REVIEW ARTICLES

Spontaneous intracerebral supratentorial hemorrhage: general aspects and updates in surgical treatment

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Abstract

Background: Spontaneous intracerebral hemorrhage (SIH) accounts for 9 to 25% of all strokes and is associated with a high morbidity and mortality, with less than 40% of affected persons surviving 1 year. The condition commonly presents a sudden onset of focal neurological deficits with accompanying headache, nausea, vomiting, elevated blood pressure and altered consciousness. Medical treatment commonly includes airway support, blood pressure control, management of cerebral edema, symptomatic therapy such as anticonvulsive medication, anticoagulation reversal etc. Different surgical options such as open craniotomy, stereotactic aspiration, endoscopic evacuations with or without thrombolysis have also been considered. Most of these techniques have already been implemented successfully in the Republic of Moldova. According to the data of the Institute of Neurology and Neurosurgery and the Institute of Emergency Medicine for the period 2011-2014, just within these two institutions were performed 137 neurosurgical interventions, including 67 interventions involving minimally invasive techniques with local fibrilolysis and 70 interventions involving other minimally invasive surgery or conventional craniotomy. The obtained results are in concordance with those reported by other European institutions.

Conclusions: The continuous efforts to improve the outcome of SIH during the recent years have led to the development of a variety of minimally invasive techniques, most of which have already been adopted by the autochthonous surgeons. New randomized controlled trials are required to establish the suitability of these techniques for different clinical situations and SIH localizations.

Key words: spontaneous intracerebral hemorrhage, supratentorial hematoma.

Introduction

Definition. Intracranial hemorrhages can be classified by anatomical and etiological aspects. According to anatomical aspects, can be distinguished parenchymatous, subarachnoid, subdural, epidural, supratentorial and infratentorial hemorrhages. From etiological point of view, intracranial hemorrhages can be further categorized into primary or spontaneous and secondary hemorrhages [1,2]. Spontaneous intracerebral hemorrhage (SICH) represents blood effusion in cerebral parenchyma that is nontraumatic and without any known cause of hemorrhage (AVM, cerebral aneurysm or tumor). Spontaneous intracerebral hemorrhages (SICHs) are considered medical emergencies, commonly having a clinical course similar to an intracranial expansive process, with early neurological deterioration within the first few hours after onset [3.5]. Based on their location, supratentorial SICHs can be further divided into lobar or superficial (situated in cortical and subcortical areas of frontal, temporal, parietal and occipital lobes) and central or deep (localized in the areas of nucelus caudatis, globus pallidus, thalamus, internal capsule, white periventricular substance or cerebral ventricles), while infratentorial SICHs can involve the cerebellum, pons and the brain stem. About 1/3 of SICHs have lobar localizations, and about 2/3 of SICHs have bazal or infratentorial localizations [2,6,7]. Overall, supratentorial SICHs represent over 80% of all SICHs [8,9]. According to the results of STICH (Surgical Trial in Intracerebral Hemorrhage) trial, about 39-40% of supratentorial SICHs were lobar, 42% were deep (involving basal ganglia and thalamic nuclei), 17-19% had mixed locations and 1% could not be evaluated [10].

Epidemiology. Worldwide incidence varies between 10 and 40 cases per 100,000 population and increases with age [4, 11, 12]. The pathology affects a substantial proportion of the population in Europe and worldwide, representing 9-27% of all strokes [262]. Studies performed in the last decade indicate that SICH represents 10-15% of all strokes in Europe, USA and Australia, 20-30% of strokes in Asia [June 13-17], about 10% of strokes in high-income countries and 20% of strokes in middle and low-income countries [18, 19].

It is also known that intracerebral hematomas represent the third leading cause of death after cardiovascular diseases and cancers, accounting for 12.5 to 15% of overall mortality and being a major cause of disability. Reported mortality during the first month after SICHs varies between 30-59%, with an overall survival of less than 40% at 1 year and less than 20% at 10 years [13, 17, 20-23]. Among the survivors, disability reaches 70-80% [2, 3, 24], with only 10% of patients becoming functionally independent at 1 month and about 20% at 6 months [12, 17, 20, 25, 26].

Etiology, pathogenesis and pathophysiology. Predisposing factors for SICHs include modifiable risk factors (hypertension, diabetes, alcohol abuse, smoking, poor diet, obesity, anticoagulation therapy, previous stroke, illicit drugs

consumption, especially cocaine) and non-modifiable risk factors (male sex, age, ethnicity - African or Asian, genetic predisposition, brain amyloidosis, various coagulopathies). The main risk factors (male sex, age, hypertension, alcohol abuse, smoking, diabetes, poor diet, abdominal obesity and physical inactivity) account for over 80% of the overall risk of stroke worldwide [18, 27]. Association of additional risk factors, such as high serum level of certain apolipoproteins, increases the risk up to 90% [27]. Most authors agree that from all risk factors, the most important are hypertension and cerebral amyloid angiopathy [1, 2, 15, 17, 28, 29]. Thus, chronic hypertension is responsible for 50-70% of all SICHs [15, 17, 30]. The disease leads to small structural changes of the brain vessels, being associated with atherosclerosis, lipohialinosis and formation of micro aneurisms. A variety of risk factors can also lead to so-called *small brain vessel disease*, which is the underlying pathology in many cases of SICHs. The prevalence of cerebral small vessel disease in general population increases with age and also leads to progressive cognitive changes and vascular dementia [2, 6, 15, 18, 26, 29].

As the brain hematoma expands, it increases local pressure affecting the brain tissue and tearing adjacent vessels. Coagulation disorders and hypertension predispose to rebleeding in the early stages. The mass effect of the hematoma further increases intracranial pressure, causing significant damage to adjacent brain structures and also affecting distant regions by shifting the midline structures to the contralateral side and even resulting in various degrees of brain herniations. If the circulation of cerebrospinal fluid is disturbed, hydrocephalus occurs [18, 31, 32].

Pathophysiological changes of supratentorial SICH were studied in detail clinically and experimentally [29, 32, 33]. Mechanical compression of local microcirculation with subsequent release of vasoconstrictor substances from hematoma causes a marginal zone of ischemia called secondary or perilesional ischemia. Various terms such as "ischemic penumbra" or "tissue at risk" have been proposed to describe this altered functional brain area, but potentially recoverable [20, 29, 32-35]. Some authors suggest that perilesional hypoperfusion is rather a consequence of reduced metabolic demand than a true tissue ischemia [6, 14]. Various degrees of perilesional hypoperfusion with or without "spot" sign on CT angiography, have been reported in about 60% of patients with acute SICH [36]. That's why the reason for surgical treatment in SICHs is not only to eliminate the mass effect, but also to reduce the toxic effects of blood components for potential brain tissue recovery in the ischemic penumbra [29, 32, 37, 38].

Another pathogenic factor is related to the brain edema, which increases over several days, leading to mass effect and raised intracranial pressure, secondary neuronal damage and neurological deterioration. Disruption of the blood-brain barrier and serum protein leakage into extracellular space is followed by an increase in osmolarity and release of biologically active substances (arachidonic acid, histamine) with associated development of vasogenic edema (extracellular). Disruption of the energy metabolism of the cell membranes and cellular wall pumps leads to fluid shift into the cells and development of cytotoxic edema (intracellular). In the subsequent phase, the lysis of red blood cells with release of hemoglobin metabolites, inflammatory cytokines, matrix metalloproteinases, iron and thrombin triggers generation of free radicals with associated inflammatory, neurotoxic and apoptotic effects [15, 20, 29, 32, 33, 35]. Perilesional edema peaks at 72 hours and usually persists for 5 days, although it may persist for up to 2 weeks [2, 6, 20].

Re-bleeding, hematoma expansion and intraventricular eruption are major predictors of death in the acute phase of the SICHs or severe disabilities in survivors [4, 5, 14, 16, 39-43]. Intraventricular extension occurs in 30-45% of patients with SICHs, depending on the size and location of the bleeding [3, 17, 26, 30, 32, 41, 44]. The overall mortality in patients with intraventricular hemorrhage is 5 times higher than in patients with isolated SICHs [45]. Since the rigid shape of the skull limits the ability of volumetric expansion of its content, hematomas with a volume exceeding 150 ml inevitably lead to death [18]. Hematoma growth is also associated with increased mortality and poor functional outcomes, regardless of its initial volume or other associated factors.

Three definitions have been used to define the growth of SICHs: (1) any increase in size of SICH, (2) an increase of ≥ 33% or ≥ 12.5 ml and / or (3) interval radial increase in size over 1 mm confirmed at computed tomography (CT) at 24 hrs compared with the original CT [39, 46]. Identification of techniques for predicting the expansion of SICHs remains a priority of many research studies [21, 47]. Among the proposed methods for estimating the probability of hematoma growth can be mentioned determination of density and hematoma shape at CT scanning [18, 46] or the presence of the "spot" sign on CT angiography [18, 36, 47, 48]. According to the published results, heterogeneous density on CT independently predicts expansion of SICH, the irregular shape of hematoma being also associated with its expansion [48]. The presence of the "spot" sign on CT angiography represents another independent predictor of hematoma expansion, increased mortality and a poor prognosis [36, 47]. In addition, the "spot" sign allows patient selection for individualized therapeutic regimens such as administration of early hemostatic treatment (recombinant activated factor VII), more aggressive reduction of blood pressure and / or surgical interventions [36].

Staging of intraparenchimal hemorrhage. SICH is not a monophasic event and includes three distinct phases: (1) initial hemorrhage, (2) expansion of the hematoma and (3) perihematomal edema [14, 42]. Disease progression and subsequent results are influenced primarily by two factors: hematoma expansion and cerebral perihematomal edema. After the initial bleeding, hematoma reaches its maximum size in 15-20 minutes, even though occasionally the bleeding may continue for up to 6 or even 24 hours. Elucidating the cause of hematoma expansion (on-going bleeding or re-bleeding from one or more vessels) confirmed by CT is particularly useful for selecting the treatment strategy [6, 14].

Histologically can be distinguished 5 phases of intraparenchymal hematomas that are based on cellular changes during the process of degradation and absorption of blood

products. These phases are also distinguished at brain MRI as follows: hyperacute phase (from onset to 12 hours), acute phase (from 12 hours to 2 days), early subacute phase (from 2 to 7 days), late subacute phase (from 8 days to one month) and chronic phase (after one month) [49].

Clinical picture

Symptoms of SICHs can be divided into general and focal. The clinical manifestations may vary depending on hematoma location, size and eruption into the ventricular system [1, 4, 5, 12, 14, 30, 41]. The onset is usually sudden with headache, vomiting, seizures and / or development of focal neurological deficits. In the acute phase can be encountered alterations of consciousness (from sleepiness to coma), signs of meningeal irritation, motor deficits (hemiparesis, hemiplegia), dysmetria, cranial nerve palsy (especially involving oculomotor nerve), various autonomic dysfunctions, etc [4, 6, 12, 18, 30, 50]. Depending on the affected brain regions, the clinical presentation can range from minor neurological deficits to fatal herniation syndromes resulting from hematoma expansion, prominent mass effects and increased intracranial pressure [42]. Although the clinical picture alone is insufficient to reliably differentiate SICHs from ischemic strokes [14, 30, 50], it maintains its relevance for prompting imaging and laboratory investigations as well as for initiating a treatment plan, taking into account the fast dynamics of SICHs.

For obtaining a consensus among institutions, a better communication and a more accurate assessment of neurologic status and its dynamics, a number of neurological deficit scales and functional status scores have been adopted internationally.

Table 1

Glasgow Score(GCS)

Components	Grading	Points
Eye opening	Does not open eyes, even under pressure	1
	Opens eyes in response to painful stimuli	2
	Opens eyes on verbal command	3
	Opens eyes spontaneously	4
Motor responce	No response	1
	Extension to painful stimuli (decerebrate response)	2
	Abnormal flexion to painful stimuli (decorticate response)	3
	Flexion / Withdrawal to painful stimuli	4
	Localizes painful stimuli	5
	Obeys commands	6
Verbal responce	Makes no sounds	1
	Incomprehensible sounds	2
	Utters inappropriate words	3
	Confused, disoriented	4
	Oriented, converses normally	5

Among the most common can be listed: Glasgow Coma Scale (GCS) is the most common scoring system used to describe the level of consciousness in a person with brain injury. It is composed of three parameters (best eye opening, best motor response and best verbal response), the overall score varying between 3 and 15 (Table 1). A score of 13 or higher correlates with a mild brain injury, a score of 9 to 12 correlates with a moderate injury, and a score of 8 or less correlates with a severe brain injury. A diagnosis of coma corresponds to a

Table 2

ICH score and ICH-GS score [53]

Components	ICH-GS Score		ICH Score	
	Grading	Points	Grading	Points
Age (years)	< 45	1	< 80	0
	45 - 64	2	≥ 80	1
	> 65	3		
GCS (points)	13 - 15	1	13 - 15	0
	9 - 12	2	5 - 12	1
	3 - 8	3	3 - 4	2
ICH Localization	Supratentorial	1	Supratentorial	0
	Infratentorial	2	Infratentorial	1
IVH	Yes	1	Yes	0
	No	2	No	1
ICH Volume (ml)			<30	0
			≥30	1
Supratentorial ICH volume (ml)	< 40	1		
	40 - 70	2		
	> 70	3		
infratentorial ICH volume (ml)	< 10	1		
	10 - 20	2		
	> 20	3		

score below 7-8. The summation to provide an overall score for coma (from 3 to 15) results in some loss of information, but still proves valuable for a variety of purposes, including triage and epidemiological studies [45, 51].

ICH (intracerebral hemorrhage) **score**, original and modified, represents reliable grading scales for patients with intracerebral hemorrhage evaluated at presentation, allowing risk stratification and predicting the mortality in the first 30 days. The ICH scale uses such factors as age, volume of ICH, GCS score and presence of intraventricular hemorrhage (Table 2). Scale range is between 0 and 6 points. Higher ICH scores are associated with increasing mortality during the first month – all patients with a score 0 survive and all patients with a score greater than or equal to 5 die within 30 days [6, 42, 52, 53].

ICH-GS Score (intracerebral hemorrhage-grading scale) developed for SICHs, appears to possess greater sensitivity in predicting in-hospital mortality, mortality at 30 days and post-therapy functional results compared with the original ICH score (Table 2) [53].

FUNC score is another prediction tool for risk stratification and functional outcome at 90 days after stroke [42]. FUNC score ranges from 0 to 11 based on the volume of ICH, age, location of ICH, GCS and cognitive dysfunction (Table 3) [42]. For each patient with ICH, a particular FUNC score value corresponds to the percentage probability of attaining functional independence (Glasgow Outcome Score greater than or equal to 4) at 90 days. A higher score is associated with a greater likelihood of functional independence, defined as GOS ≥ 4 at 90 days. No patients with a FUNC score ≤ 4 reach functional independence and more than 80% of patients with FUNC score of 11 achieve functional independence at 90 days. However, only scores at the extreme ends appear to be clinically useful, while the average scores have a lower predictive value [42].

Table 3

FUNC Score [42]

Components	Grade	Points
ICH Volume (cm3)	< 30	4
	30 - 60	2
	> 60	0
Age (years)	< 70	2
	70 - 79	1
	≥ 80	0
ICH Localization	Lobar	2
	Deep	1
	Infratentorial	0
GCS (points)	≥ 9	2
	≤ 8	0
Pre-ICH cognitive impairment	No	1
	Yes	0
Total FUNC Score	0 - 11	

Rankin Scale is a commonly used scale for measuring the degree of disability or dependence in the daily activities in patients with stroke or other acute neurological disabilities. The scale was developed in 1957 and modified in 1988. The modified Rankin scale ranges between 0 and 6, running from perfect health without symptoms to death: 0 - without symptoms; 1 - no significant disability; able to carry out all usual activities, despite some symptoms; 2 - mild disabilities; able to look after own affairs without assistance, but unable to carry out all previous activities; 3 - moderate disabilities; requires some help, but able to walk unassisted; 4 - moderately severe disabilities; unable to walk without assistance or to care unassisted to own bodily needs; 5 - severely disabled, bedridden, incontinent and requiring constant care; 6 - dead [54, 55].

Barthel Index evaluates 10 basic activities of daily living, which include: (1) feeding, (2) bathing (3) grooming (washing face, combing hair, brushing teeth), (4) dressing (5) bowel control (6) bladder control, (7) the ability to use the toilet, (8) chair transfer, (9) ambulation (10) stair climbing. The total score ranges between 100 points (independent) and 0 points (completely dependent) [54, 56].

GOS score (Glasgow Outcome Score) is a scale for assessing the final state after an acute brain disease. Depending on their recovery, the patients are grouped into 5 categories: (1) good recovery with resumption of normal life despite minor deficits, (2) moderate disability, but relatively independent without needs for assistance in everyday life (employment is possible but may require special equipment), (3) severe disabilities – conscious, but dependent for daily support, (4) persistent vegetative state with prolonged periods of unresponsiveness or minimal responsiveness (5), deceased [45, 52, 54]. The correlation between ICH score and GOS score is negative and statistically significant [52].

Paraclinical diagnosis

Neuroimaging studies are vital to elucidate the diagnosis and etiology of SICHs [4, 6, 42, 57]. Brain imaging is the cornerstone for diagnosing SICHs because hemorrhagic and ischemic strokes can not be differentiated by clinical data alone [4, 6, 42, 57]. Neuroimaging studies are needed not only for diagnosis, but also provide valuable information related to the type of bleeding, its etiology and pathophysiology [4, 49, 57]. Neuroimaging studies include a compulsory brain CT scanning, an optional brain MRI followed by angiography of the cerebral vessels obtained by CT and / or MRI [4, 5, 18, 33, 58].

Brain CT is the investigation of choice for the diagnosis of SICHs, able to establish the diagnosis within minutes from the onset of symptoms and to provide additional details such as the bleeding size and localization. Non-contrast CT remains the "gold standard" for diagnosis, although a variety of new neuroimaging techniques can provide additional information related to pathophysiology of SICHs and their prognosis in individual patients [3, 5, 6, 30, 42]. Brain CT also enables rapid calculation of the volume of bleeding, which may be performed by two methods: the "ellipse" method based on routine CT images and the planimetric method using the neuronavigation station equipment [59]. CT angiography in hyperacute phase, followed by a post-contrast scan can also identify the "spot" sign – one or more hyperintense spots in

hematoma caused by the leak of contrast material into its cavity. Its presence is an independent predictor associated in 60% of cases with hematoma expansion and a reserved prognosis [4, 18, 35, 41, 47, 48]. Carotid angiography is performed when the cause of the bleeding remains equivocal or when a vascular malformation is suspected.

MRI identifies SICHs shortly after their onset [5, 6, 18, 42, 49], being also reliable for detecting chronic iron deposits related to previous bleedings [6, 18, 42, 49]. MRI is especially indicated when the clinical picture and cerebral CT exams cannot establish the final diagnosis or the etiology of bleeding [14, 18, 42, 49]. Initial MRI can be also performed as part of prognostic score protocols for predicting clinical outcomes in acute SICHs [18, 30]. Micro-hemorrhages detected by MRI can be occasionally useful in elucidating the pathophysiology and development of SICHs. Recent studies indicate that transcranial ultrasound has an excellent correlation with cerebral CT for evaluating the degree of bleeding in patients with hyperacute SICHs, therefore the modality can be also considered for early diagnosis and non-invasive monitoring of SICHs [60].

Due to the rapid advances in the field of medical imaging during the last decade and the absence of a standardized international protocol related to SICHs imaging [3, 18, 50], the imaging modalities and employed protocols for managing SICHs may vary considerably across different countries. In most institutions, CT is recommended as a standard imaging procedure for differentiating hemorrhagic from ischemic strokes. CT angiography is performed immediately in case of suspected aneurismal hemorrhages. In general, a younger age and a lobar location of SICH without pre-existing hypertension require a wider variety of diagnostic investigations beyond the initial cerebral CT [18, 61]. The relevance of other investigations such as MRI angiography may depend upon the clinical situation, the choice being also affected by local resources and recommended protocols by the national healthcare systems [18].

Management

While the search for a specific targeted therapy for SICHs continues, excellent medical care likely has a potent, direct impact on morbidity and mortality even now, before a specific therapy is found [3]. Current treatment is targeting a variety of components such as preventing hematoma expansion, reducing the mass effect, minimizing brain injuries and preventing secondary neurological and nosocomial complications [4, 29]. Hospital admission is mandatory, preferably in a specialized neurosurgical department. If such facilities are not available, admission to a Neurology department is also acceptable [18]. Before admission, the treatment is directed at providing basic airway and breathing support, blood pressure control and hemodynamic stabilization, lowering the intracranial pressure, monitoring vital signs etc. [3, 5, 6, 29, 41].

Medical treatment

Medical management is initiated immediately and continues in the intensive care unit, including cardio-respiratory and blood pressure control, reversal of coagulation defects, cerebral edema, intracranial hypertension and seizure management, addressing the risk factors and associated medical conditions etc [15, 17, 26 62]. Most studies show superior results for patients admitted into an intensive care unit, preferably of neurological or neurosurgical profile [5, 6, 18, 63]. Patients with a low level of awareness often require ventilatory support [29]. Although the treatment may vary depending on the patient's condition, it also addresses a number of general principles such as blood pressure control, management of coagulation deficiencies, management of cerebral edema and elevated intracranial pressure, neuroprotective therapy etc [4, 5, 35, 41, 63, 65].

Management of coagulation deficiencies. Congenital or acquired coagulation factor deficiencies worsen the prognosis for SICHs by increasing the rate of hematoma expansion as well as by affecting its subsequent resorption [4, 6, 41]. Patients at risk also include those taking oral anticoagulants and those with qualitative or quantitative platelet abnormalities. Recognition of the underlying coagulopathy allows developing a treatment strategy. For example, in patients with thrombocytopenia or a coagulation factor deficiency, administration of platelets or the appropriate deficient factor is indicated [2-4, 6, 41]. Acquired coagulopathy may be attributed to longstanding liver and/or renal disease, malignancy, or medication. For patients being treated with oral anticoagulants, the medications are immediately canceled and specific antidotes are administered to correct the international normalized ratio (INR) as rapidly as possible [4-6, 14, 41]. Infusions of vitamin K and fresh-frozen plasma (FFP) have usually been recommended for this purpose, but more recently, prothrombin complex concentrates (PCCs) and recombinant factor VIIa (rFVIIa) have emerged as potential therapies [3]. Concominant use of vitamin K with FFP, cryoprecipitate, or clotting factor concentrates can be also used to hasten reversal of oral anticoagulants. Even in patients without any coagulation deficiencies, administration of various hemostatic agents such as aminocaproic acid, tranexamic acid and recombinant activated factor VII has been proposed [5, 18, 63]. Although their routine usage in patients without coagulation deficiencies was associated with enhanced hemostasis and reductions in hematoma growth, the medication did not alter severe disability or mortality rates [14, 35, 41].

Management of hypertension. Arterial hypertension is associated with hematoma expansion and poor prognosis, although a clear causal effect has not been established [4, 14, 35, 41, 64]. Current guidelines suggest aggressive reduction of systolic blood pressure (BP) with intravenous infusion of vasoactive drugs (labetalol, esmolol and nicardipine) only if systolic BP is over 180 mm Hg and/or mean BP is over 130 mm Hg [3-5, 64]. Given the altered cerebral perfusion, the blood pressure reduction should be also gradual, most authors suggesting reducing systolic BP just below 160 mm Hg and/or mean BP just below 110 mm Hg as an initial step [3, 4, 64]. The Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) I Trial, a multi-center prospective study performed during 2004-2008 to determine the appropriate level of systolic

BP reduction with intravenous nicardipine infusion for 18 to 24 hours postictus in subjects with intracerebral hemorrhage who are present within 6 hours of symptom onset, showed that the treatment was well tolerated and reduced the risk of hematoma expansion, neurological deterioration and hospital mortality [6, 14, 35]. The results of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage (INTERACT) I randomized trial also suggested that early intensive blood pressure reduction to systolic values ≤ 140 mmHg initiated within 6 hours of symptom onset appeared to attenuate hematoma expansion in patients with intracerebral hemorrhage. In subgroup analyses, patients recruited within 3 hours and patients with an initial SBP ≥181 mm Hg appeared to have the greatest benefit with intensive blood pressure reduction [14, 35, 66]. The INTERACT-2 trial found that intensive blood pressure lowering in patients with intracerebral haemorrhage reduced the risk of major disability and improved the chances of recovery by as much as 20%, even though no changes in mortality rates were reported [14, 66, 67]. A variety of new studies are also underway. One such trial is the perioperative antihypertensive treatment in patients of spontaneous intracerebral hemorrhage (PATICH) trial, which aims to determine if the intensive preoperative BP reduction improves the overall prognosis and the postoperative outcome [68].

Cerebral edema and intracranial hypertension management. The Intracranial hypertension is an important cause of secondary brain injuries. Elevation of the head of the bed to about 30° promotes displacement of cerebrospinal fluid from the intracranial compartment to the spinal compartment. Medical management can also include sedation, analgesia, osmotherapy with either mannitol or hypertonic saline, controlled transient hyperventilation as well as drainage of cerebrospinal fluid depending on the degree of intracranial hypertension [3, 4, 41, 50, 64, 66]. Even though randomized clinical trials have failed to demonstrate a significant benefit of bolus therapy with mannitol on cerebral blood flow and mortality rates [5, 20, 35], monitoring of intracranial pressure is commonly associated with better functional results in patients with SICHs [23]. Intracranial pressure monitoring and its maintenance within 50-70 mm Hg is especially indicated in patients with a GCS score < 8 and/or evidence of brain herniation, significant intraventricular hemorrhage and hydrocephalus.

Anticonvulsant therapy. Seizures are reported in 4-8% of patients with SICHs, and are more prone to occur in lobar (superficial) hematomas: about 4.2% of cases occur in the first 24 hours and about 8.1% - within 1 month after the onset of SICHs [2, 4, 14]. Their presence is commonly associated with higher rates of complications, increased mortality, and poor functional outcomes in survivors [69]. Seizures in SICHs are usually treated with intravenous administration of lorazepam (0.05–0.10 mg/kg) followed by an intravenous loading dose of phenytoin or fosphenytoin (15–20 mg/kg), valproic acid (15–45 mg/kg), or phenobarbital (15–20 mg/kg). The anticonvulsant therapy can be discontinued if no seizures are noted for one month. Although, no randomized trials have addressed the efficacy of prophylactic antiepileptic medication in SICHs, the option may be considered for patients with lobar hematomas and higher risks for seizures [3, 20, 35, 41, 50, 69]. In addition, 24-hrs electroencephalography (EEG) monitoring should be considered for patients with reduced consciousness and depressed mental status out of proportion to the degree of brain injury [3, 5, 35, 41].

Deep venous thrombosis prophylaxis. Immobilized state and paresis predispose SICHs patients for deep vein thrombosis and pulmonary embolism. The reported incidence of symptomatic venous thromboembolism in SICHs varies between 0.5% - 13%, and that of pulmonary embolism between 0.7% - 5% [41]. Intermittent pneumatic compression devices and elastic stockings are indicated and should be placed on admission on all immobilized patients. Low doses of unfractionated heparin or low-molecular-weight heparins can be considered in patients with hemiplegia, 3-4 days after the onset of SICHs and after ensuring that the intracerebral bleeding stopped [2-5, 35, 50].

Glycemic control. Hyperglycemia has a deleterious effect on cerebral ischemia, being associated with increased mortality and reduced rates of early functional recovery [5, 14, 23, 70]. Even though studies performed in SICHs patients suggest that early glycemic control can improve the outcome [5, 26, 70], there is growing evidence that "enhanced" glycemic control (<2.8 mmol/l or <50 mg/dL) obtained by insulin infusions in patients with acute brain injury may be associated with significantly reduced concentrations of extracellular glucose in the brain [5, 14, 70]. Because of this, many clinicians are reluctant to lower serum glucose if the level is below 10.0 mmol/l (180 mg/dL) [14, 70]. At the moment the optimal management of hyperglycemia in SICHs and the target glucose levels remain to be clarified; however, hypoglycemia should be avoided [3].

Neuroprotection. The goal of neuroprotective agents (such as magnesium, minocycline, deferoxamine) is to favorably influence the cascade of biochemical events triggered by the intracerebral hemorrhage, subsequently leading to neuronal deterioration an cell death [35]. Various neuroprotective management strategies have been studied in SICHs [71]. Although the results suggest that neuroprotective agents may provide incremental improvements, new trials are required to further elucidate their effects and to define their clinical indications [71]. Hypothermia has also been studied among the neuroprotective strategies in patients with ischemic and hemorrhagic strokes. Thus, a pilot study of therapeutic hypothermia in patients with SICHs reported reduction in cerebral edema and perihematomal inflammation [5, 35]. Several other clinical studies, however, showed incremental or little benefits for patients with SICHs treated with NXY-059, mannitol, glycerol, and citicoline [5, 35, 66, 72].

Surgical treatment

Surgical management of SICHs may be required in many clinical situations such as intracranial hematomas greater than 3 cm, a structural vascular lesion or lobar hemorrhage in a young patient, increasing intracranial pressure with neurological deterioration, etc. A variety of procedures including

conventional open craniotomy, simple aspiration, ventriculostomy, endoscopic evacuation, stereotactic aspiration with local fibrinolysis or various combinations have been used for this purpose [20, 35]. However, the decision about whether and when to surgically remove the hematoma and the type of procedures to be used still remain controversial. Surgical evacuation of SICHs is aimed at reducing the mass effect, decreasing intracranial pressure, improving of regional blood flow, minimizing the release of blood degradation products, minimizing cerebral edema and secondary brain injury [5, 29, 64]. The interval from the initial onset of SICHs is commonly divided into 3 stages: ultra-early (less than 7 hours), early (from 7 to 24 h) and delayed (over 24 hours) [73]. Most studies indicate that early stage (7-24 hours) appears the optimal time for surgical interventions [73], while ultra-early brain surgery (within first 4 hours of symptom onset) is often associated with higher rates of rebleeding [73, 74]. The employed surgical techniques used in the evacuation of SICHs can be grouped into several categories such as evacuation by conventional craniotomy, evacuation by endoscopy, evacuation via stereotactic techniques and aspiration methods with local fibrinolysis [1, 3, 63, 75].

Conventional craniotomy involves removing a portion of the skull (a bone flap ranging from about 5x5cm to 10x10cm in size) and conducting open surgery to drain the hematoma and repair the ruptured blood vessel. This represents a major surgical procedure that is typically used when the hematoma is very large, or when it is compressing the brain stem or other centers that control vital functions. Hematoma cavity is cleared and a hemostatic sponge can be applied if needed. The cavity is also drained and the bone flap is fixed. In cases of severe cerebral edema or prolapsing cortex through the surgical wound, the bone flap can be temporarily preserved in the subcutaneous fat of the abdominal region (for later use to close the skull defect).

Evacuation via endoscopy involves drilling a small burr hole in the skull and draining the hematoma using an endoscope. It represents an advanced technique that allows simultaneous monitoring of intracranial pressure and using a variety of instruments for microsurgery such as an operating microscope, laser and ultrasound equipment for clot lysis and aspiration etc. A supraorbital approach through an eyebrow incision has been frequently used for this purpose, being originally described by Justin et al in 2012 [31]. The method is particularly useful for anterior basal ganglia hematomas that are usually elongated in shape, allowing an optimal trajectory along their longitudinal axis with a complete evacuation after a single pass of the endoscopic tube [31]. Other endoscopic approaches may involve using small burr holes on coronal suture for accessing anterior basal ganglia hemorrhages, or in the parietal-occipital region for accessing basal ganglia and thalamus. In superficial lobar SICHs, a small burr hole can be applied just above the hematoma in its closest proximity to the surface [31].

Stereotactic evacuation represents an advanced technique that uses a special stereotactic frame for immobilizing the patient's head. The technique allows a preliminary computer calculation of the puncture route and a greater degree of precision and accuracy than otherwise possible. Apart from aspirating the content of the hematoma, the method also allows ultrasound clot lysis or local administration of fibrinolytic agents (streptokinase, urokinase, recombinant APT etc) [3, 37].

Puncture and aspiration with local fibrinolysis uses CT for guidance and includes several steps: 1) applying a burr hole according to the automatically calculated puncture site and catheter trajectory based on CT data, 2) guiding the puncture cannula into hematoma cavity according to the calculated trajectory, 3) aspiration of the liquid part of hematoma and application of a special catheter in the hematoma cavity for subsequent infusion of thrombolytic agents to enhance clot drainage [63, 74, 76, 77]. Local fibrinolysis and aspiration of the remaining content is then carried out in the postoperative period. A major advantage of this technique is the possibility of being carried out within 20 minutes under local anesthesia in the emergency department relying on a routine brain CT scan [78]. In many institutions, a special navigation system that allows calculating the optimal puncture site and catheter trajectory based on CT data is integrated into the CT angiography scanner for convenience. The catheter can be also inserted under the fluoroscopic guidance and its placement is evaluated by a post-procedural CT scan [79].

Early studies have failed to demonstrate superior outcomes following conventional craniotomy in supratentorial SICHs compared with best medical therapy [5, 16, 80, 81]. This resulted in a more conservative attitude and application of tighter selection criteria for surgical interventions in SICHs [13]. The increasing requirements for convincing evidence in clinical decision making led to the initiation of STICH (Surgical Trial in Intracerebral Haemorrhage) trial, the largest prospective randomized study that was conducted in 83 centers across 27 countries. The study was initiated in 1995 and the final results were published in 2005, concluding that in cases where surgical intervention is not heavily favored by current clinical judgement, early clot evacuation does not offer clinical benefit over conservative management [6, 10, 66]. Thus, after 6 months of follow up, 26% of surgically treated patients versus 24% of patients treated with medication had a favorable outcome. The trial results affected the clinical decision making and surgical interventions were employed less frequent [82]. Noteworthy, however, is that in STICH trial less than 25% of surgeries were minimally invasive [5, 10, 66, 83, 84]. The subgroup analysis of the STICH trial also revealed that patients with lobar superficial hematomas (≤1 cm from the brain surface) without intraventricular hemorrhage who underwent surgery had a more favorable outcome, about 49% of them demonstrating positive results (representing an 8% absolute increase in good outcomes compared with similar subjects in the medical arm). This subgroup of patients was the target of the STICH II study, an international, parallel-group trial undertaken in 78 centers in 27 countries, comparing early surgical hematoma evacuation within 12 hrs of randomization plus medical treatment versus initial medical treatment alone (later evacuation was allowed if judged necessary) [3, 6, 84].

The results of STICH II trial confirmed that early surgery does not increase the mortality or disability at 6 months and might have a small but clinically relevant survival advantage for patients with superficial SICHs without intraventricular hemorrhage, the greatest benefits being obtained in patients with GCS between 9-12 [5, 66, 83, 84]. Other studies and meta-analyses also confirmed the benefits of surgical interventions for superficial SICHs compared to conservative management alone [10].

The continuous search to improve the outcomes of SICHs has lead to the development of minimally invasive techniques. During the last decade, a variety of techniques of minimally invasive surgery, including endoscopic neurosurgery and stereotactic aspiration have emerged and are widely used for treating supratentorial SICHs. Among the advantages of minimally invasive methods can be listed: 1) significantly lower invasiveness and the possibility of being applied earlier than the standard surgical treatment 2) reduced operation time, 3) the option of being performed under local anesthesia, and 4) reduced brain trauma, especially for deep lesions [50, 66]. Recent studies showed that clot reduction with minimally invasive surgery plays an important role in limiting brain edema, reducing cellular damage and neurological deficits after SICHs [40, 85]. A meta-analysis published in 2012, reported that patients with supratentorial SICHs may benefit more from minimally invasive surgery compared with other treatment options [86]. Candidates who can have the greatest benefit from minimally invasive procedures within the first 72 hours from the onset of symptoms are patients of both sexes, aged 30-80 years, with superficial hematomas, GCS ≥ 9, and a hematoma volume between 25-40 ml [86]. However, conventional craniotomy for hematoma evacuation maintains its actuality in patients with GCS between 4 - 8 at admission, those with large hematomas associated with cerebral edema or mass effect compressing the brain stem or centers that control vital functions etc [3, 87-89].

Stereotactic evacuation and the method of puncture and aspiration with local fibrinolysis added new values to the minimally invasive techniques by allowing clot lysis inside the hematoma (using ultrasound waves or irrigation with fibrinolytic agents). Recent studies actually report that the enthusiasm for endoscopic aspiration seems to be declining in the context of emerged options allowing local instillation of fibrinolytic agents in the hematoma cavity for clot thrombolysis (streptokinase, urokinase, rTPA [65, 90]. The rate of reported favorable results of SICHs treated with stereotactic aspiration varies between 20.3% and 55.6% [74, 81, 91]. The puncture does not cause significant brain damage and accelerates the recovery of cerebral function, avoiding the need for an open craniotomy or general anesthesia [37, 38]. An increasing number of studies have also shown that stereotactic aspiration and local thrombolysis are safe and effective techniques in reducing the volume of SICHs [37, 85, 92]. However, none of these studies provided conclusive evidence for the choice of a treatment method according to patient's clinical condition, hematoma location, neurological status and associated disorders [93, 94]. To answer these questions, a number of randomized clinical trials such as MISTICH or MISTIE have been started. The MISTICH (Minimally invasive surgery treatment for the Patients with spontaneous supratentorial intracerebral hemorrhage) study is a multi-center, prospective, randomized, assessor-blinded, parallel group, controlled clinical trial that began in 2012 and was designed to determine whether minimally invasive surgeries could improve the prognosis for patients with SICHs compared with craniotomy [95]. The MISTIE (Minimally Invasive Stereotactic Surgery plus recombinant tissue plasminogen activator for intracerebral hemorrhagic Evacuation) trial was designed to investigate the difference between surgical intervention plus rtPA and standard medical treatment for SICHs management [16, 80, 96, 97]. Preliminary results revealed that minimally-invasive surgery plus rtPA shows greater clot resolution than traditional medical management. As a result of this, a phase II (MISTIE II) trial was designed to determine the safety and efficacy of using minimally invasive surgeries combined with rt-PA administration. A variety of other studies exploring new approaches and new avenues to improve the outcome of minimally invasive surgical techniques are also underway.

Surgical techniques applied in the Republic of Moldova

Neurosurgical institutions in Moldova have accumulated valuable experience in the treatment of supratentorial SICHs, including minimally invasive techniques that are used worldwide. According to statistical data from the National Centre for Health Management, the incidence of intracerebral bleeding in Moldova comprised 677 cases in 2010, 632 cases in 2011 and 707 cases in 2012, with an average record of 672 cases annually. According to the latest publications, SICHs (primary bleedings into the brain parenchyma without a known cause) represent 66% of intracerebral bleedings [58], and supratentorial SICHs represent about 86.7% of all SICHs [8]. Thus, the annual incidence in the Republic of Moldova represents about 447 cases of SICHs, from which 388 are supratentorial.

According to institutional statistics reported by the Institute of Neurology and Neurosurgery and the Institute of Emergency Medicine, only in these two institutions, during 2011-2014 were performed 137 nerosurgical interventions for SICHs. From these, 67 interventions employed the puncture and aspiration technique with application of local fibrinolysis, and 70 interventions employed other minimally invasive techniques or conventional craniotomy. Of note is that almost 50% of surgical interventions were performed using the puncture and aspiration with application of local fibrinolysis, which is one of the most advanced methods for treating SICHs at the international level. Moreover, some details of the technique were further refined by our experts, who obtained two patented inventions in this area.

An example of supratentorial SICH treated using the puncture and aspiration method with application of local fibrinolysis is shown in fig. 1. The technique can be divided into 4 steps:

1. **Application of the burred hole**. The procedure was

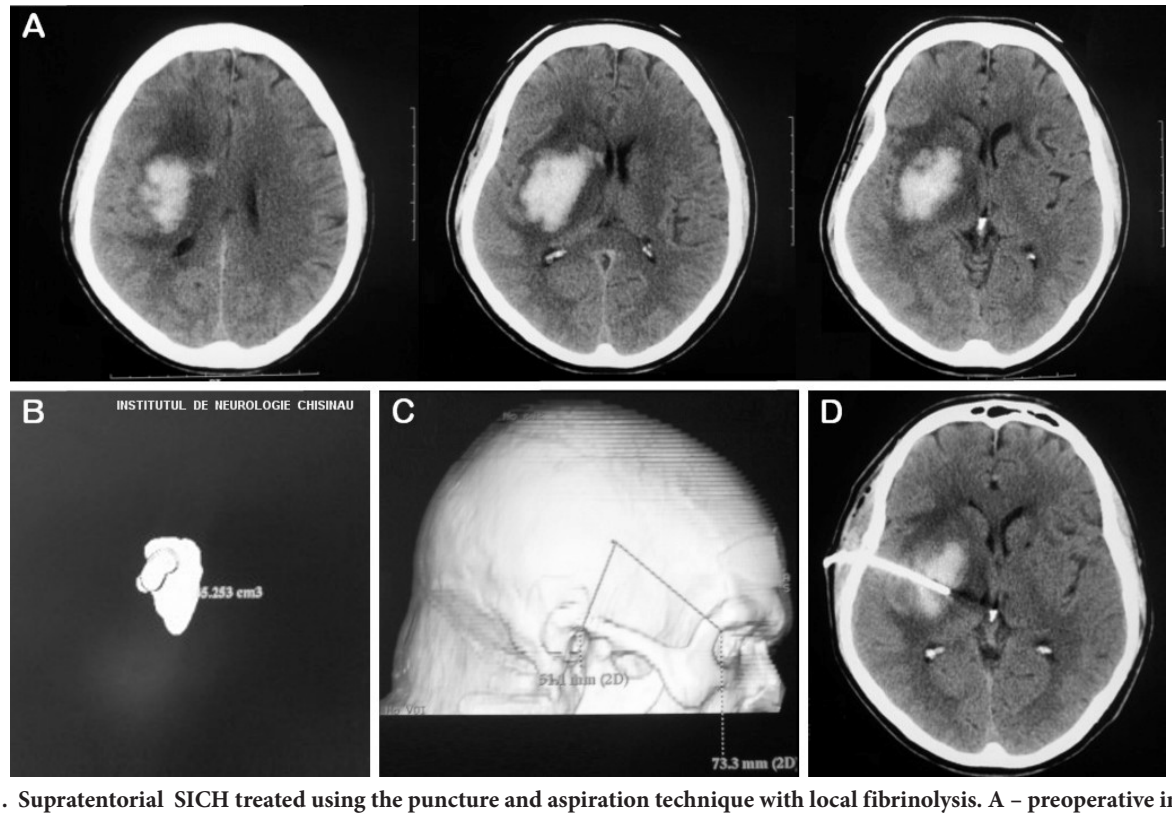

Fig. 1. Supratentorial SICH treated using the puncture and aspiration technique with local fibrinolysis. A – preoperative images showing an intracerebral hemorrhage into the right cerebral hemisphere, B – estimation of the volume of hematoma, C – 3D computer modelling allowing calculation of the puncture trajectory and its correlation with external anatomical structures, D – postoperative images confirming the position of the catheter and post-therapy changes.

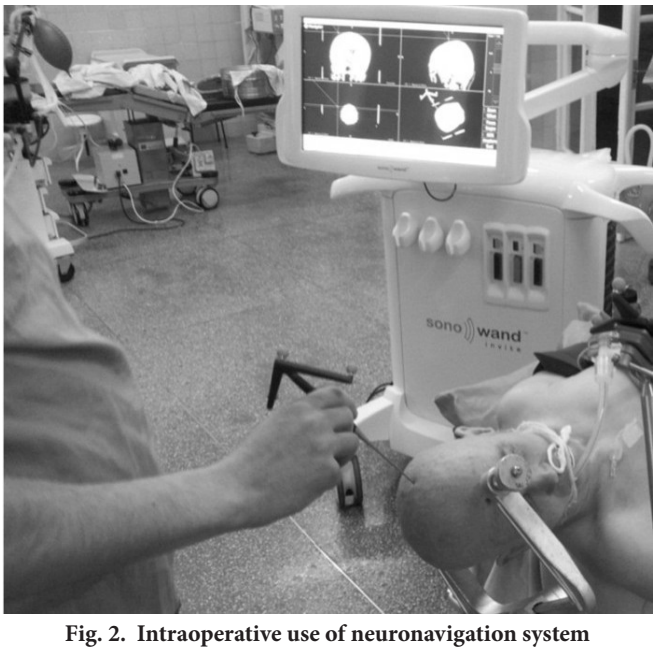

Fig. 2. Intraoperative use of neuronavigation system (SonoWand, USA) in the Institute of Neurology and Neurosurgery in Chisinau. The patient's head is stabilized with rigid pinning fixation (Mayfield frame).

performed using preoperative CT images, allowing 3D modelling of external anatomical landmarks (such as the external acoustic meatus and the lateral margin of the orbit). The calculations were subsequently applied intraoperatively for carrying out the procedure using a special device patented by our team (patented invention no. 824 of 11.06.2013).

2. Puncture and drainage of intracerebral hematoma. Standard radiopaque silicone catheters for external ventricular drainage can be also used for draining intracerebral hematomas. The catheters should have an internal diameter of 1.5 -2.5 mm, a 30 cm length, visible gradations at 5, 10 and 15 cm, as well as additional side perforations at the blunt end of the catheter to increase the irrigation surface with a fibrinolytic agent. In some cases, a special intraoperative neuronavigation system (SonoWand and Medtronic, USA, fig. 2) was also employed. The neuronavigation system provides a higher precision and allows a more accurate placement of the catheter, which proved particularly useful for accessing small SICHs (≤30 ml) located deeply within basal ganglia.

3. Aspiration of the liquid part of hematoma. In most cases, about 2-10 ml of the liquid content can be aspirated immediately after the puncture, depending on the evolution stage of hematoma. After aspirating the liquid content, the catheter is secured for subsequent fibrinolysis. An intraoperative image of an inserted catheter is displayed in fig. 3. As the hematoma decreases in size, the catheter may require repositioning. A special guided catheter was developed for this purpose in the Institute of Neurology and Neurosurgery in Chisinau (patent invention no. 795 of 01.16.2014). The end of the catheter can change its direction at any angle, allowing an easy re-positioning without the need for a surgical intervention.

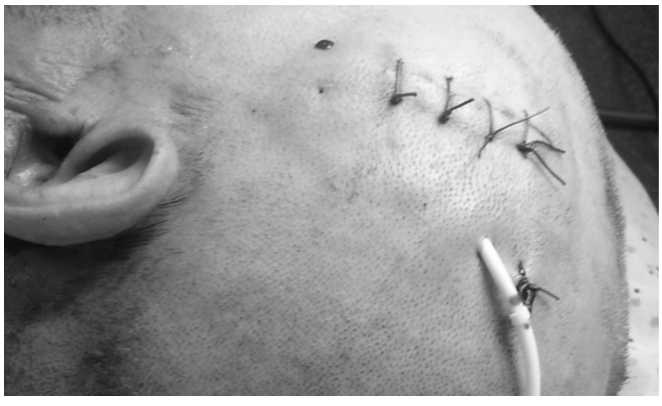

Fig. 3. An inserted catheter applied for external drainage of an intracerebral hemorrhage. Following the aspiration of the liqid part of hematoma, the catheter was secured. A fibrinolytic agent is then injected through the catether in the hematoma cavity for local fibrinolysis of the remaining blood clots.

4. Performing local fibrinolysis. A second-generation fibrinolytic agent – recombinant prourokinase (Hemaza) was administered for this purpose (5,000 IU every 6-10 hours). The number of procedures varied from 3 to 6 depending on the size of residual hematoma, with an average duration of 48 hours. The decision to stop the fibrinolysis and remove the catheter was based on the follow-up CT scans.

The obtained results showed many advantages of this technique such as: a lower rate and a reduced period of tracheal intubation, a lower rate of local postoperative complications, a reduced length of hospital stay, a lower overall mortality, a more frequent initiation of an early rehabilitation program with relatively better functional outcomes. The results are in agreement with those reported by many leading institutions at the European and international level. It should be noted that other treatment methods maintain their actuality depending on the type of hematoma and a variety of other factors, including the bleeding size and location as well as the patient's clinical condition and associated pathology. The experience gained in the Institute of Neurology and Neurosurgery allowed the development of a formal protocol for managing patients with suspected supratentorial SICHs that can be applied in neurological and neurosurgical units throughout the country (fig. 4).

Conclusions and recommendations

1. All patients with symptoms suspicious for SICH require a complex assessment, regardless of hematoma stage.
2. Consulting a neurologist or a neurosurgeon is mandatory for detailed evaluation and for establishing an early treatment strategy.
3. Immediate admission of patients with SICHs in specialized ICU departments or Stroke units increases the chances for survival and for a better recovery of neurological deficits.
4. After discharge from specialized institutions, patients with SICHs require periodic assessments at 1, 3, 6 and 12-month intervals for detailed evaluation of their functional status, interval response to therapy and for preventing recurrences by controlling risk factors and associated diseases.

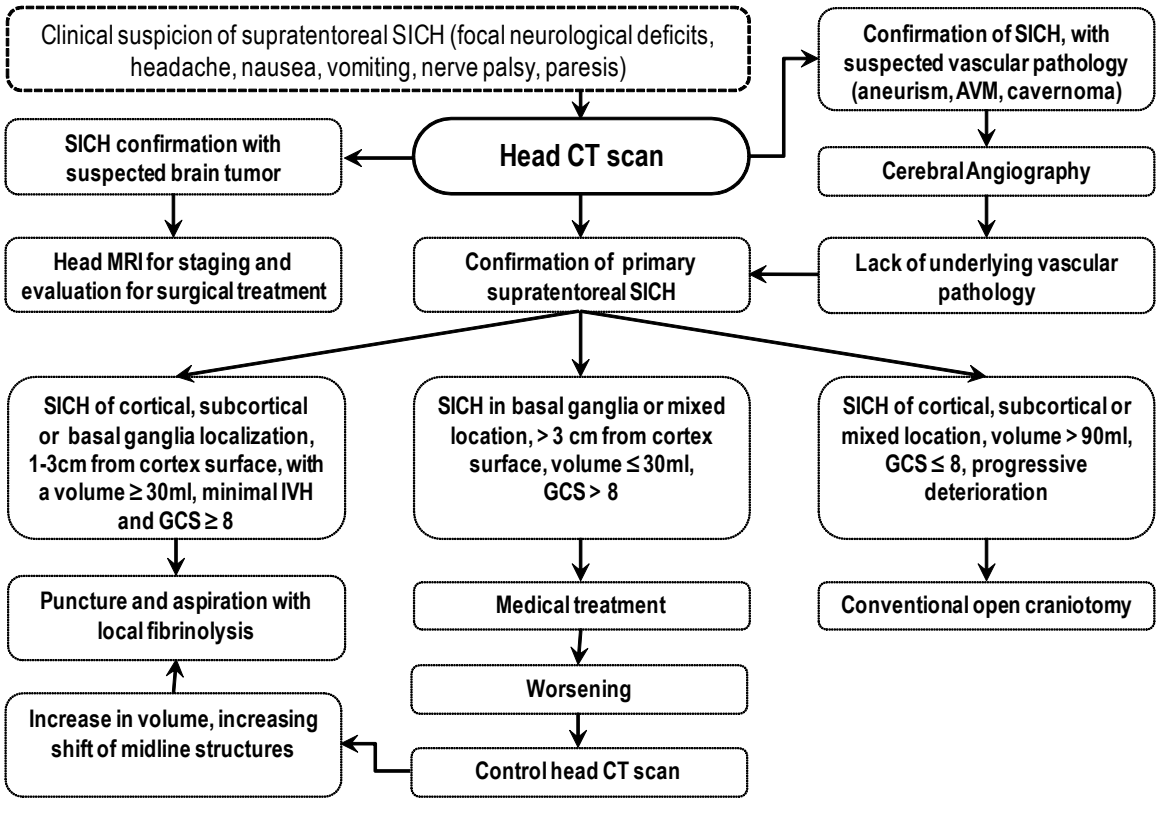

Fig. 4. Developed protocol for managing patients with suspected supratentorial SICHs.

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