Current approaches to diagnosing in intracerebral hemorrhage

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Intracerebral hemorrhage (ICH) is the same etiologically heterogeneous variant of stroke as cerebral infarction. The most common causes of the disease are hypertensive and cerebral amyloid microangiopathy, the use of oral anticoagulants (OACs) and their combination, and arteriovenous malformations, which are of the greatest importance for young patients. The SMASH-U or H-ATOMIC classification of ICH requires a structured diagnostic search that includes an analysis of the clinical presentations of the disease and neuroimaging and angiographic findings. Although brain computed tomography remains a basic diagnostic technique for ICH, most patients need brain magnetic resonance imaging, by mandatorily assessing the ischemic and hemorrhagic markers of cerebral small vessel diseases. This examination is necessary not only to verify the cause of ICH and to select the appropriate method of its treatment, but also to determine the risk of recurrent hemorrhage. The article considers the epidemiology and etiological characteristics of ICH and approaches to its classification. It characterizes the most significant causes of the disease, such as hypertensive and cerebral amyloid angiopathy, vessel structural abnormalities, and the use of OACs. The diagnosis of ICH and its clinical neuroimaging diagnostic algorithm are presented.

Keywords: *intracerebral hemorrhage; hypertensive intracerebral hemorrhage; cerebral amyloid angiopathy; oral anticoagulants; diagnosis.*
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For reference: *Kulesh AA. Current approaches to diagnosing in intracerebral hemorrhage. Nevrologiya, neiropsikhiatriya, psikhosomatika = Neurology, Neuropsychiatry, Psychosomatics. 2020;12(2):4–11.* ***DOI****: 10.14412/2074-2711-2020-2-4-11*

Intracerebral hemorrhage (ICH) occupies 10–20% in the structure of stroke, and its frequency varies depending on the population [1]. ICH is the most common type of intracranial hemorrhage and develops annually in 2 million people in the world, with more than one third of patients dying in the first month, and 54% in the next year. Only 12–39% of patients achieve long-term functional independence. In contrast to ischemic stroke, in which reperfusion therapy methods are actively used, which allow not only to achieve a better functional outcome, but also to reduce mortality using mechanical thrombectomy [1, 2], there is no effective treatment for ICH. The functional outcomes of ICH have not improved over the past decades [3], hemorrhagic stroke remains an important cause of post-stroke cognitive impairment [4]. Like ischemic stroke, ICH is etiologically heterogeneous; this determines the variability of its immediate and long-term outcomes and requires a thorough diagnostic search. Finally, the development of ICH stigmatizes the patient in the eyes of the doctor, which often leads to excessive caution when prescribing antithrombotic prophylaxis and increasing the risk of ischemic events.

Etiology and classification approaches

The key risk factors for ICH include old age, male gender, arterial hypertension, alcoholism, high salt intake with a deficiency of fruit and vegetables, as well as some genetic causes. The INTERSTROKE study showed that modifiable factors (hypertension, smoking, waist-to-hip ratio, alcohol abuse) account for 88% of the additional population risk of ICH [5]. These causes, especially hypertension, lead to damage of the arterioles through the mechanism of arteriolosclerosis, lipohyalinosis and fibrinoid necrosis with vascular occlusion and / or the formation of microaneurysms. Among other risk factors for ICH, the role of reduced concentrations of low-density lipoproteins and triglycerides is discussed [1]. In patients under the age of 50, risk factors such as drug use (amphetamine, methamphetamine, cocaine, heroin, etc.), pregnancy, and the postpartum period are of particular importance [6].

About 80% of the etiological structure of ICH is accounted for by hypertension and cerebral amyloid angiopathy (CAA) associated primary ICH. In addition, ICH develops on the background of structural anomalies of the arteries (aneurysms, arteriovenous malformations – AVM, cavernomas and dural arteriovenous fistulas – AVF), other cerebrovascular diseases (cerebral venous thrombosis, reversible cerebral vasoconstriction syndrome, mycotic aneurysms in infectious endocarditis, hemorrhagic transformation of cerebral infarction, vasculitis), hypocoagulation, as well as brain tumors (metastasis) (see the Table) [2, 7].

First of all, the ICH should be classified anatomically, for example, into lobar / non-lobar and supratentorial / infratentorial, which is possible using the CHARTS scale. In clinical practice, it is convenient to use the etiological classification SMASH-U (structural vascular lesions – S, medication – M, amyloid angiopathy – A, systemic disease – S, hypertension – H, or undetermined – U) [8]. A more detailed approach to establishing the cause of ICH is reflected in the H-ATOMIC classification (Hypertension, cerebral Amyloid angiopathy, Tumour, Oral anticoagulants, vascular Malformation, Infrequent causes and Cryptogenic), in which each of the seven categories is represented by three degrees of significance - possible, probable and definite [9].

Etiological structure. According to the results of the SMASH-U study (n = 1013, average age 68 years), 55% of ICHs are associated with hypertension (35%) or amyloid (20%) angiopathy, 25% are associated with structural anomalies of blood vessels, systemic diseases, and oral anticoagulants (OAC), with every fifth ICH remaining cryptogenic [8].

According to the analysis of the cohort of the H-ATOMIC study (n = 439, mean age 71 years), the most common cause of ICH was hypertension (70.5%), vascular malformations (AVM and cavernomas) and rare causes (aneurysms, cerebral venous thrombosis), intravenous thrombolysis, vasculitis, reversible cerebral vasoconstriction syndrome, etc.) accounted for 11.4%. In general, a reliable cause was identified only in 40.1% of patients; 45.5% of patients had two or more causes of ICH of varying degrees of significance. The most common combinations of causes: possible hypertension and possible / probable CAA, probable hypertension and probable administration of OAC. Hypertension of varying degrees of significance caused the development of ICH in 80.6% of patients, CAA in 30.9%, OAC in 16.6%, infrequent causes in 11.8%, vascular malformations in 7.2%, tumors – in 5.4%; cryptogenic ICH was noted in 1.6% of patients [9]. Thus, it is most difficult to identify the causes of ICH, for example, in an 80-year-old patient with hypertension who takes OAC and is admitted to hospital with lobar hematoma.

The etiology of the ICH depends on the age of the patients: in patients younger than 35 years, the structural cause of hemorrhage is most often observed, while in patients over 35 years of age, the leading role belongs to hypertension [6]. Most elderly patients with lobar ICH have a combination of hypertension and amyloid angiopathy [3].

Diagnostic search

The authors of H-ATOMIC offer a diagnostic search, which in the basic version includes computed tomography (CT) of the brain, magnetic resonance imaging (MRI, if possible), complete blood count, coagulogram and angiography (CT, MRI or digital subtraction angiography) is a structural anomaly is suspected, in particular with a SIH score (Secondary Intracerebral Hemorrhage) >2 points (high risk: the presence of dilated vessels or calcifications along the edge of the hematoma or hyperattenuation in the region of sinuses / cortical veins, age younger than 45 years, female gender, lack of hypertension and coagulation disorders). The DIAGRAM scale (age, localization of ICH and CT signs of SVD) can also be used to identify patients with a possible macrostructural cause of hemorrhage [10].

CT angiography is considered an ideal screening tool to exclude vascular abnormalities, but it may not identify about a quarter of the structural vascular causes of ICH. Therefore, conducting digital subtraction angiography is advisable with a normal result of CT angiography in patients without signs of SVD according to MRI (confluent WMH or lacunar infarction) and history of hypertension (the predicted detection rate of macrovascular causes is 22%) [10].

The advanced diagnostic algorithm involves repeated angiography, brain MRI with the ability to evaluate CMB and cSS (requires MRI sequence SWI), contrast enhancement and analysis of the vascular wall, as well as lumbar puncture, biopsy and oncological search.

Hypertensive ICH

The diagnosis of a reliable hypertensive ICH is established in the presence of hypertension according to

Differential diagnosis of the main causes of ICH

Clinical clues	Neuroimaging clues
Hypertensive ICH	
Hypertension, high blood pressure when admitted to hospital	Localization in the thalamus, basal ganglia or brainstem; the presence of other markers of SVD - deep lacunae, PVS, CMB and WMH;
CAA-associated ICH	
Transient focal neurological episodes, age ≥55 years	Lobar hematomas and CMB, strictly superficial cerebellar CMB, cSS; SAH and finger-like projections; lacunas and PVS in the centrum semiovale, gradient of WMH
AVM	
Migraine with aura or stereotypic aura	Distribution to other parts of the brain, "flow voids", calcifications
Aneurysm	
Thunderclap headache, age> 40 years, neck pain or stiffness, loss of consciousness, physical activity at the onset (Ottawa rule)	Disproportionate distribution into the subarachnoid space
Cavernoma (cavernous malformation)	
History of hemorrhages of the same localization	Small, homogeneous, purely parenchymal hemorrhage
AVF	
Pulsating tinnitus	Subarachnoid and subdural distribution, pathologically dilated cortical (pial) vessels, edema
Sinus thrombosis	
Headache at onset, pulsating tinnitus, pregnancy or the puerperium, deep vein thrombosis and pulmonary embolism, hormonal contraceptives	The proximity of the ICH to the sinuses / veins, marked edema compared with hematoma
Reversible cerebral vasoconstriction syndrome	
Thunderclap headache, female gender, vasoactive drugs, triggers (bath / shower, Valsalva maneuver, sexual activity, strong emotions), pregnancy, puerperium, normal or nearly normal CSF	Asymmetric brain edema areas in the parietal and occipital lobes; multifocal, multivessel, segmental vasoconstriction
Infective endocarditis	
Reception of injection drugs, fever at the onset, HIV, source of bacterial infection, vegetations	Multiple infarcts in different areas, CMB, small aneurysms with irregular contour
Hemorrhagic transformation of cerebral infarction	
Atrial fibrillation without anticoagulants	Significant ischemic infarction area, adjacent to the ICH, or diffuse acute infarctions in other vascular areas
Vasculitis	
Headache, systemic manifestations	Small infarcts in different vascular areas, focal and diffuse narrowing of the arteries
Systemic diseases accompanied by hypocoagulation	
Hematologic disorders and coagulopathies, bleeding history, severe hepatic insufficiency, cutaneous hemorrhagic syndrome, anemia, thrombocytopenia, abnormalities in coagulogram	Multicenter ICH
Medication hypocoagulation	
Anticoagulation or antiplatelet agents, systemic thrombolysis, abnormal coagulogram	Cerebellar involvement, lobar hematoma (on warfarin therapy)
Tumor / metastasis	
Extracerebral tumor in anamnesis, paraneoplastic syndrome, the presence of symptoms not attributable to the ICH	Severe perifocal edema

Note. SVD - small vessel disease; PVS - perivascular spaces; CMB - cerebra microbleeds; WMH - white matter hyperintensity; cSS - cortical superficia siderosis; SAH - subarachnoid hemorrhage.

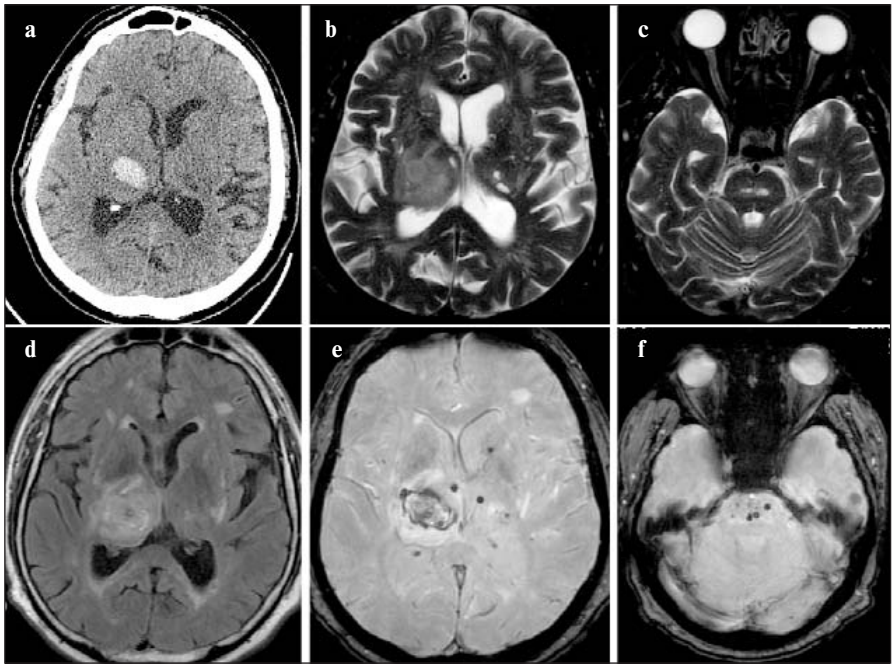

Fig. 1. *Hypertensive ICH on the background of sporadic SVD in a 58-year-old patient suffering from hypertension for a long time without adequate therapy: a – CT. Hematoma of the right thalamus; b – MRI, T2. Lacunae in the left thalamus, PVS; c – MRI, T2. Lacunas in the pons; d – MRI, FLAIR. WMH; e – MRI, SWI. Hematoma of the right thalamus and deep CMB; f – MRI, SWI. CMB in the pons.*

the anamnesis or objective data (signs of left ventricle hypertrophy, detected by electrocardiography or echocardiography) and the deep location of the hematoma (thalamus, putamen, globus pallidus, caudate nucleus, internal capsule, deep white matter, pons, isolated intraventricular hemorrhage) [9]. Hypertensive angiopathy also underlies most cases of cerebellar ICH [11].

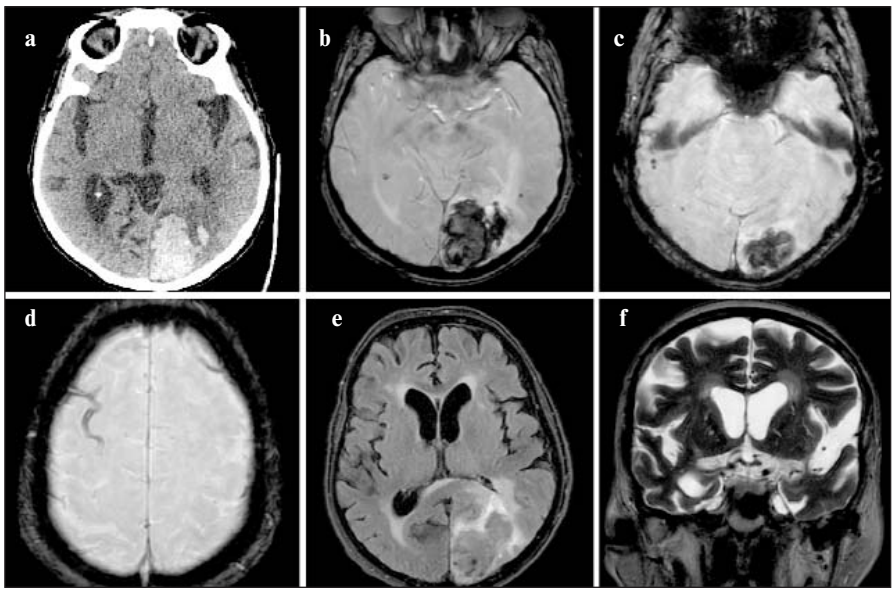

Fig. 2. *ICH associated with probable CAA in a 74-year-old patient: a – CT. Hematoma of the left occipital lobe; b, c – MRI, SWI. Hematoma and subcortical lobar CMB; d – MRI, SWI. Focal cSS; e – MRI, FLAIR. WMH with fronto-occipital gradient; f – MRI, T2. PVS in the subcortical white matter.*

The diagnosis is confirmed in the presence of other MRI signs of sporadic SVD, in particular, deep lacunae, PVS and CMB [12–14] (Fig. 1). Thus, incidental CMBs after ICH are observed in 40–62% of patients [15], cerebellar CMBs in 44% [16] and mixed (lobar and deep) in 26% [17]. The presence of hypertension without signs of SVD does not allow to exclude other causes of ICH, for example, small deep AVMs, and requires continuation of the diagnostic search. It should be borne in mind that patients with hypertensive ICH typically have the highest (on average 167 mm Hg) systolic blood pressure on admission to hospital and in the next 3 days, compared with that for other causes of stroke [18]. The early stages of brain damage in hypertension may not be accompanied by macrostructural markers of SVD, but its microstructure and perfusion worsen [19], which determines the feasibility of using specific MRI modalities – diffusion-weighted images with the assessment of fractional anisotropy and mean diffusion, as well as non-contrast perfusion MRI using the method of labeled spins [20, 21].

CAA-associated ICH

This type of ICH accounts for one third of hemorrhages on the background of SVD and 54% in the structure of lobar hematomas. In addition to the lobar localization of the hematoma, its frequent combination with SAH (89%) and the phenomenon of finger-like projections (39%), CAA is characterized by an increase in PVS in the centrum semiovale (55%), lobar CMB (67%), cSS (52%), microinfarctions (21%), frontal-occipital gradient of WMH (51%), as well as the genotype APOE ε4 (50%) [14, 22–24] (Fig. 2). Strictly superficial cerebellar CMB located in the areas of β-amyloid deposition recently have been proposed as a marker of CAA in patients with supratentorial ICH [25]. Despite the important role of lobar and cerebellar CMB in the diagnosis of CAA, their presence does not allow predicting the development of the first or recurrent ICH. cSS associated with the genotype APOE ε2+ is considered to be the main marker of CAA progression and the risk of ICH. This MRI phenomenon is observed in 44% of patients with CAA without ICH and progresses within 2 years in 28% of patients [26].

For the diagnosis of CAA, modified Boston criteria [24] are used. In the absence of MRI, if it is possible to evalu-

ate the APOE genotype, the Edinburgh criteria [23] can be used. According to the modified Boston criteria, the diagnosis of probable CAA is established in a patient age ⩾55 years; with multiple ICH or CMB restricted to lobar, cortical or cortico-subcortical regions on CT or MRI; or with a single lobar, cortical or cortico-subcortical ICH in addition to cSS [3].

CAA-associated ICH is the most aggressive phenotype of hemorrhagic stroke, as it is characterized by large hematoma volume, severe clinical course and a high recurrence rate, compared with hypertensive ICH (7.4% vs. 1.1% per year) [27]. The risk of recurrences after CAA-associated ICH is 9–26% per year and is especially high with disseminated cSS [28]. The presence and degree of cSS are the only independent predictors of recurrent ICH [29]. Visualization of two or more CMBs increases the risk of recurrence of CAA-associated ICH by 3–4 times, while the risk of a recurrent hypertensive ICH increases only with more than 10 CMBs (5.6 times) [27].

Observation of a cohort of 310 patients over 5 years showed that in lobar hematoma localization, the frequency of recurrent ICH (7.9%) exceeds that of ischemic stroke (5.3%), while the risk of ischemic stroke is significantly higher with hypertensive hemorrhage (11, 2% versus 3.2%) [30]. Thus, patients with CAA-associated ICH, especially in the presence of disseminated cSS, belong to the group of high cerebral hemorrhagic risk and require the most careful prescription of antithrombotic therapy.

Structural vascular anomalies

These abnormalities are the cause of ICH in 15–23% of patients. Vascular malformations include AVM (most often), AVF, and cavernous malformations. AVMs are a parenchymal network of dysplastic arteries that are shunted into the venous system. AVMs are observed in 0.01% of the population and are associated with a 2% annual risk of primary rupture and a 4–6% risk of recurrent hemorrhage. An increased risk of bleeding is observed with deep venous drainage (through the Galen vein), deep localization of AVM and associated aneurysms.

AVFs, most often dural, are direct arteriovenous communication in the dura mater. An anomaly is associated with a 3% annual risk of primary hemorrhage and a 46% risk of recurrent ICH. Cavernous malformations (cavernomas) are accumulations of low-flow dilated and lined with endothelium sinusoids. The presence of cavernoma indicates a 0.4–0.6% annual primary risk and a 23% chance of a recurrent ICH, as well as low mortality and a good functional outcome. Their visualization is possible only with MRI [2, 10].

In patients with structural vascular lesions, the lowest systolic blood pressure is observed on admission to hospital – less than 140 mm Hg [18].

ICH associated with hypocoagulation

ICH associated with OAC administration accounts for 15% of the structure of hemorrhagic stroke; it develops in 0.3–3.7% of patients per year during warfarin therapy and in 0.2–0.5% of patients using direct oral anticoagulants (DOAC). Taking warfarin causes 9–14% of all cases of intracranial hemorrhage and 11 times increases the risk of hemorrhagic stroke. Use of DOAC is characterized by a 2-fold decreased risk of developing ICH compared with warfarin [31, 32].

With the inevitable increase in the incidence of atrial fibrillation in the population, the proportion of drug-induced ICH will increase [33]. This is especially true for patients with

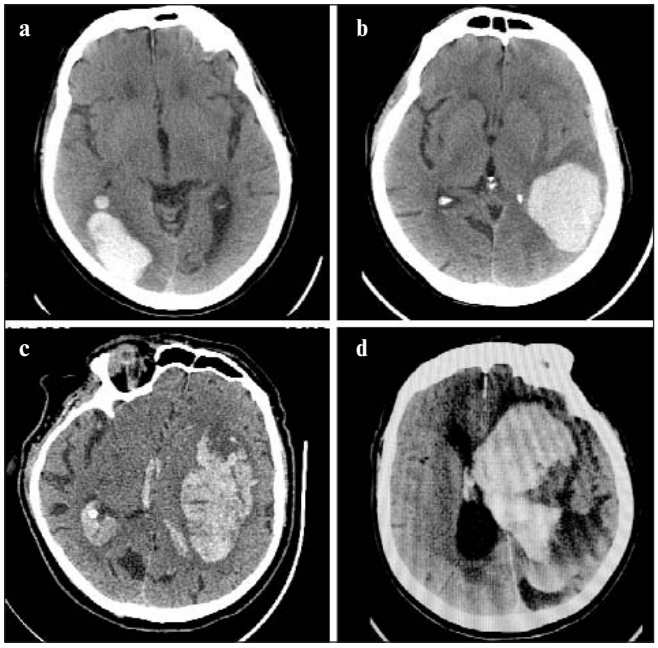

Fig. 3. *CT scan of the brain in ICH associated with hypocoagulation: a – combined antithrombotic therapy for myocardial infarction and primary percutaneous intervention; b–d – an overdose of warfarin (INR 3.9; 5.7; 9.3 respectively)*

increased cerebral hemorrhagic risk. It is important to emphasize that the administration of the anticoagulant is not the cause of ICH, but only contributes to hemorrhage on the background of macro- or microvascular pathology. Therefore, when prescribing OAC, an assessment of bleeding risk factors, such as age, impaired renal function, hypertension, history of ICH, and CAA is required [32]. The results of multicenter observational trials CROMIS-2 and HERO showed that the presence of CMB, as well as moderate and severe WMH, is a risk factor for the development of ICH in patients taking OAC due to atrial fibrillation [34, 35]. Nevertheless, the identification of the most vulnerable subgroups of patients requires further research.

ICH arising from hypocoagulation is characterized by a large volume of hematoma, its frequent growth (both early and delayed), worse outcome and high mortality [31, 36]. The main risk factors that affect the fatal outcome of intracranial hemorrhage when taking OAC include age, previous stroke, and decreased level of consciousness [32].

OAC-associated ICHs do not have a strictly defined pattern. In 60% of patients taking warfarin, lobar hematoma is noted, while when taking DAOC, only one third of patients have lobar hematomas (Fig. 3) [37]. OAC-associated ICHs are often localized in the cerebellum and spread to the ventricles of the brain. The increased vulnerability of the cerebellum when taking OAC may be associated with a combination of hypertensive and amyloid angiopathy on the background of a decrease in the protective role of microglia and expression of tissue coagulation factors [38].

The relationship between the type of anticoagulant and the outcome of ICH remains controversial. So, observational study by V.A. Lioutas et al. [37] demonstrated that patients taking DOAC are characterized by a lower baseline hematoma volume and less severe neurological deficit, which is accompanied by a tendency to a better functional outcome after 3 months. At the

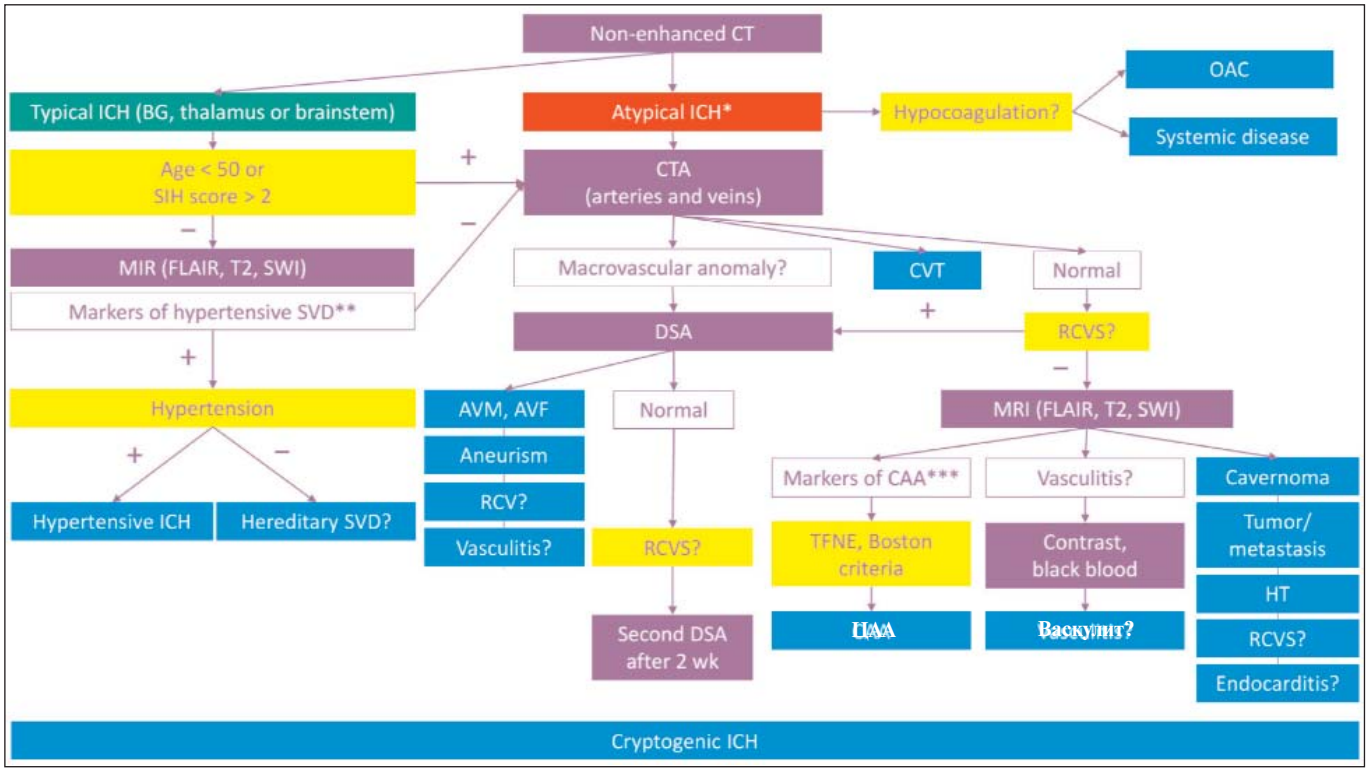

Fig. 4. *The algorithm for establishing the cause of the ICH. * – lobar hematoma, hematoma in the cerebellum, SAH, multifocal hematoma, hematoma near the venous sinuses, severe perifocal edema, bilateral cerebral edema, calcifications in the hematoma zone, dilated vessels; ** – deep lacunes, PVS and CMB; severe WMH; *** – lobar CMB, strictly superficial cerebellar CMB, cSS, PVS in centrum semiovale, gradient of WMH. BG – basal ganglia; CTA – CT angiography; DSA – digital subtraction angiography; RCVS – reversible cerebral vasoconstriction syndrome; CVT – cerebral venous thrombosis; TFNE – transient focal neurological episodes; HT – hemorrhagic transformation*

same time, a recent analysis of the data of 1328 patients with OAC-associated ICH (190 patients with DOAC) showed that with effective anticoagulation (drug concentration on admission > 30 ng / ml or the last dose taken within the previous 12 hours for dabigatran and 24 hours for rivaroxaban) there are no differences between warfarin and DOAC regarding hematoma characteristics and functional outcome. It is noteworthy that no differences were recorded depending on the dose of DOAC (full or reduced) [39]. Thus, a significant advantage of DOAC over vitamin K antagonists is in reducing the risk of intracranial hemorrhage, but if an ICH has developed, the further clinical scenario will be similar [32].

Establishing a reliable diagnosis of a hypocoagulative ICH requires a history of warfarin use and an international normalized ratio (INR) of ⩾2 in the absence of other causes, whereas in the presence of an alternative etiology or INR <2, the diagnosis is just possible. Taking DOAC can be considered a reliable cause of ICH in case of abnormal results of coagulatory tests and as a possible reason in the presence of alternative explanations or normal coagulogram [9]. Routine coagulation tests are not informative enough to evaluate the anticoagulant effect of DOAC. Dabigatran has a greater effect on activated partial thromboplastin time, while rivaroxaban, apixaban and edoxaban have different effects on prothrombin time. Thrombin time is considered the most sensitive routine test for dabigatran, so a normal indicator eliminates the clinically significant concentration of the drug in the blood [31].

Diagnostic algorithm

Given the characteristics of the clinical and neuroimaging picture of the ICH, we can propose an algorithm for establishing the cause of cerebral hemorrhage (Fig. 4).

Conclusion

Thus, ICH is no less etiologically heterogeneous type of stroke than cerebral infarction. The most common causes of the disease are hypertensive and cerebral amyloid microangiopathy, use of OAC and their combination, as well as the AVM that are most significant in young patients. Classification of ICH, according to SMASH-U or H-ATOMIC, requires a structured diagnostic search, including analysis of the clinical picture, as well as neuroimaging and angiographic data. Although a CT scan of the brain remains the basic method for diagnosing ICH, most patients will need MRI with a mandatory assessment of ischemic and hemorrhagic markers of SVD. This examination is necessary not only to verify the cause of the ICH and to select the appropriate treatment method, but also to determine the risk of recurrence of hemorrhage.

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Received/Reviewed/Accepted
29.01.2020/2.03.2020/6.03.2020

The investigation has not been sponsored. There are no conflicts of interest. The author is solely responsible for submitting the final version of the manuscript for publication. The author has participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by the author.

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