intervention is associated with the risk of traumatization of the edematous brain and aggravation of cerebral vasospasm, therefore endovascular surgery is preferable, only in isolated cases (removal of the IMH, decompressive craniotomy) microsurgical surgery is used. The two specified methods are allowed to be used as a second stage in the cold period of SAH.

In the study of the outcomes of GI, it was found that after endoscopic aspiration of the IMH, the mortality rate is significantly lower than after open removal (Fig. 4). In general, with a more gentle method of removing hypertensive subcortical IMH, more patients had a good recovery. The effectiveness is complemented by the simplicity of the method [17].

Further studies are needed to determine the correlation between the increased rate of complete IVH removal with alteplase and the improvement in functional status [7]. In most cases, increased ICP and acute hydrocephalus caused by IVH are managed by placement of an external ventricular drain [14], which is still under debate.

The efficacy and safety of surgical treatment of intracerebral hemorrhage (ICH) have long been the subject of research and debate. Recent results of the minimally invasive surgery plus alteplase for intracerebral hemorrage evacuation (MISTIE) III trial demonstrated the safety of the procedure and reduced mortality compared with medical treatment. Although an improvement in functional outcome was not demonstrated, the study showed that the benefits of the intervention depend on surgical efficiency: a greater reduction in ICH, defined as <15 ml of ICH volume at the end of treatment or >70% volume reduction, correlated with significant functional improvement. Recent meta-analyses have shown the benefits of neurosurgical hematoma evacuation, especially when performed earlier and using minimally invasive procedures. In MISTIE III, to confirm hemostasis and reduce the risk of rebleeding, the median time from initiation to surgery and completion of treatment was 47 and 123 h, respectively. Theoretically, the earlier the hematoma is evacuated, the better the outcome. Thus, a higher rate of hematoma reduction during an earlier period may be beneficial. Neuroendoscopic surgery allows less invasive removal of ICH under direct visualization. Minimally invasive procedures continue to evolve with the support of advanced targeting systems and devices in favor of better surgical efficacy. Ongoing randomized controlled trials using new minimally invasive techniques such as early minimally invasive removal of intracerebral hemorrhage (ENRICH), minimally invasive endoscopic surgical treatment with Apollo/Artemis in patients with cerebral hemorrhage (INVEST) and the Dutch Intracerebral Hemorrhage Surgery Trial (DIST) may provide significant information on the optimal treatment of ICH.

Local fibrinolysis is performed using various agents, in particular purolase. Less frequently, external ventricular drainage or endoscopic third ventriculostomy is used in GI, for example, in case of cerebellar hematomas with occlusion of the fourth ventricle/Sylvian aqueduct and development of hydrocephalus [2]. It is known that this intervention should be performed until regression of occlusive hydrocephalus and restoration of patency of the ventricular system [4, 5]. Bilateral intervention requires installation of invasive equipment on both sides: in the hemotamponade zone - a catheter for ventriculothrombolysis, on the opposite site - neuromonitoring using ventriculo-drainage or a ventricular sensor.

Postoperative monitoring of GI necessarily includes: (1) dynamic computed tomography (after and 24 hours after fibrinolysis), then on the 7th and 21st days if IVH was a complication; (2) monitoring of ICP until its stable normalization (less than 20 mm Hg) [2].

There is still controversy regarding rapid versus gradual drainage, as well as the need for alternating closure/opening of the drain and early placement after SAH. These approaches result in gradual or rapid CSF outflow. The strategy of early placement and intermittent drainage may be most successful in patients who will not require long-term CSF drainage

[20]. Available data also suggest that endoscopic IVH surgery may be an alternative to external drainage when comparing patients with equal hematoma volumes and diagnosed with moderate to severe IVH [21].

In general, the introduction of minimally invasive methods for the treatment of hematoma leads to a decrease in hospital postoperative mortality. Thus, in the studies of S. A. Chugunova et al. [22], a 1.5-fold decrease (from 30.6 to 19.8%) was found for 2017-2019. Microsurgical clipping and microspiral embolization of cerebral aneurysms, as well as transcranial hematoma removal, are used as surgical methods for patients with SAH. Minimally invasive surgery, including endoscopic surgery and stereotactic thrombolysis, has become available with the development of visualization techniques, which allows you to accurately achieve the designated position and establish a working channel for hematoma clearance. It has been proven that minimally invasive surgery is superior to conservative treatment or craniotomy in some respects. This achieves: (1) reduction of brain tissue damage and surgical trauma; (2) removal of hematoma compression by directly targeting its area; (3) treatment of patients with intracranial deep hematoma; (4) acceleration of hematoma removal; (5) reduction of mortality and adverse events, and improvement of surgical prognosis. In contrast, some studies have shown that minimally invasive surgery does not reduce mortality or improve long-term outcomes compared with conservative treatment or craniotomy, but overall there is a greater tendency for improved outcomes [23].

Hemostatic agents to reduce bleeding in spontaneous IVH include desmopressin, tranexamic acid, and rFVIIa (recombinant factor VIIa). Delivery of agents within the first few hours has the greatest impact on IVH growth and potential outcome. Pooled analyses suggest that earlier IVH removal is likely to be beneficial, but there are no large studies to support this. The future of IVH therapy should focus on expedited delivery of medical/surgical options [24]. Minimally invasive surgical techniques are being developed to reduce morbidity due to complications of surgical procedures. Mechanical minimally invasive surgery involves the use of tubular retractors and small bore instruments to remove the IVH. Pharmacological approaches involve placement of a catheter within the hematoma cavity to allow passive drainage over several days. One of the most favorable approaches for performing minimally invasive surgeries is the use of natural corridors to reach the lesion, such as the transsulcal parafascial approach. This approach ensures anatomical dissection of the subjective white matter tracts, causing the least amount of damage during hematoma evacuation [25]. For the first time, a side-cutting aspiration device was used and documented for an endoscopic approach to evacuate a large hematoma using neuronavigation to plan the surgical trajectory of the approach. The method was chosen due to the data on the risks and suboptimal results of open craniotomy. Evacuation took place in three main stages: (1) starting at the center of the clot to remove the bulk; (2) mobilization of clots from the parenchymal walls to a safe zone by aspiration

followed by clot homogenization; (3) re-expansion of the cavity by continuous irrigation to visualize further clots. The dual functionality of the device (suction and suction + lateral cutting functions) allowed safe execution of key maneuvers (clot homogenization, control of aspiration force). Almost complete evacuation of the hematoma was achieved without damaging the surrounding parenchyma. The method may be a promising addition to the arsenal of minimally invasive surgery for evacuation of the ICH [26].

The efficacy of surgery for supratentorial intracerebral hemorrhage remains unknown. Comparison of the Glasgow Coma Scale at seven days and six months after endoscopy and craniotomy showed no difference, but the operative time was significantly reduced in the endoscopic group compared with the craniotomy group [27]. Young age, absence of IVH, lobe location, and evacuation time were independently associated with good long-term functional outcome in patients who underwent minimally invasive endoscopic evacuation of supratentorial intracerebral hemorrhage. However, each additional hour of evacuation time resulted in a 5% decrease in the chances of achieving a favorable outcome [28]. Selection of a surgical approach that minimizes the risks of intraoperative bleeding in minimally invasive surgery remains relevant [29]. The optimal timing of hematoma evacuation and the time to its maximum removal remain unclear and it is still difficult to individually treat each patient. A distinction is made between endoscopic evacuation (a rapid process of reducing the hematoma volume) and stereotactic aspiration (a gradual process of reducing the hematoma volume) [30]. Stereotactic aspiration of spontaneous IMH can minimize damage to the brain tissue after surgery. Examples of successful use of the method without an anticoagulant after 24 hours after the onset of HI have been described, with normalization of the level of consciousness in patients, limited damage to brain tissue, shorter duration of surgery, faster postoperative healing and better functional improvement. At the same time, the choice of the patient plays an important role in determining the choice of technique [31]. Thus, it was found that the 6-month mortality rate in the group of patients with IMH after endoscopic aspiration was lower than after craniotomy, but the difference was not significant. Subgroup analysis by hematoma volume showed that mortality in the endoscopic aspiration group was significantly lower than in the stereotactic aspiration group. There was a trend toward increased mortality in the large hematoma subgroup of the craniotomy group compared with the endoscopic aspiration group. The latter method may reduce 6-month mortality from spontaneous basal ganglia hemorrhage, especially in patients with hematoma volume >40 ml [32]. Another study found that 6-month mortality was significantly higher in the stereotactic aspiration and open craniotomy group compared with the endoscopic evacuation group. Age and herniation were independent predictors of mortality. No significant difference was found in neurological functional outcome in the stereotactic aspiration and craniotomy group compared with the endoscopic evacuation group. Thus, endoscopic evacuation

significantly reduced 6-month mortality in patients with hemorrhage >40 ml and Glasgow Coma Scale score <8 [33].

Risk factors, predictors and mechanisms of hemorrhagic stroke at the present stage. The analysis of risk factors for unfavorable outcome of surgical treatment of hemorrhagic stroke and leading factors of genesis was carried out, among which hypertension and aneurysmal diseases of the brain are distinguished among 98.7% of patients [2]. The presence in the anamnesis of concomitant pathology of the heart (arterial hypertension, in particular) or lungs (chronic pathologies), diabetes mellitus, renal failure. Preoperative risk factors: (1) change in consciousness; (2) volume of the cerebral hematoma; (3) the degree of transverse dislocation of brain structures. Their unfavorable predictors include (1) depression to stupor/coma; (2) >50 cm3; (3) up to 10 mm, respectively. Postoperative risk factors include massive ventricular hemorrhage, deformation of the brainstem cisterns, the presence of cerebral edema/swelling, the development of hypostatic pneumonia, purulent tracheobronchitis, and exudative pleurisy [2, 34].

Of course, the leading role in preventing the development of intracerebral hemorrhage is played by timely and rational treatment of arterial hypertension, the overall prevalence of which can be 88% [34, 35]. A tendency for a linear increase in the risk of HI with increasing blood pressure (BP) levels was also noted in patients with type 1 diabetes mellitus [36]. Large randomized clinical trials have not previously demonstrated the benefit of lowering BP, but concomitant diseases, initial BP, and the mechanism of stroke should be taken into account, and the time and goal of lowering BP should be individualized based on this information. When reperfusion is achieved by thrombolysis or thrombectomy, lowering BP reduces the risk of hemorrhagic complications [37]. Hypercholesterolemia is a risk factor, but it has been found that the levels of total cholesterol and low-density lipoproteins in the blood are inversely proportional to the risk of developing HI [38].

Comparison of mortality depending on the type of surgical intervention showed that the use of minimally invasive methods allows to reduce the proportion of unfavorable outcomes by 1.1 and 1.8 times and reduce postoperative mortality compared to open surgical removal of the ventricular hernia and external ventricular drainage, respectively [14].

Among the pathophysiological mechanisms of postoperative outcomes of GI, special attention should be paid to the consideration of the cellular-molecular level, since it has recently been discovered that programmed cell deaths such as necro-, pyro- and ferroptosis play an important role in treatment outcomes (Fig. 6).

It has been established that necro-, pyro- and ferroptosis participate in cell death after SAH and intracerebral hemorrhage. As a result, endothelial dysfunction occurs, which can be a

critical factor in damage to the hematoencephalic system, the degree of dysfunction of which plays a critical role after HI [39]. Further study of the molecular and cellular mechanisms of HI development and postoperative recovery is necessary. Thus, it has been revealed that the P2X7 receptor can regulate programmed cell death and its genetic deletion/pharmacological blockade promotes neuroprotection [40].

Currently, many predictors of stroke outcomes are considered, in particular, the peripheral neutrophil-to-lymphocyte ratio (PNR) as an indicator of inflammation is becoming more common in stroke treatment. In stroke, an elevated PNR corresponds to a higher probability of mortality [41]. In the acute phase of stroke, hyperuricemia may be observed in approximately ^ patients. It can be considered a risk factor for stroke due to its association with cardiovascular pathologies, but the detection of elevated uric acid levels is not correlated with the severity of stroke and short-term outcomes [42]. It was found that regular measurements of serum prealbumin in patients with stroke can be a useful indicator for determining the clinical status and prognosis. The protein indicator was significantly lower in patients with HS in the presence of infections and gastrointestinal bleeding and higher in patients with good recovery at discharge than in patients with poor recovery [43].

Factors such as chronic hypertension, cerebral amyloid angiopathy, and anticoagulation are commonly associated with HI. Chronic hypertension is the major risk factor for bleeding, but the incidence of HI associated with hypertension has been declining in some regional data sets due to improvements in the treatment of chronic hypertension. There is also a reversal of the trend in the development of HI as a result of vitamin K antagonists and new oral anticoagulants, which now account for more than 15% of all cases. Although questions remain regarding the optimal medical and surgical management of intracerebral hemorrhage, recent clinical trials investigating hemostatic therapy, blood pressure control, and hematoma evacuation techniques have advanced our understanding of the

elimination of the consequences of CI [44]. It has also been established that hyperglycemia of admission to the hospital is associated with short-term mortality in patients with primary intracerebral hemorrhage. It is unclear whether the factor is related to the actual features of the severity of the latter (hematoma volume, intraventricular dilation), or the association with mortality is independent of the clinical and radiological features of ICH. Most of the evidence is based on a single glucose measurement on admission. It has been established that in patients with CI without diabetes, early persistent hyperglycemia is an independent predictor of short-term mortality regardless of the localization of the hematoma [45]. Older age is a risk factor for CI incidence and a predictor of worse outcome. Pre-morbid cognitive impairment has been identified as an independent predictor of worse outcomes after treatment, with patients starting from a lower baseline Glasgow Coma Scale score and 20% of patients deteriorating by two or more Glasgow Coma Scale

points between initial ED assessment and arrival at the emergency department. This decline in score is termed neurological deterioration [46]. The focus of current treatment is on preventing hematoma expansion, with progress being made with supportive care, blood pressure control, and timely withdrawal of anticoagulants [47].

Thus, most authors indicate that minimally invasive neurosurgery is a more effective/safe approach to the treatment of HI than conservative treatment and craniotomy. It is noted that the latter method is more traumatic, therefore it is associated with significant blood loss and requires longer anesthesia [48]. When conducting a meta-analysis of the effectiveness of such minimally invasive methods of treating HI as endoscopic evacuation and stereotactic thrombolysis, it was found that, in general and individually, these methods provide more positive results in terms of mortality than drug treatment and traditional craniotomy [49]. However, the role of open craniotomy for early drainage of hematoma after HI remains a subject of heated debate. Some experts argue that craniotomy for hematoma drainage remains a life-saving measure in critical situations [50]. Timely and aggressive treatment in the acute phase can mitigate secondary brain injury. Initial treatment should include: initial medical stabilization; rapid, accurate neuroimaging to establish diagnosis and elucidate etiology; standardized neurological assessment to determine baseline severity; profil-

lactic acid hematoma expansion (BP management and reversal of coagulopathy); consideration of early surgical intervention; prevention of secondary brain injury [44].

Conclusion. Minimally invasive surgical techniques for the treatment of hematoma are highly effective. The use of neuronavigation equipment can significantly simplify the organization of invasive intervention. It is important to note that the identification of the exact localization of the hematoma coupled with minimizing the size of the trepanation window reduces the duration of the operation and the risk of affecting functionally significant areas of the brain. Further studies of various strategies for catheter placement during drainage are needed by analyzing ICP control, catheter occlusion and the rate of blood clot removal. It is important that at the moment there is no list of molecular and cellular predictors optimal for risk stratification in hematoma, and, consequently , its outcomes. It is necessary to further search for potential therapeutic targets for the treatment of hematoma through an in-depth study of the mechanisms of disease development/remission at the molecular and cellular level. As a result, the main focus of neurosurgery for hematoma is to minimize invasive interventions. Less attention has been paid to methods for optimizing molecular diagnostics, but attempts are being made to find an effective range of biomarkers for analyzing the initial condition of the patient and predicting recovery.

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