Narrative Review

Medicine

OPEN

Pathophysiology, diagnosis and management of cerebral venous thrombosis

A comprehensive review

Redoy Ranjan, MS[a,b,*], Gie Ken-Dror, PhD[b], Pankaj Sharma, MD, PhD, FRCP[b,c]

Abstract

Cerebral venous thrombosis is a rare cause of stroke in young mostly female adults which is frequently overlooked due to its variable clinical and radiological presentation. This review summarizes current knowledge on it risk factors, management and outcome in adults and highlights areas for future research. Females are 3 times more commonly affected and are significantly younger than males. The presenting symptoms can range from headache to loss of consciousness. However, the often-nebulous nature of symptoms can make the diagnosis challenging. Magnetic resonance imaging with venography is often the diagnostic imaging of choice. While unfractionated or low molecular-weight heparin is the mainstay of treatment, endovascular intervention with thrombolysis or thrombectomy and decompressive craniectomy may be required depending on clinical status. Nevertheless, approximately 80% of patients have a good recovery but mortality rates of –5% to 10% are not uncommon. Diagnosing cerebral venous thrombosis can be challenging but with vigilance and expert care patients have the best chance of a good clinical outcome.

Abbreviations: CT = computed tomography, CVT = cerebral venous thrombosis, CTV = CT venography, DOAC = direct oral anticoagulants, DSA = digital subtraction angiography, ICH = intracranial hypertension, MRI = magnetic resonance imaging, MRV = magnetic resonance venography, SSS = superior sagittal sinus.

Keywords: cerebral venous thrombosis, CVT, diagnosis, outcome, treatment

1. Introduction

Cerebral venous thrombosis (CVT) is a relatively rare condition that comprises approximately 0.5% to 1% of all stroke and is associated with an increased mortality rate.[1,2] It is a multifactorial disease, with variable symptoms making immediate diagnosis challenging.[2–4] The clinical presentation can be divided into 3 subcategories depending on the duration of onset: Acute ≤ 48 hours; Subacute > 48 hours to ≤ 30 days; Chronic ≥ 1-month forms[5] of which the subacute presentation is the most common form which constituting almost half of all cases, while the chronic form is less frequent.[5–8] Over the last few decades, the incidence of CVT has increased 10-fold due to better recognition and improved availability of advanced imaging modalities.[4–6] Moreover, the increased incidence is found among younger adults, especially reproductive-age women (female-to-male ratio was 3:1) in low-income countries, probably associated with pregnancy, puerperium, and oral contraceptives.[5,9–14] The risk factors for cerebral venous thrombosis are presented in Table 1.

The International Study on Cerebral Vein and Dural Sinus Thrombosis documented the occurrence of CVT in different venous sinuses: superior sagittal sinus (62%), transverse sinus (41–45%), straight sinus (18%), cortical veins (17.1%), jugular veins (12%), a vein of Galen, and internal cerebral vein (11%) (Fig. 1).[5] Furthermore, in recent studies authors also reported higher incidence of superior sagittal sinus (SSS) involvement 65%,[8] 51%,[37] and 45%[38] cases and transverse sinus was 60.5%,[8] 56%,[37] and 62%[38] patients. Authors also reported multiple venous sinus involvement in 71.2%,[8] and 46%[37] cases. The superficial venous circulation has numerous anastomoses and collateral circulation with variation in the course, which may explain the better prognosis of CVT involving the superficial venous system.[7–12] However, the deep venous system is usually consistent and visible at angiography; thus, thrombosis in the deep venous sinus can be diagnosed easily.[2–6,8–12]

We searched electronic databases, especially MEDLINE, EMBASE, CINAHL, and Web of Science collection up to July 2023 to search literature on the epidemiology, clinical features, diagnostic modalities, treatment protocols, and prognosis of cerebral venous thrombosis utilizing medical subject headings terms and Boolean operators to combine search terms. This

The authors have no funding and conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

[a] Department of Cardiac Surgery, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, [b] Institute of Cardiovascular Research, Royal Holloway University of London (ICR2UL), Egham Hill, Greater London, United Kingdom, [c] Department of Clinical Neurology, Imperial College London Healthcare NHS Trust, London, United Kingdom.

** Correspondence: Redoy Ranjan, Department of Cardiac Surgery, Bangabandhu Sheikh Mujib Medical University, Dhaka-1000, Bangladesh (e-mail: redoy_ranjan@yahoo.com).*

Copyright © 2023 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Ranjan R, Ken-Dror G, Sharma P. Pathophysiology, diagnosis and management of cerebral venous thrombosis: A comprehensive review. Medicine 2023;102:48(e36366).

Received: 11 October 2023 / Received in final form: 3 November 2023 / Accepted: 8 November 2023

http://dx.doi.org/10.1097/MD.0000000000036366

literature review aims to summarize the current knowledge on the epidemiology, pathophysiology and management of adult CVT.

Table 1

Risk factors of cerebral venous thrombosis.[5,12,14–36]

Prothrombotic states	Infection (12%)[5,14,26–28]
Hereditary conditions (34–41%)[5,12,14–18]	1. ENT and face infection (8.2–11%)
1. Prothrombin G20210A mutation (9–21%)	2. Systemic infectious diseases (4.3%)
2. Factor V Leiden mutation (9–13%)	3. Meningitis (2.1%)
3. MTHFR mutation (4.5%)	Mechanical causes[5,12,27–30]
4. Antithrombin deficiency (3%)	1. Lumbar puncture (1.9%)
5. Protein C deficiency (2–5%)	2. Head trauma (1.1%)
6. Protein S deficiency (2–3%)	3. Jugular vein catheterization (1%)
Acquired conditions (15.7%)[5,12,14,17–19]	4. Neurosurgical procedures (0.6%)
1. Pregnancy and puerperium (11–59%)	5. Trauma to cerebral sinuses
2. Antiphospholipid antibody syndrome (6–17%)	
3. Nephrotic syndrome (0.6–1%)	Malignancy (7.4%)[30–32]
4. Hyperhomocysteinemia	1. CNS tumors
	2. Systemic malignancies
	3. Myeloproliferative neoplasms
Haematology[5,12,14,20]	Drugs[5,12,14,30,33,34]
1. Severe anemia (9–27%)	1. Oral contraceptives (54–71%)
2. Polycythaemia	2. Hormone replacement therapy (4.3%)
3. Thrombotic thrombocytopenic purpura	3. Cytotoxic drugs (0.8%)
4. Heparin-induced thrombocytopenia	4. Intravenous immunoglobulin
	5. Steroids
Autoimmune and Inflammatory diseases[5,14,21–25]	Miscellaneous[12,14,30,35,36]
1. Inflammatory bowel disease (1.6–3%)	1. Obesity (23%)
2. Systemic lupus erythematosus (1%)	2. Dehydration (1.9%)
3. Behçet's disease (1%)	3. Dural A-V fistulae (1.6%)
4. Sarcoidosis (<1%)	4. Arteriovenous malformations (0.2%)
5. Thyrotoxicosis (1.7%)	5. No identifiable reasons (12.5%)
6. COVID-19 vaccine (<1%)	

Methylenetetrahydrofolate Reductase (MTHFR); ENT- Ear, Nose, and Throat.
Percentage (%) denotes the prevalence of the risk factors. The data expressed in the table were obtained from original research works and review literature.[5,12,14–36]

2. Pathophysiology

The entire pathophysiology has not been experimentally proven, but CVT may present as either of the following 4 distinct clinical syndromes: Intracranial hypertension; Focal neurological syndrome; Diffuse encephalopathy, and; Cavernous sinus syndrome.[2–4,6] The pathophysiological changes in CVT evolve slowly over hours or days and can progress sufficiently for weeks to cause signs and symptoms of CVT. Cerebral vein thrombosis increases venous pressure and reduces capillary perfusion pressure, leading to a rise in cerebral blood volume; ultimately, patients develop intracranial hypertension.[8–12] However, cortical collateral circulation is engaged, but intracranial hypertension subsequently leads to disruption of the blood-brain barrier and the development of vasogenic edema. This pathophysiology causes failure of the sodium-potassium ATPase dependent pump, an indirect regulator of intracellular water volume results in cytotoxic edema development.[3,10–14,37] Figure 2 depicts the pathophysiological changes in CVT.

Superficial cortical veins drain into the SSS against the blood flow within the sinus, resulting in blood turbulence which is further aggravated by the existing fibrous septa at the inferior angle of the sinus. This is the most acceptable explanation of the higher prevalence of thrombosis in SSS.[3–6,14] Furthermore, in addition to draining the cerebral hemisphere, the SSS and other dural venous sinuses also drain blood from diploic, meningeal and emissary veins. This explains the relationship between the occurrence of CVT following infective pathologies in their draining areas, For example, cavernous sinus thrombosis in facial infections, lateral sinus thrombosis in chronic otitis media and sagittal sinus thrombosis in scalp infections.[3,12–14,37]

The dural venous sinuses contain most of the arachnoid villi and granulations, especially in the SSS, responsible for cerebrospinal fluid absorption. So, thrombosis of the dural venous sinus causes blockage of villi and granulations and prevention of cerebrospinal fluid absorption, which eventually leads to intracranial hypertension and papilloedema provoked coma and mortality.[14,37–40]

3. Clinical presentations

The clinical presentation of CVT is often vague and largely depends on the site and extent of the lesion, age of onset, and

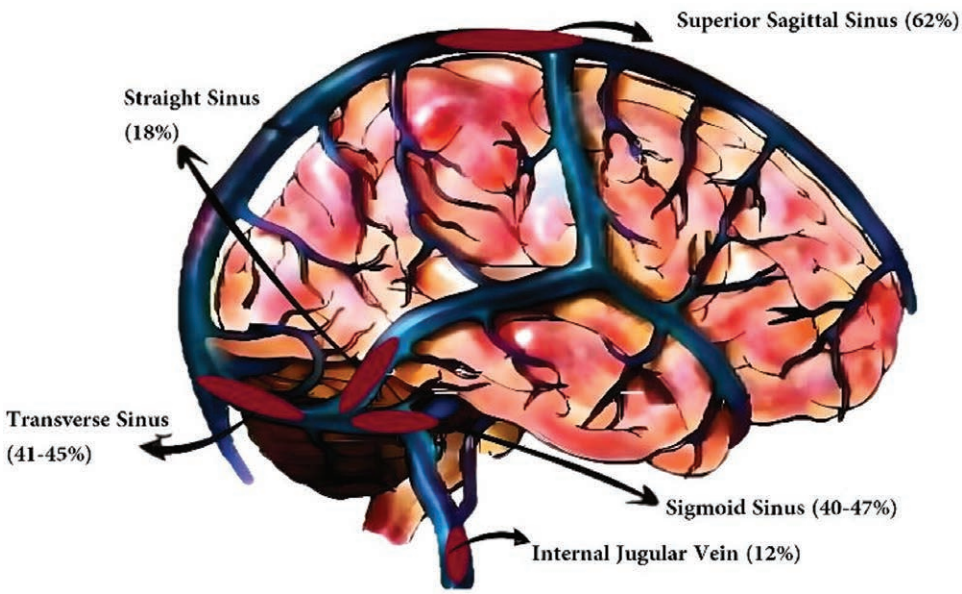

Figure 1. Anatomy of Dural venous sinus with distribution of CVT in percentage (Ferro et al[5]). CVT = cerebral venous thrombosis.

associated comorbidities.[8–12] CVT patients may present with a constellation of symptoms, which broadly categorize either as isolated such as intracranial hypertension (ICH) and a focal brain lesion, or a combination of both based on the extent of ICH and brain parenchymal lesion.[15,16,37–40] However, about 40% of patients present with acute stroke-like syndrome within 48 hours of onset, and acute or subacute headache is the most common clinical presentation of CVT, often with a normal neurological finding. The most common clinical presentations are signs of intracranial hypertension and parenchymal drainage: headache (70–90%), seizure (30–40%), papilloedema (30–60%), focal neurological deficits (30–50%), aphasia (15–20%), altered level of consciousness (15–25%), coma (5–15%), and rarely movement disorder.[16–18]

The clinical symptoms corresponding to each type of dural venous sinus thrombosis or overviewed in Table 2. Physicians should be alert for CVT if a patient presents with the following potential symptoms:[16,18,29,42,43]

1. Headache in a young woman who recently started taking oral contraceptive pills or in a woman of the third trimester of pregnancy.
2. Persistent atypical headache in young adults.
3. Stroke of unknown etiology.
4. Haemorrhagic infarcts with abnormal cerebral vasculature or multiple hemorrhagic infarcts.
5. Eye symptoms following a recent attack of sinusitis.
6. New onset of seizures and focal neurological signs.
7. Altered level of consciousness.

4. Diagnosis

4.1. Overview of diagnostic modalities

The diagnosis of CVT is based on a high degree of clinical suspicion confirmed by either computed tomography (CT) or magnetic resonance imaging (MRI) with contrast-enhanced venography to demonstrate venous sinus thrombosis.[5,14,37–40] The radiological findings of CVT can be direct visualization of venous sinus without blood flow; or maybe ischemic changes associated with the venous outflow obstruction.[3,11,18] There is no specific laboratory test that can positively exclude CVT in the acute phase of the disease, and blood tests are performed to evaluate coagulation abnormalities like an underlying hypercoagulable state, systemic infection, or an inflammatory process. Furthermore, screening for potential prothrombotic conditions that may predispose to CVT is recommended.[6,8,12,27–30] Details of the radiological findings of adult CVT are illustrated in Table 3.

4.2. CT scan and CT venography

Prompt investigation with an unenhanced CT scan of the brain is the noninvasive imaging method of choice when CVT

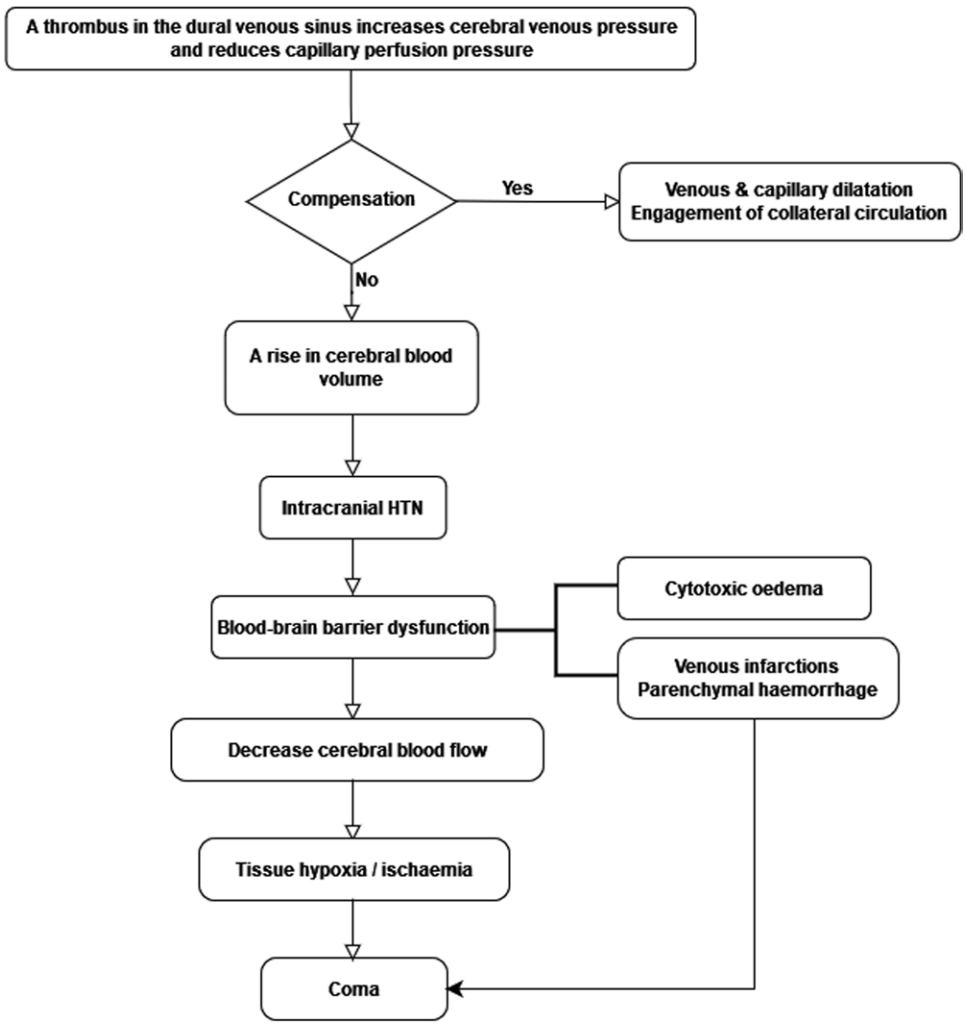

Figure 2. The flowchart illustrates the pathophysiological changes in CVT. The data for constructing this flowchart were obtained from the original studies evaluating the adult CVT population.[2,3,10,11,14,37] CVT = cerebral venous thrombosis.

Table 2

Clinical presentations according to the affected dural venous sinuses.[2–6,11–14,18,29,30,37–39,41–43]

Site of CVT	Clinical presentation
Superior sagittal sinus (39–62%)	Cranial nerve palsies and intracranial hypertension lead to common symptoms: 1.Headache, nausea, vomiting 2.Blurred vision, occasionally loss of vision 3.Seizures 4.Aphasia, hemianopia 5.Hemisensory loss and/or hemiparesis 6.Rarely, isolated psychiatric symptoms
Transverse sinus (44–73%)	Isolated TS involvement without infarction: 1.Asymptomatic or 2.Headache, seizures Left TS involvement with venous infarction: Aphasia. Involvement of contiguous sinuses: 1.Intracranial hypertension 2.Cranial nerve IX–XXI palsies
Sigmoid sinus (40–47%)	1.Pain in the mastoid region 2.Cranial nerve VI–VIII palsies
Deep venous system (10.9%)	1.Diminished level of consciousness, or coma 2.Diffuse encephalopathy 3.Bilateral or fluctuating motor deficits
Cortical veins (3.7–17.1%)	Focal neurological deficits and seizures
Cavernous sinus (1.3–1.7%)	Headache, fever and ocular signs (ocular pain, chemosis, proptosis, ocular nerve palsy)
Inferior sagittal sinus	Motor deficits, seizures
Straight sinus	Motor deficits, mental status changes
Internal jugular vein	Neck pain, tinnitus, and cranial nerve palsies

The data for the construction of this table were obtained from reviews and original studies that evaluate clinical presentation and Dural venous sinuses involvement in the adult CVT population.[2–6,11–14,18,29,30,37–39,41–43]

CVT = cerebral venous thrombosis, TS = transverse sinus.

is clinically suspected. Acute CVT may demonstrate an elongated hyper-attenuating clot known as a "cord sign," which may persist for 2 weeks and then become isodense to brain parenchyma.[18,40] Generally, a non-contrast CT scan produces an indirect sign that includes the early and late signs of venous ischemia known as sulcal effacement and diffuse parenchymal edema, ventricular effacement, or diminished differentiation between gray and white matter. However, a cerebral infarct not following a typical arterial territory, involving only a subcortical area, multiple unilateral and bilateral lesions with or without hemorrhagic changes should raise a concern about the venous origin.[3,5,12] Further, a cerebral infarct comprising multiple arterial territories should raise concerns about potential venous pathology, particularly CVT.[5,12,27]

CT venography (CTV) is particularly useful in acute and emergency cases and can be utilized as the initial test for assessing the patency of the deep and cortical venous system in a comatose or uncooperative patient.[8–11,18] The most frequent findings on CTV is vascular filling defects and an "empty delta sign" when the superior sagittal sinus is involved.[44,45] However, an artifact from dense cortical bones significantly reduces the diagnostic accuracy of the CT venography, and also, arachnoid granulations may protrude into the venous sinuses, mimicking filling defects by thrombus, which is another potential disadvantage of CTV imaging.[44–47] In infants, a false dense clot sign may result from the relatively high density of the blood in the sagittal sinus, and a false, empty delta sign may cause hyperdense empyema.[5–10,48] Occasionally, engorged and dilated venous malformations produce a hyperdense lesion on unenhanced CT and demonstrate a characteristic linear enhancing focus converging on a single dilated vein known as "caput medusa" or "candelabra" appearance on CT venography.[3,5–12,18,44]

Table 3

At a glance merits and demerits of CT, MRI, and DSA techniques.[3,5,11,12,27,44–50]

Techniques	Traits	Description
CT Venography	Advantages	1.Good visualization of major venous sinuses 2.Simple, less time consuming, and less motion artifacts 3.Useful in claustrophobic patients, pacemaker, or defibrillator.
	Disadvantages	1.Ionizing radiation exposure 2.Diabetes, and CKD patients may develop contrast nephropathy. 3.Poor resolution for small parenchymal lesion.
	Sensitivity and specificity	1.CT and CTV has 95% sensitivity and 91% specificity. 2.Based on the lesion, overall accuracy is 90% to 100%
	Typical findings	1.Hyperdensity and lack of flow in thrombosed sinuses 2.Dense triangle sign, empty delta sign and Cord sign
MR Venography	Advantages	1.No radiation exposure and good delineation of brain parenchyma. 2.Identify both of cortical and deep venous thrombosis. 3.Early ischemic changes can be detected.
	Disadvantages	1.Time consuming, unavailability and produce motion artifacts. 2.Unavailable for claustrophobic patients, and pacemaker. 3.Risk of gadolinium-induced nephrogenic systemic fibrosis
	Sensitivity and specificity	1.Not known; however, MRV with echoplanar T2 susceptibility-weighted image are considered as the most sensitive sequences.
	Typical findings	1.≤1 wk: Isointense in T1 and hypointense in T2W images. 2.Up to 2 weeks: Hyperintense on T1 and T2W images 3.>2 wk: Variable appearances; Hypointense in GRE and SWI images; Hyperintensity in DWI enhancement venous wall, and lack of flow in thrombosed sinuses.
DSA	Advantages	1.Precise dynamic information on collateral venous system. 2.Only performed when planned for an endovascular intervention.
	Disadvantages	1.Invasive procedure with associated procedural risks. 2.Skilled person required. 3.Usually, unavailable outside of tertiary hospital.
	Sensitivity and specificity	1.Not clearly known
	Typical findings	1.Absence of sinus opacification. 2.Venous congestion with dilated cortical, scalp, and facial veins. 3.Reversal of the flow and enlarged collateral venous drainage.

AV = arteriovenous, CT = computed tomography, CKD = Chronic kidney disease, CVT = Cerebral venous thrombosis, CTV = CT venography, DSA = digital subtraction angiography, MRI = magnetic resonance imaging, MRV = magnetic resonance venography, TOF = time-of flight.

4.3. MRI and MR venography

Conventional T1 and T2 weighted MRI is more sensitive than an unenhanced CT scan to diagnose a case of CVT.[45–47] On standard sequences, the early signs include the absence of a typical venous flow pattern and abnormal signal within the dural

venous sinus. A brief description of the evolution of thrombus signal intensity caused by the paramagnetic effects of hemoglobin degradation products is provided in Table 3.

Magnetic resonance venography (MRV) is helpful in either acute or subacute and emergency or ambulatory cases and to confirm suspected cases of deep venous thrombosis where CT venography was inconclusive or normal.[5,7–12,40,44,45] Contrast-enhanced MRV offers improved visualization of the cerebral venous system and is unlikely to be affected by complex blood flow.[8,18,42] However, in MRI venography, aplasia and hypoplasia of the transverse sinus can be mistaken. There is also the chance of signal loss due to in-plane flow, and hyperintense

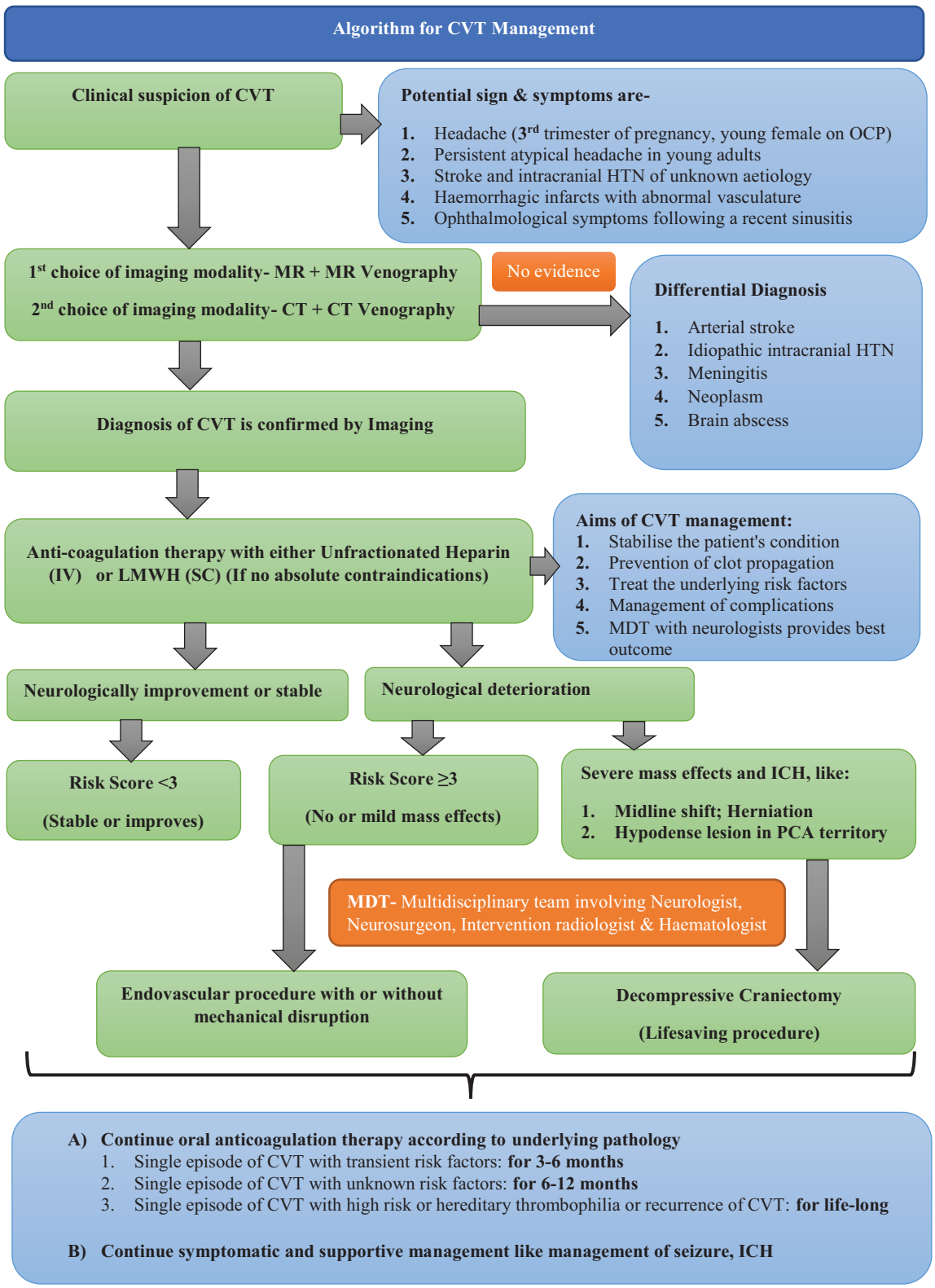

Figure 3. Algorithm of cerebral venous thrombosis management. The management algorithm of adult CVT was based on the published review literature and original studies that focus on the treatment outcome.[5,11,14,18,41,49–56] CVT = cerebral venous thrombosis.

thrombi can mimic patent sinus during time-of-flight angiography. Nonetheless, both MR venography and CT venography are adequate for CVT diagnosis, but MRV has higher diagnostic accuracy for the visualization of brain parenchymal lesions.[6,41–45]

4.4. Digital subtraction angiography (DSA)

Although DSA is considered a gold standard technique it usually only performed in the presence of either unclear CTV and MRV imaging or when endovascular intervention is planned because of its associated risk.[29,44–49] Generally, there are filling defects in the dural venous sinuses or cortical veins, delayed venous drainage, and dilated collateral circulation. There may also be an abrupt cutoff of cortical veins with surrounding tortuous and dilated "corkscrew" collateral circulation.[5,18,29] Furthermore, DSA can identify vascular aneurysm and dural arteriovenous fistula, which might cause the formation of a false "corkscrew" sign due to sluggish venous drainage and vascular congestion.[50] Nevertheless, DSA has a unique ability to measure venous pressure and pressure > 10 mm H_2O indicates a probability of parenchymal damage, which carries significant value for treatment outcome.[41,45]

5. Treatment and guidelines

5.1. Overview of treatment protocols

Prompt diagnosis to identify and treat the associated factors, initiate anticoagulation therapy, and manage ICH should maximize the chance of a favorable outcome.[18,39,41] The management algorithm of CVT is illustrated in Figure 3.

5.2. Anticoagulation therapy

In 2011, American Heart Association-American Stroke Association guidelines proposed using full-dose unfractionated or low molecular weight heparin, followed by oral anticoagulant warfarin and acetazolamide.[11] Furthermore, in the absence of significantly powered evidence from anticoagulant therapy trials, European Stroke Organization guidelines from 2017 recommend using low molecular weight heparin except heparin-induced thrombocytopenia, or vaccine-induced immune thrombotic thrombocytopenia, decompressive craniectomy if ICH is present, and anticonvulsant medication in seizures.[18] However, neither European Stroke Organization nor American Heart Association-American Stroke Association guidelines suggested using glucocorticoids for raised intracranial pressure and cerebral edema.[11,18] The duration of oral anticoagulant treatment is usually between 3 and 12 months with a target international normalized ratio 2.0 to 3.0, but a longer duration may be required depending on the pathophysiology of CVT.[11,41,52] Despite the controversy, antiphospholipid antibody syndrome and genetic thrombophilia may require continued life-long anticoagulation therapy because of a higher recurrence rate, and the benefits outweigh the risk of bleeding.[11–14,41,51,52]

In a recent randomized control trial, Connor and colleagues[48] evaluated 114 children with CVT treated with rivaroxaban or standard anticoagulation therapy and observed favorable clinical outcomes with low risk of recurrence and fewer bleeding complications similar to other existing literature.[41,48–52] In another study, Ferro and coworkers[53] evaluated the safety and efficacy of dabigatran and warfarin in 120 patients from December 2016 to June 2018, with a follow-up of 25 weeks. This trial observed a low risk of recurrence and bleeding (about 1% and 3% in dabigatran and warfarin group, respectively), and recanalization rates were 60% and 67%, respectively, and recommended both dabigatran and warfarin safe and effective for preventing recurrent venous thrombosis in CVT.[53]

Furthermore, recent small non-randomized studies by Wasay et al[54] and Nguyen et al[55] also suggested that direct oral anticoagulants (DOACs), especially rivaroxaban and dabigatran, are safe and effective as warfarin in patients with CVT in reducing the bleeding risk and improving recanalisation rates. In addition to rivaroxaban and dabigatran, Lurkin and coworkers[56] also found the efficacy of apixaban appears encouraging in CVT management despite variability in timing and dose of DOACs, similar to other study findings.[57,58] The dosage of DOACs is variable ranging between 5 to 20 mg daily for rivaroxaban and 75 to 150 mg twice daily for dabigatran.[54–59] Despite inconsistency in dosing, in a recent systemic review, Bose and colleagues[60] observed the benefits of the DOACs over warfarin, including reduced dose adjustments and with no need to maintain a therapeutic international normalized ratio level similar to existing literature.[48,53–60] Although DOAC do not require dose adjustment, several published papers observed that measuring plasma DOAC concentration is helpful in managing anticoagulated patients.[61,62] Furthermore, clinicians and laboratory professionals should be aware that standard hemostatic parameters, especially the activity of antithrombin III, activated Protein C and S, and fibrinogen, may be affected by DOAC, which is why prothrombin time or activated partial thromboplastin time should not be performed as standalone tests to monitor the DOAC effect. The British Committee for Standards in Haematology recommended tests to assess DOAC effects are thrombin time and dilute thrombin time for dabigatran and anti-factor Xa activity for rivaroxaban, apixaban, and edoxaban.[61–63]

5.3. Endovascular intervention

In the late 1980s, endovascular treatment for CVT was first introduced. There are 2 distinct approaches; chemical thrombolysis and mechanical thrombectomy.[14] Although favorable results for both are shown in case series, mechanical thrombectomy demonstrated better outcomes than thrombolysis.[50–53,64] Use of mechanical thrombectomy is increasing, presumably because interventionalists use these techniques in ischemic stroke cases and have gained more experience.[41,49,64,65]

However, a recent RCT (Thrombolysis or anticoagulation for cerebral venous thrombosis; TO-ACT) trial by Coutinho and coworkers[66] showed that endovascular treatment with standard medical care carries no significant difference in improving the clinical outcome of a severe form of CVT patients in comparison to standard medical care only. Nevertheless, endovascular treatment approaches to thrombolysis and thrombectomy are promising in the presence of large venous infarctions, brain herniation or intracranial hypertension.[5,11,41,50–53,64–66]

6. Prognosis and consequences

The treatment outcome of CVT is usually favorable with around 57% to 86% of the patients making a complete recovery, and mortality between 5.5% and 18%.[5,7–11,45–49] However, approximately 6% to 10% of surviving patients have severe and permanent disability, and approximately 14% of patients require bed rest or hospital admission due to severe attacks of headaches.[5,18,67] To date, there is no conclusive relationship between disease severity and treatment outcome; however, the cause of death is generally due to transtentorial herniation, status epilepticus or medical complications such as sepsis and pulmonary embolism.[12,15–18,39,40,53] Several studies have presented potential predictors of poor outcome that include extreme age (infant and older age),[6,9,10] altered mental status, rapid deterioration of consciousness (GCS < 9 on admission), coma and ICH,[5,18,53] CNS infection,[26–29] malignancy,[30–32] thrombosis of the deep venous system,[53,64–67] and hyperglycemia on admission.[68]

Approximately 12%, 14%, and 10% of the patients suffer from recurrence, different venous thrombosis, and seizures, respectively.[37,67,69] Late seizures are more like to develop in those with a history of previous seizures, motor deficits, and supratentorial hemorrhagic lesions. Rarely intracranial hypertension might cause visual loss; thus, evaluation of the ophthalmological system should be performed in patients with papilloedema or altered vision.[5,27,37,53,65–70]

7. Conclusion

Cerebral venous sinus thrombosis is a rare but potentially fatal neurological condition that commonly affects young women of reproductive-age. It often remains underdiagnosed due to its nonspecific clinical presentation. A high degree of clinical suspicion is required as appropriate treatment at an early stage can improve the outcome. Low molecular weight heparin is recommended for acute treatment, while longer term treatment for 3 to 6 months is probably best undertaken with a direct oral anticoagulant.

Author contributions

Conceptualization: Redoy Ranjan, Gie Ken-Dror, Pankaj Sharma.
Data curation: Redoy Ranjan.
Resources: Redoy Ranjan, Pankaj Sharma.
Supervision: Gie Ken-Dror, Pankaj Sharma.
Validation: Redoy Ranjan, Gie Ken-Dror, Pankaj Sharma.
Visualization: Redoy Ranjan.
Writing – original draft: Redoy Ranjan.
Writing – review & editing: Redoy Ranjan, Gie Ken-Dror, Pankaj Sharma.

References

[1] Agnelli G, Verso M. Epidemiology of cerebral vein and sinus thrombosis. Front Neurol Neurosci. 2008;23:16–22.
[2] Piazza G. Cerebral venous thrombosis. Circulation. 2012;125:1704–9.
[3] Goyal G, Charan A, Singh R. Clinical presentation, neuroimaging findings, and predictors of brain parenchymal lesions in cerebral vein and dural sinus thrombosis: a retrospective study. Ann Indian Acad Neurol. 2018;21:203–8.
[4] Cotlarciuc I, Marjot T, Khan MS, et al. Towards the genetic basis of cerebral venous thrombosis-the BEAST consortium: a study protocol. BMJ Open. 2016;6:e012351.
[5] Ferro JM, Canhao P, Stam J, et al. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). Stroke. 2004;35:664–70.
[6] Bousser MG, Ferro JM. Cerebral venous thrombosis: an update. Lancet Neurol. 2007;6:162–70.
[7] Green M, Styles T, Russell T, et al. Non-genetic and genetic risk factors for adult cerebral venous thrombosis. Thromb Res. 2018;169:15–22.
[8] Sassi SB, Touati N, Baccouche H, et al. Cerebral venous thrombosis: a Tunisian monocenter study on 160 patients. Clin Appl Thromb Hemost. 2016;23:1005–9.
[9] Deveber G, Andrew M, Adams C, et al. Cerebral sinovenous thrombosis in children. N Engl J Med. 2001;345:417–23.
[10] Wasay M, Dai AI, Ansari M, et al. Cerebral venous sinus thrombosis in children: a multicenter cohort from the United States. J Child Neurol. 2008;23:26–31.
[11] Saposnik G, Barinagarrementeria F, Brown RD, et al. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42:1158–92.
[12] Dentali F, Poli D, Scoditti U, et al. Long-term outcomes of patients with cerebral vein thrombosis: a multicenter study. J Thromb Haemost. 2012;10:1297–302.
[13] Lanska DJ, Kryscio RJ. Risk factors for peripartum and postpartum stroke and intracranial venous thrombosis. Stroke. 2000;31:1274–82.
[14] Stam J. Sinus thrombosis should be treated with anticoagulation. Arch Neurol. 2008;65:984–5.
[15] Ken-Dror G, Cotlarciuc I, Martinelli I, et al. Genome-wide association study identifies first locus associated with susceptibility to cerebral venous thrombosis. Ann Neurol. 2021;90:777–88.
[16] Pai N, Ghosh K, Shetty S. Hereditary thrombophilia in cerebral venous thrombosis: a study from India. Blood Coagul Fibrinolysis. 2013;24:540–3.
[17] Martinelli I, Battaglioli T, Pedotti P, et al. Hyperhomocysteinemia in cerebral vein thrombosis. Blood. 2003;102:1363–6.
[18] Ferro JM, Bousser M-G, Canhão P, et al. European stroke organization guideline for the diagnosis and treatment of cerebral venous thrombosis- endorsed by the European Academy of Neurology. Eur J Neurol. 2017;24:1203–13.
[19] Xu H, Chen K, Lin D, et al. Cerebral venous sinus thrombosis in adult nephrotic syndrome. Clin Nephrol. 2010;74:144–9.
[20] Coutinho JM, Zuurbier SM, Gaartman AE, et al. Association between anaemia and cerebral venous thrombosis: case-control study. Stroke. 2015;46:2735–40.
[21] Cognat E, Crassard I, Denier C, et al. Cerebral venous thrombosis in inflammatory bowel diseases: eight cases and literature review. Int J Stroke. 2011;6:487–92.
[22] Aguiar de SD, Mestre T, Ferro JM. Cerebral venous thrombosis in Behçet's disease: a systematic review. J Neurol. 2011;258:719–27.
[23] Debeij J, Dekkers OM, Asvold BO, et al. Increased levels of free thyroxine and risk of venous thrombosis in a large population based prospective study. J Thromb Haemost. 2012;10:1539–46.
[24] Wang L, Chen H, Zhang Y, et al. Clinical characteristics of cerebral venous sinus thrombosis in patients with systemic lupus erythematosus: a single-centre experience in China. J Immunol Res. 2015;2015:540738.
[25] Sánchez van Kammen M, Aguiar de Sousa D, Poli S, et al. Characteristics and outcomes of patients with cerebral venous sinus thrombosis in SARS-CoV-2 vaccine–induced immune thrombotic thrombocytopenia. JAMA Neurol. 2021;78:1314–23.
[26] Vergouwen MD, Schut ES, Troost D, et al. Diffuse cerebral intravascular coagulation and cerebral infarction in pneumococcal meningitis. Neurocrit Care. 2010;13:217–27.
[27] Zuurbier SM, Coutinho JM, Stam J, et al. Clinical outcome of anticoagulant treatment in head or neck infection-associated cerebral venous thrombosis. Stroke. 2016;47:1271–7.
[28] Ghuman MS, Salunke P, Sahoo SK, et al. Cerebral venous sinus thrombosis in closed head trauma: a call to look beyond fractures and hematomas! J Emerg Trauma Shock. 2016;9:37–8.
[29] Coutinho JM, Gerritsma JJ, Zuurbier SM, et al. Isolated cortical vein thrombosis: systematic review of case reports and case series. Stroke. 2014;45:1836–8.
[30] Silvis SM, Middeldorp S, Zuurbier SM, et al. Risk factors for cerebral venous thrombosis. Semin Thromb Hemost. 2016;42:622–31.
[31] Dentali F, Ageno W, Rumi E, et al. Cerebral venous thrombosis and myeloproliferative neoplasms: results from two large databases. Thromb Res. 2014;134:41–3.
[32] Zuurbier SM, Lauw MN, Coutinho JM, et al. Clinical course of cerebral venous thrombosis in adult acute lymphoblastic leukemia. J Stroke Cerebrovasc Dis. 2015;24:1679–84.
[33] Dentali F, Crowther M, Ageno W. Thrombophilic abnormalities, oral contraceptives, and risk of cerebral vein thrombosis: a meta-analysis. Blood. 2006;107:2766–73.
[34] Vander T, Medvedovsky M, Shelef I, et al. Postmenopausal HRT is not independent risk factor for Dural sinus thrombosis. Eur J Neurol. 2004;11:569–71.
[35] Zuurbier SM, Arnold M, Middeldorp S, et al. Risk of cerebral venous thrombosis in obese women. JAMA Neurol. 2016;73:579–84.
[36] Christiansen SC, Lijfering WM, Naess IA, et al. The relationship between body mass index, activated protein C resistance and risk of venous thrombosis. J Thromb Haemost. 2012;10:1761–7.
[37] Sidhom Y, Mansour M, Messelmani M, et al. Cerebral venous thrombosis: clinical features, risk factors, and long-term outcome in a Tunisian cohort. J Stroke Cerebrovasc Dis. 2014;23:1291–5.
[38] Uzar E, Ekici F, Acar A, et al. Cerebral venous sinus thrombosis: an analyses of 47 patients. Eur Rev Med Pharmacol Sci. 2012;16:1499–505.
[39] Canhao P, Ferro JM, Lindgren AG, et al. Causes and predictors of death in cerebral venous thrombosis. Stroke. 2005;36:1720–5.
[40] Wasay M, Bakshi R, Bobustuc G, et al. Cerebral venous thrombosis: analysis of a multicenter cohort from the United States. J Stroke Cerebrovasc Dis. 2008;17:49–54.
[41] Einhäupl K, Stam J, Bousser MG, et al. EFNS guideline on the treatment of cerebral venous and sinus thrombosis in adult patients. Eur J Neurol. 2010;17:1229–35.

[42] Tentschert S, Wimmer R, Greisenegger S, et al. Headache at stroke onset in 2196 patients with ischemic stroke or transient ischemic attack. Stroke. 2005;36:e1–3.
[43] Lindgren E, Silvis SM, Hiltunen S, et al. Acute symptomatic seizures in cerebral venous thrombosis. Neurology. 2020;95:e1706–15.
[44] Qu H, Yang M. Early imaging characteristics of 62 cases of cerebral venous sinus thrombosis. Exp Ther Med. 2013;5:233–6.
[45] Leach JL, Fortuna RB, Jones BV, et al. Imaging of cerebral venous thrombosis: current techniques, spectrum of findings, and diagnostic pitfalls. Radiographics. 2006;26:S19–41; discussion S42.
[46] Khandelwal N, Agarwal A, Kochhar R, et al. Comparison of CT venography with MR venography in cerebral sinovenous thrombosis. AJR Am J Roentgenol. 2006;187:1637–43.
[47] Pond JB, Suss RA, Scott HD, et al. CT angiography of the cerebral venous system: anatomic structure, pathologic features, and pitfalls. Radiographics. 2015;35:498e9.
[48] Connor P, Sánchez van Kammen M, Lensing AWA, et al. Safety and efficacy of rivaroxaban in pediatric cerebral venous thrombosis (EINSTEIN-Jr CVT). Blood Adv. 2020;4:6250–8.
[49] Siddiqui FM, Dandapat S, Banerjee C, et al. Mechanical thrombectomy in cerebral venous thrombosis: systematic review of 185 cases. Stroke. 2015;46:1263–8.
[50] Conforto AB, Nader SN, Puglia Junior P, et al. Dural arteriovenous fistula and cerebral venous thrombosis. Arq Neuropsiquiatr. 2015;73:548.
[51] Coutinho J, de Bruijn SF, Deveber G, et al. Anticoagulation for cerebral venous sinus thrombosis. Cochrane Database Syst Rev. 2011;8:CD002005.
[52] Miranda B, Aaron S, Arauz A, et al. The benefit of extending oral anti coagulation treatment (EXCOA) after acute cerebral vein thrombosis (CVT): EXCOA-CVT cluster randomized trial protocol. Int J Stroke. 2018;13:771–4.
[53] Ferro JM, Coutinho JM, Dentali F, et al. Safety and efficacy of dabigatran etexilate vs dose-adjusted warfarin in patients with cerebral venous thrombosis: a randomized clinical trial. JAMA Neurol. 2019;76:1457–65.
[54] Wasay M, Khan M, Rajput HM, et al. New oral anticoagulants versus warfarin for cerebral venous thrombosis: a multi-center, observational study. J Stroke. 2019;21:220–3.
[55] Nguyen TH, Ngo TM, Phan BV, et al. The novel oral anticoagulants (NOACs) for the treatment of cerebral venous thrombosis: a case study of 32 vietnamese patients. J Stroke Med. 2021;4:105–10.
[56] Lurkin A, Derex L, Fambrini A, et al. Direct oral anticoagulants for the treatment of cerebral venous thrombosis. Cerebrovasc Dis. 2019;48:32–7.
[57] Powell M, Tremolet de Villers K, Schwarz K, et al. A single-center retrospective evaluation of the use of oral factor Xa inhibitors in patients with cerebral venous thrombosis. Ann Pharmacother. 2021;55:286–93.
[58] Hsu A, Mistry H, Lala N, et al. Preliminary findings regarding the use of direct oral anticoagulants in cerebral venous thrombosis. Clin Neurol Neurosurg. 2020;198:106204.
[59] Esmaeili S, Abolmaali M, Aarabi S, et al. Rivaroxaban for the treatment of cerebral venous thrombosis. BMC Neurol. 2021;21:73.
[60] Bose G, Graveline J, Yogendrakumar V, et al. Direct oral anticoagulants in treatment of cerebral venous thrombosis: a systematic review. BMJ Open. 2021;11:e040212.
[61] Baglin T, Keeling D, Kitchen S, et al. British committee for standards in haematology effects on routine coagulation screens and assessment of anticoagulant intensity in patients taking oral dabigatran or rivaroxaban: guidance from the British Committee for Standards in Haematology. Br J Haematol. 2012;159:427–9.
[62] Tripodi A, Ageno W, Ciaccio M, et al. Position Paper on laboratory testing for patients on direct oral anticoagulants a consensus document from the SISET, FCSA, SIBioC, and SIPMeL. Blood Transfus. 2018;16:462–70.
[63] Kitchen S, Gray E, Mackie I, et al. BCSH committee measurement of non-coumarin anticoagulants and their effects on tests of haemostasis: guidance from the British Committee for Standards in Haematology. Br J Haematol. 2014;166:830–41.
[64] Ilyas A, Chen C-J, Raper DM, et al. Endovascular mechanical thrombectomy for cerebral venous sinus thrombosis: a systematic review. J Neurointerv Surg. 2017;9:1086–92.
[65] Li G, Zeng X, Hussain M, et al. Safety and validity of mechanical thrombectomy and thrombolysis on severe cerebral venous sinus thrombosis. Neurosurgery. 2013;72:730–8; discussion 730.
[66] Coutinho JM, Zuurbier SM, Bousser MG, et al. Effect of endovascular treatment with medical management vs standard care on severe cerebral venous thrombosis: the TO-ACT randomized clinical trial. JAMA Neurol. 2020;77:966–73.
[67] Koopman K, Uyttenboogaart M, Vroomen PC, et al. Long-term sequelae after cerebral venous thrombosis in functionally independent patients. J Stroke Cerebrovasc Dis. 2009;18:198–202.
[68] Zuurbier SM, Hiltunen S, Tatlisumak T, et al. Admission hyperglycemia and clinical outcome in cerebral venous thrombosis. Stroke. 2016;47:390–6.
[69] Palazzo P, Agius P, Ingrand P, et al. Venous thrombotic recurrence after cerebral venous thrombosis: a long-term follow-up study. Stroke. 2017;48:321–6.
[70] Hiltunen S, Putaala J, Haapaniemi E, et al. Long-term outcome after cerebral venous thrombosis: analysis of functional and vocational outcome, residual symptoms, and adverse events in 161 patients. J Neurol. 2016;263:477–84.