Cerebral venous thrombosis and its hemorrhagic complications

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Cerebral sinus thrombosis or cerebral venous thrombosis (CVT) is an important cause of nontraumatic intracranial hemorrhage in younger patients. CVT is associated with multiple risk factors and clinical conditions, is often undetected or verified late, and most importantly, has a relatively good prognosis if the treatment is started early. In this review, we describe CVT epidemiology and risk factors, analyze its pathophysiology and clinical symptoms and discuss modern diagnostic approaches to diagnosis, treatment and secondary prevention. The article emphasizes the hemorrhagic presentations of CVT, which in clinical settings are difficult to diagnose and treat.

Keywords: *cerebral venous thrombosis; venous infarction; intraparenchymal hemorrhage; diagnostic; treatment; prevention.*
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For reference: *Kulesh AA. Cerebral venous thrombosis and its hemorrhagic complications. Nevrologiya, neiropsikhiatriya, psikhosomatika = Neurology, Neuropsychiatry, Psychosomatics. 2021;13(2):10–18. DOI: 10.14412/2074-2711-2021-2-10-18*

Cerebral venous thrombosis (CVT) is one of the causes of non-traumatic intracranial hemorrhage in young patients. Unlike arterial thrombosis, CVT is much less common; affects young patients, usually women; often has a subacute course; characterized by a wide range of clinical manifestations; associated with a variety of risk factors (RF) and clinical conditions other than the pathology of the arterial bed; often not diagnosed or verified with a delay, and also, which is especially important, with timely treatment, it has a relatively good prognosis [1]. Hemorrhagic manifestations of CVT are a serious clinical problem, since they are associated with a worse prognosis and require non-standard therapeutic solutions, which include anticoagulant therapy and endovascular treatment.

Epidemiology

The incidence of CVT in high-income countries is 1.3–1.6 per 100,000 population per year [2, 3]. CVT causes 0.5–1.0% of admissions to stroke units [4]. Women aged 31 to 50 years are characterized by a higher incidence – 2.8 per 100 000 population per year [5]. The average age of patients is 33 years, women suffer 1.5–3 times more often [4, 5].

Risk factors and associated clinical conditions

Conditions associated with CVT are subdivided into predisposing (genetic prothrombotic diseases, antiphospholipid syndrome, cancer, etc.) and provoking (oral contraceptives, infections, drugs with a prothrombotic effect; Table 1) [1, 6] .

Most (85%) patients with CVT have at least one RF, most often taking hormonal contraceptives and prothrombotic conditions (often hereditary) [7]. In patients with hemorrhagic manifestations of CVT more often than in patients without them, hematological diseases (thrombocytosis, severe anemia, polycythemia vera, thrombocytopenia) occur – 14% vs 5%, the rest of the etiological structure is similar [8]. Publications in recent months suggest that CVT is associated with COVID-19 [9–11].

The pathogenesis

CVT can be caused by partial or complete occlusion of cerebral venous sinuses (sinus thrombosis) or cortical veins (cortical venous thrombosis) [4]. The development of CVT is based on violations in the Virchow triad with the emergence of an imbalance between prothrombotic and fibrinolytic processes. Obstruction of the venous vessels leads to an increase in venous pressure, a decrease in capillary perfusion, and a local increase in cerebral blood flow. Initially compensated by the expansion of cerebral veins and the involvement of collaterals, a further increase in venous pressure leads to

Table 1. *Main risk factors associated with CVT*

Group of RF	RF
RF characteristic of women	Oral contraceptives Pregnancy and the postpartum period Hormone replacement therapy
Genetic thrombophilia	Deficiency of proteins C and S, antithrombin III, Leiden factor mutation, prothrombin gene mutation
Acquired prothrombogenic diseases	Tumors disease, leukemia, solid tumors, meningioma Inflammatory disorders (antiphospholipid syndrome, systemic lupus erythematosus, inflammatory bowel disease, nephrotic syndrome)
Infections	Infections of the head and neck: otitis media, mastoiditis, sinusitis, rhinitis, the defeat of the face and skull Systemic infections
Diagnostic and therapeutic procedures	Chemotherapy, placement of a central venous catheter Lumbar puncture, neurosurgical surgery
Discussed RFs	Obesity Iron deficiency anemia

the development of vasogenic edema, decreased cerebral perfusion, and heart attack. Cerebral edema in CVT is of a mixed (vasogenic and cytotoxic) nature. CVT also blocks the absorption of cerebrospinal fluid through arachnoid granulation, which contributes to an increase in intracranial pressure, especially with occlusion of the superior sagittal sinus. The localization of thrombosis, as well as the individual characteristics of pathological and compensatory mechanisms, determine a significant variability in the clinical manifestations of CVT [4].

Cerebral venous thrombosis causes ischemic neuronal damage, venous infarction and petechial hemorrhage, which transforms into a large hematoma, while cerebral sinus thrombosis, hindering the absorption of cerebrospinal fluid, leads mainly to intracranial hypertension [12]. The development of hemorrhagic venous infarction and intracerebral hematoma occurs due to an increase in venous capillary pressure, a violation of the blood-brain barrier with insufficient compensatory mechanisms and is accompanied by severe cerebral edema [13].

Hemorrhagic parenchymal foci develop in 35–39% of patients with CVT [7, 8, 14], while 12% of patients have intracerebral hemorrhage (ICH) [15]. In the majority of cases, the ICH is located supratentorially [7]. 63% of patients with hemorrhagic manifestations of CVT have parenchymal hemorrhage, 29% have slight juxtacortical, 24% have subarachnoid and 11% have subdural hemorrhage. In 23% of patients, several types of hemorrhages develop simultaneously [8] (Fig. 1).

The development of intracranial hemorrhage is associated with age (mean age – 46 years) and thrombosis of the superior sagittal sinus (in 55% of patients), but is not associated with the number of occluded sinuses [8]. In half of the patients, hemorrhagic manifestations of CVT develop acutely, in the first 48 hours of the disease [16].

Clinical presentations

The clinical manifestations of CVT can be attributed to one of three syndromes: isolated intracranial hypertension syndrome, focal brain lesion syndrome, and encephalopathy syndrome [17].

In a large study VENOST (n=1144) [18], it was shown that acute development of symptoms occurs in 47% of patients, subacute – in 34% and chronic – in 19%. The most

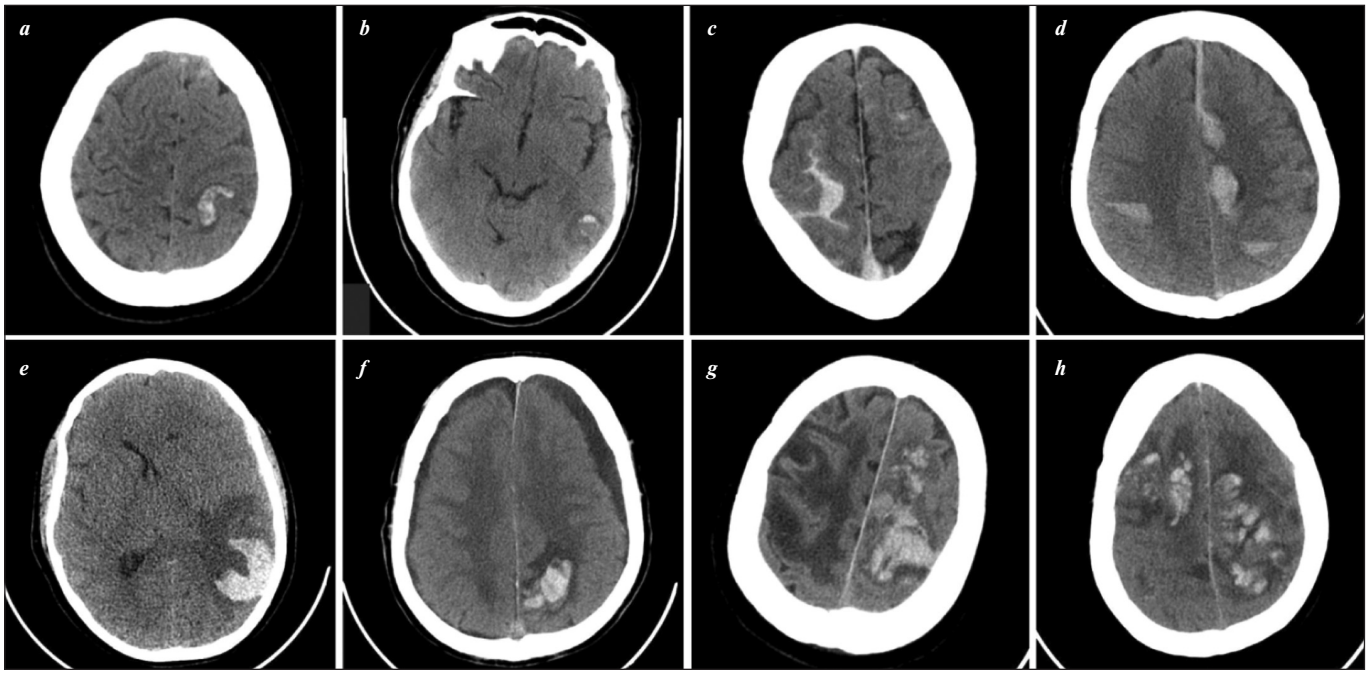

Fig. 1. *Computed tomography scans of the brain in patients with hemorrhagic manifestations of CVT. a – small cortical parenchymal hemorrhage in 17-year-old female due to superior sagittal sinus thrombosis in the early postpartum (presented with acute-onset right hemiparesis and subsequent seizure); b – left temporal lobe hemorrhagic infarct in 43-year-old female due to left transverse sinus thrombosis after an acute respiratory viral infection (presented with headache and seizure); c – convexity subarachnoid hemorrhage in 30-years-old male due to superior sagittal ("dense vein sign") and left transverse sinus thrombosis (presented with thunderclap headache and subsequent left hemiparesis); d – subcortical parenchymal hemorrhages extending into the interhemispheric fissure and subdural hygroma in 58-years-old female due to superior sagittal sinus thrombosis of unknown etiology (presented with right hemiparesis); e – see fig. 2; f – parenchymal hemorrhage and bilateral subdural hygromas in 61-years-old male due to superior sagittal sinus thrombosis of unknown etiology (presented with weakness in the left extremities and subsequent refractory status epilepticus); g – multifocal parenchymal hemorrhage in 65-years-old male due to superior sagittal and right transverse sinus thrombosis (presented with aphasia) – massive zone of gliosis and cyst in the right hemisphere due to atherothrombotic stroke; h – bilateral multifocal parenchymal hemorrhages in 25-years-old female due to superior sagittal sinus thrombosis that developed in 10 days after giving birth (presented with headache and subsequent weakness in the right extremities and refractory status epilepticus)*

common clinical manifestations are headache (87%; in a quarter of cases – isolated), nausea and vomiting (28%), seizures (24%), visual field disturbance (27%), other focal symptoms (18%), changes in consciousness (18%) and cranial nerve damage (18%).

Headache with CVT does not have a specific phenotype. In 32% of patients, it is thundering, in 26% it is subacute, in 42% it is acute. Abnormalities in neurological status are observed in 79% of patients with CVT [19].

The clinical picture of CVT depends on the localization of thrombosis, which is reflected in table 2 [4].

Young patients are characterized by intracranial hypertension syndrome, while for elderly patients – changes in mental status and a decrease in the level of wakefulness [4].

In patients with hemorrhagic manifestations of CVT, seizures (47%), focal neurological symptoms (78%) and changes in mental status (40%) are more common, while isolated headache is less common (9%) [8].

For patients with secondary supratentorial ICH, associated, as a rule, with thrombosis of the superior sagittal sinus, the development of convulsive syndrome is characteristic [20, 21]. RF of epileptic seizures in CVT include: female sex, the presence of focal neurological deficits and altered consciousness, thrombosis of the superior sagittal sinus and cortical veins, and hemorrhagic infarction [22]. In addition, these patients are at high risk for refractory status epilepticus. In general, status epilepticus develops in 18% of patients with CVT [23]. Every tenth patient with CVT develops late (more than 7 days from the moment of diagnosis) seizures, one of which is the ICH [24].

In some patients with CVT, especially with thrombosis of several sinuses, deep veins, bilateral parenchymal lesions, diffuse edema and dislocation, coma develops; one third of these patients die, and one third achieve full recovery [25]. The presence of parenchymal hemorrhage appears as one of the points for assessing the outcome of the disease in patients with CVT according to the CVT-GS scale (Cerebral Venous Thrombosis Grading Scale; Table 3) [26].

«Red flags» and risk stratification

When collecting anamnesis, one should pay attention to RFs listed in Table. 1. Suspicion of CVT should be caused by the following headache characteristics (present in 63% of patients): headache new to the patient, its thundering character, one-sidedness, aggravation in the supine position, during physical exertion and Valsalva maneuver, increase and

Table 2. *Clinical signs of CVT depending on thrombosis localization*

Localization of thrombosis (proportion of patients)	Clinical presentation
Transverse sinus (44–73%)	If isolated without infarction, asymptomatic or headache Seizures Contralateral pyramidal symptoms If left transverse sinus with venous infarction and vein Labbe occlusion – aphasia If it spreads to adjacent sinuses: – intracranial hypertension, impaired consciousness, focal neurological symptoms and damage to the cranial nerves If it spreads to the cerebellar veins – headache, vomiting and ataxia.
Superior sagittal sinus (39–62%)	Headache Visual impairment Seizures Focal symptoms due to venous infarction (cranial nerve damage, aphasia, hemianopsia, hemihypesthesia, or hemiparesis) Isolated psychiatric symptoms (rare)
Sigmoid sinus (40–47%)	Mastoid pain Combined lesion of the VI, VII and VIII cranial nerves
Deep venous system (11%)	Impaired mental status – decreased wakefulness Diffuse encephalopathy or coma Motor deficit (bilateral or fluctuating alternating paresis)
Cortical veins (4–17%)	Focal neurological symptoms in accordance with localization Seizures
Cavernous sinus (1.3–1.7%)	Headache, orbital pain, chemosis, exophthalmos, lesions of the cranial nerves (III, IV, VI and first branch V) Fever (with septic thrombosis)

Table 3. *CVT grading scale (CVT-GS)*

Parameter	Points
Size of parenchymal lesion >6 cm	3
Bilateral Babinsky signs	3
Male gender	2
Parenchymal hemorrhage	2
Level of consciousness:	
awake and alert	0
somnolence	1
stupor	2
coma	3

CVT severity according to the CVT-GS scale	Interpretation of results: 30-day mortality,%	Interpretation of results: 30-day functional deficit >2 points on the Rankin scale,%
Mild (0–2 points)	0.4	6.8
Medium (3–7 points)	9.9	34.5
Severe (8–13 points)	61.4	97.7

refractoriness to analgesics. The presence of isolated vomiting, seizures, behavioral changes, confusion / amnesia, visual impairment, fever, rigidity, papilledema, and focal neurological symptoms are also red flags [19].

To stratify the risk of CVT, the following scale was proposed: seizures at the onset (4 points), thrombophilia (4 points), oral contraceptive use (2 points), duration of symptoms > 6 days (2 points), severe headache (1 point) and focal neurological deficit on admission (1 point). The sum of 0P2 points determines a low, and i6 points – a high probability of CVT. Taking into account the D-dimer concentration (> 500 ng/ml) improves prediction [27].

We present a clinical observation of the development of ICH against the background of CVT.

***Patient A.**, 34 years old, took hormonal contraceptives. On the day of illness, she suddenly developed an intense headache, and the next day she developed speech disorders. With suspected stroke, the patient was admitted to the primary stroke unit, where an epileptic seizure occurred, after which weakness in the right extremities was added to the clinical manifestations. On the 4th day of the disease, the patient was transferred to the regional vascular center. On admission, severe sensorimotor aphasia and mild right-sided hemiparesis were observed. The results of neuroimaging (day 4) are shown in Fig. 2. Computed tomography (CT) of the brain (Fig. 2, a) shows an intracerebral hematoma of the left parietal lobe with pronounced perifocal edema; CT angiogram (Fig. 2, b) shows a contrast defect in the left transverse sinus. When performing magnetic resonance imaging (MRI) on T1-weighted image (T1-weighted image; Fig. 2, c), an image obtained using the FLAIR sequence (Fig. 2, d), and on T2-weighted image (Fig. 2, e) intracerebral hematoma of the left parietal lobe is also visualized, a thrombus is visible in the left transverse sinus. Three-dimensional time-of-flight angiography (3D-TOF; Fig. 2f) shows no signal from the left transverse sinus blood flow on the angiogram. From the moment of admission to the regional vascular center, the patient received a therapeutic dose of low molecular weight heparin. After 12 days, she was transferred to the medical rehabilitation department with regression of motor disorders and persisting mild aphasia. For the purpose of secondary prevention, warfarin was prescribed warfarin with a target international normalized ratio (INR) of 2.0–3.0.*

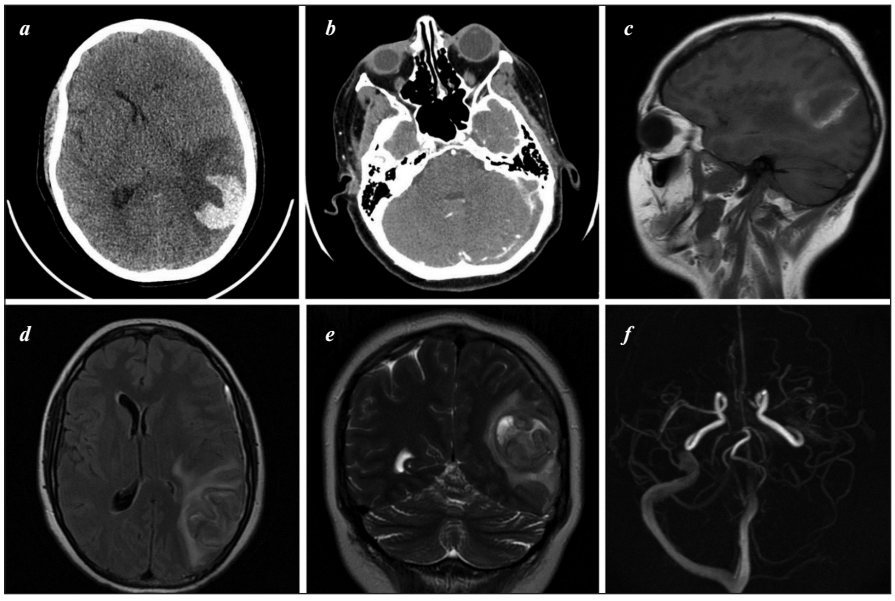

Fig. 2. *Intracerebral hemorrhage due to left transverse sinus thrombosis in the 34-years-old female patient A. Explanation is in the text*

Diagnostics

Verification of CVT as a cause of ICH is a challenging clinical task. So, only a quarter of patients have direct signs of thrombosis on computed tomograms: a «dense triangle» sign (with thrombosis of the superior sagittal sinus), a «empty delta» sign (a thrombus surrounded by collateral veins of the sinus wall after the injection of a contrast agent) and a «string» sign (thrombosis of the cortical or deep veins), as well as hyperatenuation of the thrombosed sinus [28, 29]. Bilateral or multiple ICH are suspicious of venous origin [12].

CT venography is a sensitive method for verifying CVT and is advisable if MRI is unavailable or if there are contraindications to MRI. However, it should be noted that the diagnostic value of CT venography as the only diagnostic method is limited, since the presence of anatomical variants (atresia, hypoplasia, asymmetry, pachyon granulation, septa) can simulate thrombosis [28, 30].

During MRI, T1- and T2-WI can demonstrate a false-negative result in the acute phase (first 5 days); therefore, it is advisable to use T2* or SWI (SWAN) MR sequences, which allow visualizing a thrombus in the form of a hypointense zone [31]. In the subacute phase (5–15 days), the thrombus becomes hyperintense at T1 and T2-weighted. In the chronic phase (> 15 days), the thrombus is homogeneous and the signal intensity in all sequences decreases [32].

An important MRI phenomenon in CVT is vasogenic and cytotoxic edema (often in combination). In the case of ICP, the MRI picture often shows bilateral hemorrhages, multifocal hemorrhages, or hemorrhagic infarctions, which are atypical for lesions of the arterial bed. In this case, the localization of parenchymal lesions may indicate the localization of venous thrombosis. For example, involvement of the frontal, parietal and occipital lobes in the pathological process is typical for thrombosis of the superior sagittal sinus, and damage to the temporal lobe is typical for thrombosis of the transverse and sigmoid sinus. If edema or cortical / subcortical local hemorrhage is detected, it is necessary to assess the signal intensity of the nearby cortical veins, especially if the lesion does not match the arterial bad [12, 30].

The use of MR angiography as the only technique is not recommended. Contrast MR angiography has a higher sensitivity compared to time-of-flight [33].

Subtraction digital angiography should remain a backup method and should be used when the CT and MRI

results are inconsistent, to exclude arteriovenous fistulas, or when planning endovascular intervention [34].

Determination of the D-dimer level is advisable before neuroimaging in patients with suspected CVT, with the exception of isolated headache and duration of symptoms >1 week. The search for thrombophilia in patients with CVT is not advisable, but it can be performed in patients with a high probability of its presence (personal and/or family history of venous thrombosis, young age, absence of transient and permanent RF). Routine search for hidden malignant neoplasms is not recommended [35].

Treatment

In accordance with the recommendations of the European Stroke Organization (ESO) 2017, patients with CVT, including those with the development of ICH, should receive heparin therapy in a full-dose (therapeutic) regimen. In this case, it is preferable to use low molecular weight heparins (LMWH), except in situations where they are contraindicated (renal failure) or rapid neutralization of the anticoagulant effect is required (the need for neurosurgical intervention). During pregnancy or postpartum, only LMWH can be used [35].

Decompressive surgery may be required in patients with dislocation syndrome (temporo-tentorial herniation, median displacement >5 mm, ischemia in the posterior cerebral artery basin, persistent increase in intracranial pressure >20 cm H_2O) [4, 35]. In this case, the beginning / resumption of the administration of anticoagulants is possible after 24–48 hours [36].

While anticoagulant therapy is aimed at preventing the progression of the thrombus and accelerating its lysis, the goal of endovascular treatment is to rapidly decrease the thrombus mass by the administration of fibrinolytic agents or mechanical removal. Small nonrandomized studies and clinical series demonstrate a recanalization rate of 70–90% with an ICH rate of about 10% [37, 38]. However, in the TO-ACT study (Thrombolysis or Anticoagulation for Cerebral Venous Thrombosis; n=67), endovascular treatment – thrombectomy and/or local thrombolysis (indicated by the presence of at least one RF of poor outcome: mental disorder, coma, ICH, thrombosis of the deep venous system) – in combination with standard care did not improve the functional outcome of patients, which may be associated with a small sample [39]. A series of clinical observations have shown that thrombectomy with a stent retriever in combination with prolonged local thrombolysis can be a safe and effective method of treating severe hemorrhagic CVT with ineffective intravenous anticoagulation [40]. Thus, at present, endovascular treatment is not considered as a routine method in patients with CVT, but it may be advisable if the risk of an unfavorable clinical outcome is high [4].

Prescribing antiepileptic drugs is advisable only in the presence of seizures. In case of epileptic seizures associated with cerebral edema, stroke or ICH, the drug should be taken for at least 1 year [4].

Secondary prevention

For patients with CVT, for the prevention of recurrence of thrombosis and other venous thromboembolic events, oral anticoagulants (OAC; warfarin) with a target INR of 2.0–3.0 for 3–12 months are recommended. Patients with recurrent venous thrombosis or a prothrombotic condition (protein C and S deficiency, antithrombin III, antiphospholipid syndrome) with a high thrombotic risk may require life-long therapy.

At the time of this writing, ESO and the European Academy of Neurology (EAN) [41] discouraged the use of direct OAC (DOAC), especially in the acute phase of the disease. This was due to the very low level of evidence due to the fact that the single studies that evaluated the safety and efficacy of these drugs were small and observational [42, 43]. In 2019, the results of the only randomized clinical trial comparing the effectiveness of warfarin and DOAC in the secondary prevention of CVT RE-SPECT CVT (A Clinical Trial Comparing Efficacy and Safety of Dabigatran Etexilate With Warfarin in Patients With Cerebral Venous and Dural Sinus Thrombosis) were published [44]. The study included patients with acute CVT who had a stable clinical condition after 5–15 days of parenteral treatment with heparin; patients with an infectious or traumatic nature of the disease were not included. 120 randomized patients received dabigatran 150 mg twice daily or warfarin with a target INR of 2–3 (1:1) for 24 weeks. The primary outcome was assessed by the number of new venous thromboembolic events (repeated CVT, deep vein thrombosis of the extremities, pulmonary embolism, and splenic vein thrombosis) and major bleeding during the study period. Secondary outcomes included cerebral venous recanalization and clinically significant minor bleeding. The average age of the patients was 45 years, 55% were women. The median duration of treatment was 22 weeks in the dabigatran group and 23 weeks in the warfarin group. Hemorrhagic parenchymal foci were observed in 30% of patients in the dabigatran group and in 32% of patients in the warfarin group. No recurrent venous thromboembolic events were recorded in any of the groups. One patient (1.7%) in the dabigatran group developed major (intestinal) bleeding, and two (3.3%) in the warfarin group developed intracranial bleeding. Another patient in the warfarin group developed clinically significant minor bleeding. Recanalization occurred in 35 (60%) patients in the dabigatran group and in 35 (67%) patients in the warfarin group. Thus, the study showed that when taking OAC, patients with CVT have a low risk of recurrent thromboembolic events and the risk of bleeding is the same for both drugs. In 2020, a systematic review and meta-analysis was published that included data from RESPECT-CVT and five observational studies (151 patients in total) [45]. The studies by A. Lurkin et al. [46] (2019; n=41: warfarin – 25 vs apixaban – 1, dabigatran – 2 and rivaroxaban – 13), M. Wasay et al. [47] (2019; n=111: warfarin – 66 vs dabigatran – 9 and rivaroxaban – 36); C. Geisbüsch et al. [42] (2014; n=16: warfarin – 9 vs rivaroxaban – 7); C. Herweh et al. [48] (2015; n=95: warfarin vs DOAC), J. Wells et al. [49] (2019; n=29: warfarin – 19 vs apixaban – 8 and rivaroxaban – 2). Based on the presented meta-analysis, it cannot be ruled out that DOAC can serve as an effective and safe alternative to warfarin in the secondary prevention of CVT.

The timing of the transition from parenteral administration of anticoagulants to oral administration is not regulated, but the approach used in the RESPECT-CVT study seems to be logical – after 1–2 weeks of CVT with a stable clinical state.

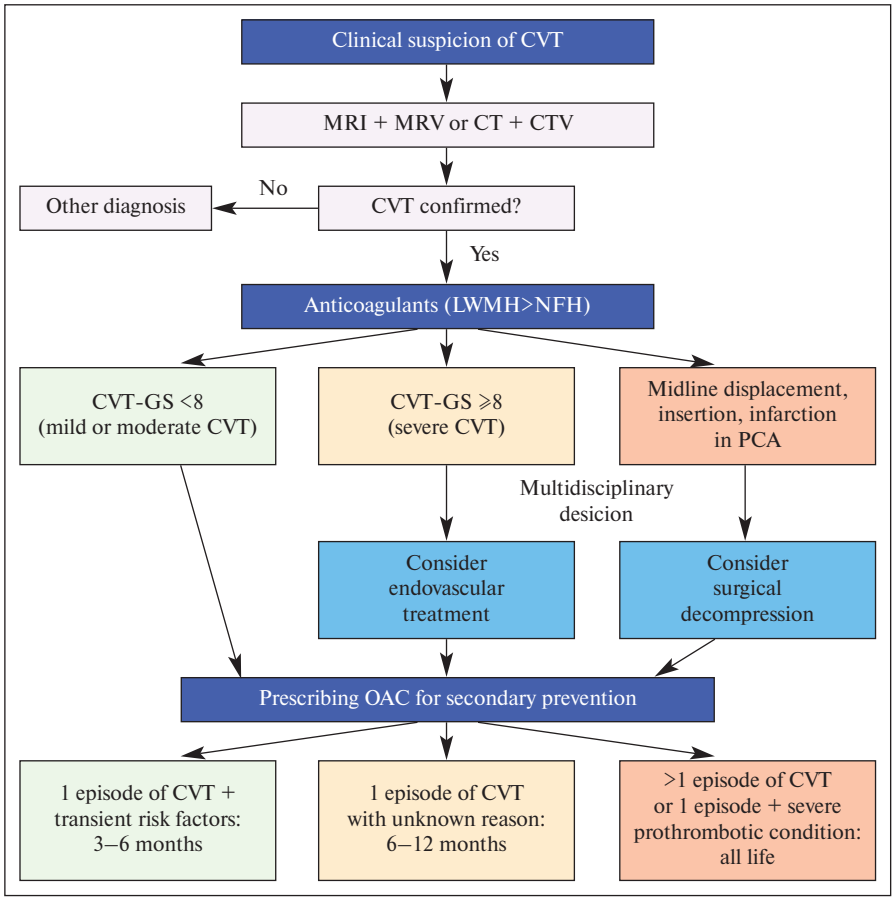

Fig. 3. *Diagnostic and treatment algorithm in CVT*

The duration of anticoagulant prophylaxis varies from 3 to 12 months [35]. According to the recommendations of the American Heart Association/American Stroke Association (AHA/ASA) 2011 [50], patients with a single episode of CVT and transient RF (dehydration, oral contraceptive use, infection, trauma , operation) should receive a OAC within 3–6 months; patients with a single episode of CVT, the cause of which remains unknown – 6–12 months; patients with two or more episodes of CVT or in the presence of one episode in combination with high-risk prothrombotic status – throughout life.

The therapeutic and diagnostic algorithm proposed by L. Ulivi et al. [4], with some changes is shown in Fig. 3.

Prognosis and outcomes

Patients with CVT are characterized by a good prognosis – full clinical recovery is achieved by 3/4 of patients, but 15% of patients die or lose independence [7]. In some surviving patients, depression or anxiety, as well as cognitive impairment, may persist [51]. The risk of recurrent CVT is 2–7% [7]; it is higher in patients with thrombophilia and with refusal to take OAC [50]. The overall recanalization rate for anticoagulants is 85% [52]. Complete recanalization is associated with a favorable clinical outcome [53]. Venous recanalization begins in the first 8 days of therapeutic anticoagulation in most patients with CVT and is associated with early regression of non-hemorrhagic foci, including venous infarctions. Occlusion persistent on the 8th day is associated with an increase in non-hemorrhagic foci [54]. Recanalization lasts up to 11 months, and the predictors of complete recanalization are age up to 50 years and isolated thrombosis of the superior sagittal sinus [55].

Conclusion

Thus, CVT is an important cause of ICH, especially in young patients. For the timely diagnosis of CVT, it is necessary to take into account the RF, the peculiarities of the clinical picture and conduct multimodal neuroangio imaging. The clinical picture and course of CVT is extremely variable: many factors determine the manifestations of the disease, ranging from headache to dislocation syndrome or status epilepticus. Timely parenteral administration of anticoagulants with the advantage of LMWH is an essential element of CVT therapy, including in the presence of hemorrhagic manifestations. In severe hemorrhagic CVT, the only way to save the patient's life may be endovascular treatment. Patients who have undergone thrombosis require secondary anticoagulant prophylaxis, the duration of which depends on the cause of the disease. With timely treatment and adequate prevention, CVT is characterized by a good short-term and long-term prognosis.

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Received/Reviewed/Accepted
1.10.2020/17.11.2020/20.11.2020

Conflict of Interest Statement

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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