

## supplemental material

Cerebral venous sinus thrombosis (CVST) is a particular type of cerebrovascular disease, characterized by increased intracranial pressure due to impaired cerebral venous drainage and absorption of cerebrospinal fluid. The incidence of CVST is 2-5/10000000/year, accounting for 0.5%-1% of all stroke<sup>1-9</sup>. Recently, the incidence of CVST has been rising with the advent of diagnostic techniques. Two studies in Iran have reported CVST affects 12.3-13.49/10000000/year<sup>3,10</sup>, and another study in Saudi Arabia has shown that CVST affects 70/10000000/year<sup>11</sup>. Moreover, the incidence of CVST has also been increasing in European and America, approximately 13.2-15.7/10000000/year<sup>12,13</sup>. CVST occurs in neonates and juveniles with a frequency of 6.7/10000000/year<sup>1,14,15</sup>. Internationally, ISCVT has been reported 487 of 624 cases occur in patients < 50 years-old<sup>16</sup>. During pregnancy, the incidence of CVST is 100/10000000, accounting for 5%-20% of all CVST<sup>4</sup>. The epidemiological data of CVST in China is scarce. Nevertheless, CVST is not uncommon in China, especially in women taking oral contraceptives or in the perinatal period. CVST can affect superficial cerebral veins, deep cerebral veins, or dural venous sinuses. The isolated thrombosis of superficial cerebral veins is rare. The involvement of superficial veins, for the most part, is caused by the thrombosis of dural venous sinuses. The thrombosis of deep cerebral veins usually occurs in the internal cerebral vein and vein of Galen. About 60% of patients with CVST involve multiple dural venous sinuses, with the superior sagittal sinus the most frequently affected. As there are multiple anatomical anastomoses between cerebral veins and dural venous sinuses, clinical manifestations vary from an asymptomatic state to death, depending on the site of thrombosis and collateral circulation.

Chinese stroke association commissioned the authors of the current guideline to review literatures in recent years, reach a consensus with domestic experts of neurology, and make the following recommendations. The intended audiences of this guideline are physicians of neurology and other related disciplines, providing references for the clinical management of CVST in China. As the low incidence of

CVST, it is difficult to perform large randomized controlled trials. Most of the evidence is based on the retrospective studies or case reports. The level of evidence is relatively low.

### **Part 1. Diagnostic Evaluation**

CVST can be acute (less than 48 hours), subacute (48 hours to 30 days) or chronic (more than 30 days) onset, with the latter two more common. CVST not only increases the pressure of venules and capillaries directly, but also increases intracranial pressure by reducing the absorption of cerebrospinal fluid (CSF), resulting in the decrease of cerebral artery perfusion, destruction of blood-brain barrier (BBB), and ischemic stroke or cerebral parenchymal hemorrhage<sup>17, 18</sup>. Therefore, the symptoms and signs of CVST mainly depend on the location, nature, extent of venous (sinus) thrombosis and the degree of secondary brain damage and so on. In addition to cavernous sinus thrombosis, the clinical manifestations of CVST are mostly lack of specificity<sup>19, 20</sup>.

### **History and Clinical Manifestations**

#### **1. Medical History**

Detailed medical history inquiry should include the characteristics of onset, the course of disease development, the related risk factors and the precipitating factors. Risk factors for CVST are suppurative infection or non-specific inflammation in the head and face, the presence of hypercoagulable state/blood stasis/vascular wall injury, such as pregnancy and puerperium, oral contraception, cancer history, eclampsia, etc. Most of the initial symptoms of CVST are headache, vomiting and visual impairment. Attention should be paid to the nature, location and evolution of headache (most of which are localized or diffuse headaches with persistent aggravation), symptoms of increased intracranial pressure (nausea and vomiting), and deterioration of visual acuity in patients. In those with unconsciousness and epilepsy at admission, medical history can be collected through their family members or peers. Chief complaint of some particular symptoms, such as pulsatile tinnitus and cognitive impairment, can easily lead to misdiagnosis.

## 2. Physical Examination

Detailed physical examination of the nervous system is very important, especially the visual acuity and fundus examination. CVST has many common clinical manifestations, and different locations of thrombosis have their own features. Detailed neurological examination contributes to the diagnosis of CVST and involved sites.

### 1) Increased Intracranial Pressure and Brain Damage

Intracranial hypertension is usually presented as headache, visual impairment and papillary edema. Headache is the most common symptom and is present in nearly 90% of patients with CVST. It is typically described as progressive localized or diffuse headache, which is not directly associated with the location of thrombosis. Headache may exist in isolation or subsequently develop other neurological symptoms and signs. About 10% of patients present with thunderclap headache<sup>21-23</sup>. In those with thrombophilia, thrombosis can cause stenosis or occlusion of one or both transverse or sigmoid sinuses, which reduces the absorption of CSF and mimics "benign intracranial hypertension syndrome"<sup>24</sup>. Although it is unclear whether venous sinus stenosis is the cause or the result of intracranial hypertension, most of these patients present with obvious headache, visual impairment, optic papillary edema and pulsatile tinnitus. Reducing intracranial pressure through venous sinus stenting can significantly improve the clinical manifestations in some individuals<sup>25, 26</sup>. About 20% of patients present with unconsciousness at admission due to increased intracranial pressure. Coma at admission is a strong predictor of poor prognosis<sup>16, 27</sup>. Cognitive impairment occurs in more than 30% of patients, especially in those with thrombosis in deep cerebral venous system or with persistent brain parenchymal damage<sup>28</sup>.

### 2) Focal Brain Damage and Seizures

Focal neurological deficit is common in CVST, affecting 40%-60% of patients. It may involve unilateral or bilateral hemispheres, or alternately involve the left and right hemisphere. The symptoms include central motor disorder, sensory loss, aphasia or hemianopia. Seizures occurs in about 40% of patients with CVST and in 76% of patients in perinatal period, which is more common than arterial stroke. Seizures may

occur at different stages of CVST, from a few weeks to months or years after symptoms onset<sup>16, 29</sup>. Focal or generalized seizures can be the sole manifestation of CVST, especially in isolated cortical vein thrombosis.

### 3) Dural Arteriovenous Fistula

CVST usually coexists with dural arteriovenous fistula (DAVF), with a frequency of 39%. The thrombus is frequently located near the DAVF or downstream of the drainage vein. The return of blood flow is mostly through cortical vein. DAVF manifests as headache, pulsating tinnitus and intracranial hemorrhage. The fistula is usually closed after venous (sinus) are recanalized<sup>9, 30, 31</sup>. However, it may still exist near the thrombus after the blood flow of has partially or completely recovered. It is generally believed that CVST-induced venous (sinus) hypertension promotes the physiological arteriovenous bypass of dural meninges, leading to pathological arteriovenous shunt, angiogenesis, and finally fistula<sup>32-34</sup>.

### 4) Different Locations of Thrombosis

According to the location of thrombosis, superior sagittal sinus is the most frequently affected (<60%), followed by transverse sinus, sigmoid sinus and jugular vein (<40%), straight sinus (<18%), cortical vein (Labbe, Trolard and other anastomotic veins, <6%), and deep cerebral vein (internal cerebral vein, Galen vein, etc., <10%)<sup>35-38</sup>. CVST may involve multiple veins (sinuses) simultaneously. The clinical manifestations of CVST are usually nonspecific except for cavernous sinus thrombosis.

Isolated cortical vein thrombosis accounts for about 6% of CVST, with the anastomotic veins such as Labbe and Trolard frequently affected. The cortical vein thrombosis could be asymptomatic. However, subacute headache and focal neurological dysfunction (e.g. epilepsy, hemiplegia, hemianopia, etc.) without intracranial hypertension may occur, if focal cortical or subcortical edema, infarction or hemorrhage are formed. Thrombosis in the cortical vein may also progress to dural venous sinus and develop the relevant manifestation, which is easily misdiagnosed as tumors, vascular malformations and so on<sup>35, 39, 40</sup>.

Isolated deep cerebral vein thrombosis accounts for 10% of CVST, with the

internal cerebral veins and Galen veins most frequently affected. Because of reflux disorder in the deep venous system, edema or hemorrhage in bilateral thalamus may occur. Deep cerebral vein thrombosis usually coexists with cortical vein or dural venous sinus thrombosis. The clinical manifestations are various, mainly presenting as headache, unconsciousness, seizures and cognitive impairment<sup>36, 37, 41</sup>.

### **Recommendation**

1. Vigilance should be maintained for CVST. The possibility of CVST should be considered in patients presented with headache, papilledema or increased intracranial pressure with unknown cause. The screening for CVST is reasonable in patients presented with unexplained seizures (including eclampsia), focal brain injury, different levels of unconsciousness, cognitive disorders, psychosis, or dural arteriovenous fistula. (Class I, Level of Evidence C)

### **Auxiliary Examination**

#### **1. Laboratory Examination**

##### **1) Routine Blood Work**

A complete blood examination, including the blood routine, chemistry panel, measures of the prothrombin time, activated partial thromboplastin time, plasma protein, connective tissue disease or tumor-related indicators, are recommended for patients with suspected CVST. Although abnormality in these examinations cannot diagnose CVST directly, they may suggest an underlying hypercoagulable state, infection, or inflammation, all of which may contribute to the diagnosis of CVST<sup>9, 42</sup>.

##### **2) Risk Factors for Thrombophilia**

Screening for thrombophilia helps to determine the cause of CVST. The screening includes coagulation factor V Leiden gene mutation, prothrombin G20210A mutation, antithrombin deficiency, protein C and protein S deficiency, increased levels of coagulation factor VIII, antiphospholipid and Anticardiolipin antibodies, hyperhomocysteinemia, and so on. These examinations may contribute to identify the root cause, select the optimal treatment, and determine the prognosis in patients with undetermined etiology, recurrent CVST, or a family history of venous thrombosis<sup>9, 42-44</sup>. Until now, there is no study comparing the screening of the above risk factors

for thrombophilia in patients with suspected CVST<sup>44</sup>.

### 3) D-Dimer

D-dimer, a product of fibrin degradation, play an important role in diagnosis of deep vein thrombosis, pulmonary embolus, and CVST. In 2012, a meta-analysis showed that the average sensitivity and specificity of elevated serum D-dimer levels for the diagnosis of CVST were 93.9% and 89.7%, respectively<sup>45</sup>. The results of several studies on D-dimer level in patients with suspected CVST suggested that D-dimer level helps to diagnose CVST, with an average sensitivity of 92.4% (88.3%-95.3%), specificity of 86.1% (83.8%-88.2%) and a diagnostic value of 85.762 (39.711-185.21)<sup>46-51</sup>. However, it is still controversial whether a normal D-dimer level can completely exclude CVST. One study showed that the D-dimer level might not increase in CVST patients with isolated headache<sup>48, 52</sup> or with a long course of disease<sup>53</sup>. However, another meta-analysis showed that normal D-dimer level had a high predictive value in excluding CVST in patients with isolated headache<sup>51</sup>. Therefore, most of the current studies suggest that D-dimer can be used as an important indicator for the diagnosis of CVST.

### 4) Lumbar Puncture and Cerebrospinal Fluid Examination

Increased intracranial pressure is common in patients with CVST, accompanied by the increase of erythrocyte, white blood cell and protein level in CSF. However, these changes are not specific. CSF examination may help to determine the possible causes and guide treatment in patients with CVST caused by infection; Increased intracranial pressure may also provide valuable diagnostic clues for CVST in patients with acute headache<sup>9, 16, 42, 54</sup>.

#### **Recommendation**

1. Routine blood tests consisting of a complete blood count, chemistry panel, prothrombin time, activated partial thromboplastin time, plasma protein, and connective tissue disease or cancer markers are recommended in patients with suspected CVST. (Class I, Level of Evidence C)
2. Screening for potential prothrombotic factors (eg, antithrombin III, protein C, or protein S deficiency, factor V Leiden, prothrombin mutation, anticardiolipin

antibody, lupus anticoagulant) is recommended in patients with undetermined etiology, recurrent CVST, or a family history of venous thrombosis, to identify the root cause and select appropriate preventive and therapeutic strategies. (Class IIb, Level of Evidence C)

3. An elevated D-dimer level is considered to support the diagnosis of CVST, but a normal D-dimer level should not exclude CVST, especially in patients presented with isolated headache or chronic symptoms. (Class IIa, Level of Evidence B)
4. Lumbar puncture may identify increased intracranial pressure and underlying causes of CVST (eg, infections). (Class IIa, Level of Evidence C)

## **2. Imaging in the Diagnosis of CVST**

Over the past 2 decades, radiological imaging has played an increasingly important role in the diagnosis and management of CVST<sup>1</sup>. The imaging in the diagnosis of CVST usually depends on the combination of different image modalities: brain compute tomography (CT)、magnetic resonance imaging (MRI)、magnetic resonance venography (MRV)、CT venography (CTV) or digital subtraction angiography (DSA). In the evaluation of patients with acute, subacute headache or new-onset seizures, the diagnostic rate of CVST has gradually increased due to the wide application of MRI/MRV. At present, CT/CTV and MRI/MRV are commonly used non-invasive modalities in the diagnosis of CVST. An invasive DSA may be performed if the diagnosis of CVST is still undetermined or endovascular treatment is considered.

There are many potential pitfalls regarding the radiological diagnosis of CVST. First, it is difficult to exclude CVST by general imaging modalities due to the variation in venous anatomy<sup>55</sup>. Anatomic variants of normal venous anatomy may mimic CVST, including sinus atresia/stenosis/hypoplasia, asymmetrical sinus drainage, and normal sinus filling defects such as prominent arachnoid granulations or intrasinus septa. Second, the signal of venous thrombosis changes with time. Third, the slow blood flow in veins or sinuses may produce image artifacts similar to CVST.

### **1) Computed Tomography**

#### **(1) Plain Computed Tomography**

Thrombus presents as hyperdensity on plain CT<sup>56-62</sup>. In the acute/subacute phase, plain CT may indicate direct signs of CVST, including "Cord Sign" in the thrombosis of the transverse sinus, sigmoid sinus, Galen vein, straight sinus and cortical veins<sup>56-58,61,63-65</sup>, and "Delta Sign" on axial images in the thrombosis of the posterior portion of superior sagittal sinus<sup>56</sup>. Plain CT may also show indirect signs, namely CVST-related brain damage, such as venous infarction, vasogenic brain edema or cerebral hemorrhage, and subarachnoid hemorrhage<sup>59,62,63,66,67</sup>. An international multicenter prospective observational study involving 624 participants with CVST found that 69% of patients had brain damage<sup>16</sup>. A retrospective study of 44 participants with CVST showed that 43.2% presented with venous infarction<sup>37</sup>. Venous infarction showed focal hypodensity on plain CT, which is not consistent with the area of arterial blood supply<sup>62,63,66,68</sup>. Vascular brain edema presents as hypodensity with space-occupying effect. Shrink of ventricle may occur if brain parenchyma is diffusely swelling<sup>57, 60, 68</sup>. Venous infarction and vasogenic brain edema usually occur simultaneously. It is difficult to distinguish because both of them display hypodense on plain CT. Cerebral hemorrhage was found in 19.7%~29.3% of CVST patients<sup>37,69</sup>, and presents as focal hyperdensity of brain parenchyma on plain CT<sup>59,68,70</sup>. Subarachnoid hemorrhage is relatively rare in CVST, which shows gyrus-like hyperdensity in the sulcus of brain surface<sup>67</sup>. A cross-sectional study of 332 patients with CVST found that only 10% of patients had subarachnoid hemorrhage.

## (2) Contrast-enhanced CT Scan

Through intravenous injection of contrast medium, contrast-enhanced CT demonstrates blood flow in the lumen and indirectly shows thrombosis in cerebral venous sinus, presenting as filling defect of contrast medium within the venous sinus. On axial images of contrast-enhanced CT, thrombosis of superior sagittal sinus may show typical "Empty Triangle Sign"<sup>61,71-76</sup>. The thrombus in the lumen is relatively hypodense because it cannot be filled with contrast medium, and the surrounding dura mater is enhanced by contrast medium and display hyperdensity. A review with 76 cases of superior sagittal sinus thrombosis reported that 28.6% of the cases presented typical "Empty Triangle Sign"<sup>75</sup>. Cortical vein thrombosis may appear as filling



defect or non-filling on contrast-enhanced CT. Therefore, both plain CT and contrast-enhanced CT are rarely used in the diagnosis of cortical vein thrombosis. In a systematic review involving 106 cases with isolated cortical vein thrombosis, 73% of cases were confirmed by MRI<sup>77</sup>.

### **(3) Computed Tomography Venography**

Computed Tomography Venography (CTV), a kind of contrast-enhanced CT modality, is able to clearly demonstrate the structure of cerebral vein such as superior sagittal sinus, transverse sinus and straight sinus through three-dimensional reconstruction and subtraction technique<sup>78</sup>. CTV is mainly used in the diagnosis cerebral venous sinus or deep vein thrombosis, presenting as contrast filling defect<sup>78</sup>. A cross-sectional study using CTV was conducted in 50 patients with clinically suspected cerebral venous sinus or deep venous thrombosis. The results showed that CTV had excellent diagnostic ability, with a sensitivity of 75% - 100% and a specificity of 81.8% - 100%<sup>79</sup>.

### **(4) MR**

MR is an effective imaging modality in the diagnosis of CVST, with a high sensitivity and specificity. It not only displays the cerebral vein and the adjacent brain tissue, but also detects blood flow of the cerebral vein. There are several MRI sequences for the diagnosis of CVST, including: 1. Routine Brain MRI; 2. Susceptibility Weighted Imaging (SWI) or T2\* Weighted Imaging (T2\*WI); 3. Diffusion Weighted Imaging (DWI); 4. Magnetic Resonance Venography (MRV); and 5. other special three-dimensional reconstruction technique.

#### **(1) Conventional MRI Sequence**

Conventional MRI includes T1 Weighted Imaging (T1WI), T2 Weighted Imaging (T2WI) and Fluid Attenuated Inversion Recovery (FLAIR). Conventional MRI sequence can directly demonstrate thrombosis within the vein and CVST-related brain damage, but is not good enough for the diagnosis of CVST. The signals of thrombus on conventional sequences are various, depending on the time of thrombus formation. The thrombus contains deoxyhemoglobin 1-5 days after thrombus formation, which shows uniform isointensity on T1WI and remarkable hypointensity

on T2WI. Therefore, early thrombus cannot be easy to distinguish from normal blood flow signal on T2WI. From the 6th to 15th day, the content of methemoglobin in thrombus increases and showed high signal on T1WI. Cortical vein thrombosis may show typical high signal "strip sign"; In this period, the signal of thrombus are various on T2WI, presenting as hyperintensity, isointensity, or hypointensity<sup>80-86</sup>. From the 16th day to the 3rd month, the signal of thrombus on T1WI and T2WI decreases gradually. The signal of T2WI decreases obviously and becomes hypointensity, while T1WI shows isointensity. Owing to thrombus organization or recanalization, the signal of thrombus is not uniform<sup>83</sup>.

Vasogenic edema presents as hyperintensity in the area of brain drained by the affected veins, with or without the absence of sulci or gyri, asymmetry or shrink of ventricles<sup>87-89</sup>. Since acute and subacute venous infarction are similar to angiogenic edema on routine MRI sequence, DWI may be applied in combination with routine MRI to discriminate vasogenic edema from venous infarction<sup>90,91</sup>. Subarachnoid hemorrhage typically displays gyrus-like hyperintensity on brain surface, with hyperintensity in adjacent brain parenchyma sometimes<sup>67,92,93</sup>.

## **(2) Susceptibility Weighted Imaging**

Susceptibility Weighted Imaging (SWI) and T2\* Weighted Imaging (T2\*WI) play an important role in the diagnosis of acute CVST<sup>94-99</sup>. Deoxyhemoglobin, intracellular methemoglobin and hemosiderin in the acute phase of thrombosis all have an effect on the homogeneity of local magnetic field, leading to local signal loss. As a result, both the vein with thrombosis and surrounding tissue show remarkable hypointensity on SWI, a phenomenon called "magnetic susceptibility effect (MSE)"<sup>94,98,100</sup>. In order to detect MSE, we need to combine routine MRI sequence to differentiate the normal flow of venous blood on SWI. A retrospective analysis including 39 cases reported that SWI had a higher sensitivity in the diagnosis of acute venous sinus thrombosis or cortical venous thrombosis. The detection rate of thrombus reached 80%-90% within the first five days after onset, and was higher than T1WI, T2WI, FLAIR or DWI<sup>94</sup>. Over time, both reduction of deoxyhemoglobin in the thrombosis and release of intracellular methemoglobin outside the cell lead to

attenuation of MSE. At this time, signal of the thrombus varies from hypointensity to isointensity, or even hyperintensity. Thus, SWI has a low capacity of detecting subacute thrombus, which is similar to routine MRI<sup>94</sup>.

### **(3) Diffusion Weighted Imaging**

Diffusion Weighted Imaging (DWI) is mainly used to differentiate venous infarction from vasogenic edema<sup>101,102</sup>. When cells suffer from ischemia and hypoxia, extracellular water will flow into cells leading to cellular edema. Intracellular water is unable to diffuse freely due to hydrophobic effect of cell membrane. Acute venous infarction displays remarkable hyperintensity on DWI and hypointensity on apparent diffusion coefficient (ADC) sequence within 24 hours after onset<sup>101-103</sup>. Over time, signal on DWI gradually decreases to hypointensity while signal on ADC gradually becomes hyperintensity<sup>101,102</sup>. Owing to the elevation of capillary pressure, destruction of blood-brain barrier, and increase of vascular exudation caused by venous thrombosis, angiogenic edema occurs and shows high signal on ADC<sup>101-106</sup>. As a result of “T2 shine-through effect”, angiogenic edema displays slightly high signal on DWI<sup>102,104</sup>. The angiogenic edema of CVST patients can be relieved gradually after anticoagulation therapy. After 3-7 months of onset, it may completely return to normal, and the neurological deficit caused by edema almost recovers<sup>101,102,105</sup>.

Different from other sequences, DWI is rarely used in the diagnosis of CVST because of its low detection rate of venous thrombus. A prospective observational study involving 28 patients with new-onset CVST found that about 41% of patients with subacute CVST showed hyperintense thrombi in the venous lumen on DWI; only about 10% of these thrombi could completely or partially recanalize in 2-3 months, which were twice lower than those of non-hyperintense thrombi<sup>106</sup>.

### **(4) Magnetic Resonance Venography**

Magnetic Resonance Venography (MRV) is the most commonly used imaging modality for the diagnosis of CVST, with good consistency with invasive DSA. MRV mainly includes two types of imaging modalities: time of flight Magnetic Resonance Venography (TOF-MRV) and contrast-enhanced Magnetic Resonance Venography

(CE-MRV)<sup>79,86,107-111</sup>. Venous thrombosis presents as a filling defect or nonfilling on both TOF-MRV and CE-MRV. TOF-MRV is a kind of angiography technique sensitive to blood flow and is comparable to CTV in the diagnosis of CVST. Importantly, the potential risk of contrast agent can be avoided because contrast agent is not required for TOF-MRV<sup>109,111</sup>. CE-MRV demonstrates blood flow within the lumen by means of contrast agent and it is able to clearly show structures of cerebral vein system<sup>112,113</sup>. Compared with TOF-MRV, CE-MRV produces less artifacts and is less influenced by anatomical variants. Hence, CE-MRV has a better ability to diagnose CVST, with a sensitivity of 85.7% and a specificity of 97.2%<sup>110</sup>. Therefore, MRV should be the first option for the patients suspected of CVST. Other imaging modalities (such as SWI and conventional MRI) can be used to determine whether there is a thrombus.

#### **(5) Other Special Three-Dimensional Reconstruction Modalities**

Contrast enhanced three dimensional magnetization prepared rapid gradient echo (CE-3D-MPRAGE) is an imaging modality of T1-weighted venography with good spatial resolution and tissue contrast<sup>114,115</sup>. In comparison to MRV and CTV, CE-3D-MPRAGE has an advantage of clearly demonstrating cerebral venous sinus, cortical vein and adjacent brain tissue<sup>115</sup>. The typical manifestation of CVST on CE-3D-MPRAGE is the filling defect of contrast medium in the affected veins<sup>37,115</sup>. CE-3D-MPRAGE has high sensitivity (83%) and specificity (99%) in the diagnosis of acute or subacute CVST<sup>115</sup>, and can be used to identify acute and subacute cortical venous thrombosis<sup>37</sup>. Moreover, it can be used to discriminate CVST from non-thrombotic venous sinus stenosis (such as arachnoid granulations and membrane of vein), owing to its capability of clearly demonstrating brain tissue structure<sup>116</sup>.

Three dimensional T1 weighted sampling perfection with application optimized contrast using different angle evolutions (3D-T1-SPACE) is a three-dimension fast spin echo (3D-FASE) sequence with high signal-to-noise ratio (SNR) and resolution. By suppressing signal of normal blood flow, it can directly exhibit the intravenous thrombus<sup>117,118</sup>. 3D-T1-SPACE can clearly display the thrombus in the venous sinus or cortical venous lumen, which displays hyperintensity on T1WI at the subacute

phase. The sensitivity and specificity of 3D-T1-SPACE in the diagnosis of subacute CVST are 97% and 99% - 100%, respectively, which are significantly higher than those of MRV and conventional MRI sequences. Therefore, 3D-T1-SPACE was an efficient method for the diagnosis of CVST<sup>117,118</sup>.

#### **(5) DSA**

DSA is the first imaging modality used in the diagnosis of CVST. It can clearly and dynamically exhibit the cerebral venous sinus, deep vein, superficial cortical vein and collaterals. The manifestations of CVST include: 1. complete or partial filling defect of venous sinus; 2. delayed development of cerebral venous sinus; 3. tortuous expansion of cerebral vein; 4. prolonged capillary period; 5. bulky collateral drainage vein; 6. increased development of scalp vein around the affected vein<sup>119-121</sup>. All post-anterior, lateral and oblique films are required to identify CVST<sup>120,122</sup>. On post-anterior films, superior sagittal sinus thrombosis can present as typical “empty delta” sign<sup>122</sup>. MRV or CTV is usually unable to discriminate congenital venous aplasia from cerebral venous occlusion. By contrast, DSA can clearly identify such structures in venous phase. However, DSA is an invasive examination and is not recommended in the initial diagnosis of CVST. DSA may be applied if the initial imaging evaluation by MRV or CTV is inconclusive or endovascular therapy is being considered.

Direct percutaneous retrograde cerebral venography through catheterization from jugular or femoral vein has been reported in several cases with endovascular treatment<sup>123-128</sup>. Direct venography shows a complete or partial filling defect in the affected venous sinuses and venous manometry shows an increase of venous pressure. Normal venous pressure is < 10 mmH<sub>2</sub>O. A retrospective study with 29 cases of CVST found that brain lesions might occur when venous pressure was > 14 mmHg and venous pressure was associated with the extent of brain parenchyma lesions<sup>129</sup>. However, patients with CVST who received endovascular treatment have been diagnosed by other imaging methods, and are rarely diagnosed by direct venography. For CVST patients with stenosis, the pressure difference at the stenosis is often used as a reference index to decide whether to implant a stent or not. Most of previous

studies selected pressure difference of 8-10 mmHg as a cut-off value for stent placement<sup>130,131</sup>.

DSA makes the diagnosis of CVST through the shape of vein or sinus. It cannot directly detect the thrombus in the sinus cavity or vein, and cannot show the cortical venous thrombus very well. Besides, it is unable to evaluate whether CVST is in the acute, subacute or chronic stage. Dual hypoplasia around the superior sagittal sinus may lead to stenosis or occlusion of superior sagittal sinus. In such condition, it is easy to misdiagnose the nonfilling superior sagittal sinus as superior sagittal sinus thrombosis and results in delayed treatment. Therefore, DSA is an invasive examination with uncertainty and indirectness for diagnosis of CVST.

#### **(6) Considerations for Imaging Evaluation**

In the diagnosis of CVST, the following should be considered during imaging evaluation:

(1) Anatomical variation of venous structure: A cross-sectional study using cerebral angiography among 100 healthy participants found an asymmetric transverse sinus in nearly half of all subjects. 73.4% of participants showed a right dominance, and 19.3% exhibited a partial or complete transverse sinus agenesis, mainly affecting the left side<sup>132</sup>. Another cross-sectional study using TOF-MRV in 105 healthy participants reported that 59% of cases exhibited aplasia or agenesis of left transverse sinus<sup>133</sup>. Such venous sinus aplasia or agenesis also presents as filling defect or nonfilling on venous imaging (CTV, MRV and cerebral angiography), which is similar to CVST and may be misdiagnosed<sup>86</sup>. Therefore, when the venous imaging detects an abnormality of venous sinus (especially transverse sinus), MRI and SWI should be performed to evaluate whether there is a thrombus in the abnormal venous sinus. It has also been reported that the superior sagittal sinus may have double lumen deformity. There is no obvious abnormality in venography if one of the lumens has a thrombus, leading to a miss of diagnosis<sup>82</sup>. At present, there is no large sample study regarding the incidence of malformation of superior sagittal sinus, with the incidence in the general population unknown. Therefore, if there is no abnormal venographic finding in clinically suspicious patients, conventional MRI, SWI and other imaging

modalities should be adopted to determine whether there is a thrombus.

(2) Arachnoid granulations: Arachnoid granulations are normal intracranial structures. It may intrude into venous sinus and result in the stenosis of dural sinus. Such stenosis presents as a local filling defect on CTV or MRV and may be misdiagnosed as CVST<sup>134-136</sup>. A retrospective study involving 673 non-CVST participants reported that 22% of all cases exhibited a local filling defect on CTV or CE-MRV, with 90% observed in transverse sinus<sup>134</sup>. Arachnoid granulations exhibit isodense or hypotense on plain CT, and CSF-like isointense or hypointense on T1WI and hyperintense on T2WI on conventional MRI. Autopsy in some cases confirmed that the corresponding filling defect was caused by the intrusion of arachnoid granulations into the venous sinus<sup>134</sup>. Another retrospective study using conventional MRI and CE-3D-MPRAGE in 100 patients without venous sinus lesions reported there were 433 filling defects with round, oval or lobulated shape among 90 cases. 53.8%, 28.1% and 17.6% of the filling defect occurred in superior sagittal sinus, transverse sinus, and straight sinus, respectively. However, the signal of such filling defect was similar to that of cerebrospinal fluid on conventional MRI and is not confirmed by autopsy<sup>116</sup>. As discussed above, intrusion of arachnoid granulations into cerebral venous sinus is common. Different from hyperintensity of thrombus on T1WI, arachnoid granulations display isointense or hypointense on T1WI, which is similar to the signal of cerebrospinal fluid.

### **Recommendation**

1. CT/CTV and MRI/MRV are recommended in the initial imaging evaluation of patients with suspected CVST. MRI/MRV is able to diagnose most of CVST, and is recommended as the best noninvasive imaging in the follow-up of CVST. Contrast-enhanced (CE) MRV is more reliable than time-of-flight (TOF) MRV. (Class IIa, Level of Evidence C)
2. SWI and T2\*-GRE imaging improve the diagnosis of CVST, especially in patients with isolated cortical venous thrombosis or during acute stage. (Class IIa, Level of Evidence C)
3. CE-3D-MPRAGE and 3D-T1-SPACE are sensitive in detecting isolated cortical

venous thrombosis and non-thrombotic sinus stenosis. These techniques may be considered in the differentiation of CVST from other conditions (eg, dural sinus stenosis). (Class IIa, Level of Evidence C)

4. DSA is recommended if the initial imaging evaluation by MRV or CTV is inconclusive or endovascular therapy is being considered. The shortage of DSA in detecting isolated cortical venous thrombosis, and the risks of increased intracranial pressure caused by invasive and improper operation should be considered. (Class IIa, Level of Evidence C)
5. Venous pressure measurements via retrograde venography may be performed in patients with intracranial hypertension and dural venous stenosis. Endovascular therapy may be considered in patients with significantly increased pressure gradient between the proximal and distal segment to the stenosis. (Class IIa, Level of Evidence C)
6. A follow-up CTV/MRV is recommended in CVST patients with persistent or evolving symptoms despite the initial imaging results. (Class I, Level of Evidence C) A follow-up CTV/MRV at 3 to 6 months is reasonable to evaluate the recanalization of dural sinuses and cortical veins. (Class IIa, Level of Evidence C)

### 3. Causes and Risk Factors for CVST

There are various causes or risk factors of CVST, including infectious factors and noninfectious factors. The former is usually secondary to suppurative infection or nonspecific inflammation in the head and face or other parts; the latter is mostly related to prothrombotic condition/blood stasis/vascular wall injury, as well as intracranial hypotension. Some causes are not yet undetermined.

#### 1) Infectious Factors

Infectious factors are mainly referred to infection close to the meninges (ear, sinus, mouth, face, and neck). Infection in the head and face directly affects the corresponding cavernous sinus through the facial vein, or passes through the skull to reach the venous sinus and causes infectious thrombosis, for the infection site is adjacent to the venous sinus (such as transverse sinus and sigmoid sinus). These



causes account for only 8.2% of all cases in ISCVT study<sup>16</sup>. A study involving 62 adults with unilateral transverse sinus thrombosis in France reported that only 3 cases were associated with the infection adjacent to meninges<sup>137</sup>. However, infection is more common in children with CVST. A recent study including 70 children with CVST reported that 40% of CVST were caused by infection<sup>138</sup>.

## **2) Noninfectious Factors**

### **(1) Prothrombotic Condition**

Prothrombotic condition is susceptible to coagulation because of increased levels of plasma coagulation factors or decreased levels of plasma coagulation inhibitors. However, thrombosis does not exist yet or only a small amount of thrombosis is formed and lysing. Prothrombotic condition is one of the most widely studied risk factor for CVST. It consists of inherited prothrombotic condition and acquired prothrombotic condition. The former is mainly due to the presence of factor V Leiden gene mutation, protein C or protein S deficiency. The latter is caused by antiphospholipid antibody syndrome, acquired hyperhomocysteinemia or other diseases induced hypercoagulability.

A multicenter, prospective observational study reported that 34% of patients with CVST had either an inherited or acquired prothrombotic condition<sup>16</sup>. Studies showed that the risk of CVST for patients with protein C deficiency or protein S deficiency is 11.1 times (OR = 11.1, 95% CI = 1.87-66.05; P = 0.009) or 12.5 times (OR = 12.5, 95% CI = 1.45-107.29; P = 0.03), respectively<sup>139,140</sup>. Factor V Leiden mutation, a common inherited thrombophilic disorder, is a major cause of resistance to activated protein C. A recent meta-analysis involving 469 CVST participants and 3,023 controls in 13 studies demonstrated a pooled OR of 3.38 (95% CI = 2.27-5.05) for factor V Leiden mutation<sup>141</sup>. A study reported the positive rate of anticardiolipin antibodies were higher in patients with CVST (22.6%) than healthy controls (3.2%), which was consistent with the result (5.9%) of the ISCVT study<sup>16</sup>. Although hyperhomocysteinemia is a risk factor for deep vein thrombosis (DVT) and stroke, it is unclear whether it is associated with an increased risk for CSVT. A study in Milan containing 121 CVST patients and 242 controls found 33 (27%) and 20 (8%) cases

with hyperhomocysteinemia in patients and controls, respectively (OR = 4.2, 95% CI = 2.3-7.6)<sup>142</sup>. Similar results were found in subsequent small sample studies<sup>143-145</sup>.

## **(2) Pregnancy and Puerperium**

Pregnancy and puerperium are common causes of transient prothrombotic states<sup>146</sup>. During pregnancy, placenta produces a great amount of estrogen, which promotes the production of coagulation factors in the liver. Fibrinogen increases substantially during late pregnancy and further aggravates hypercoagulability. In addition, progesterone also promotes the formation of thrombosis. Most of the pregnancy related CVST occur during the last 3 months of pregnancy or puerperal period. About 2% of pregnancy related cerebrovascular diseases are CVST<sup>147</sup>. The incidence of CVST in puerperal period is estimated to be 12/100,000, slightly lower than that of arterial stroke<sup>148</sup>. One study showed that 50% of CVST occurred during pregnancy or puerperium in Mexico<sup>149</sup>. In another Canadian study involving 50,700 lying-in women, 7 of 8 cases with CVST occurred during postpartum<sup>150</sup>.

## **(3) Oral Contraceptives**

Oral contraceptives contain synthetic estrogen and progesterone. Long-term administration of oral contraceptives increases the plasma levels of estrogen and progesterone, leading to hypercoagulability and an increased risk of CVST. Foreign studies have found that oral contraceptives are the main cause of CVST in young non-pregnant female. The risk of CVST is higher in patients with oral contraceptive than inherited prothrombotic conditions. Combination of oral contraceptives with a prothrombotic condition may synergistically increase the risk of CVST. A study investigating the risk factors (including use of oral contraceptives) among 40 female CVST patients, 80 female lower extremity DVT patients, and 120 female controls found that oral contraceptives were almost used in all CVST patients (96%) and the OR of CVST reached 22.1 (95% CI = 5.9-84.2)<sup>16</sup>. Similarly, results from 2 meta-analysis also showed an increased risk of CVST in the oral contraceptive users, with a relative risk of 5.9 to 15.9<sup>141,151</sup>.

## **(4) Cancer and Other Uncommon Causes**

Cancer may play a role in CVST through direct compression, invasion of

cerebral sinuses<sup>46-48</sup>, or cancer-related hypercoagulability state<sup>152</sup>. Chemotherapeutic and hormonal agents for cancer treatment also increase the risk of CVST. In the ISCVT study, 7.4% of CVST were related to cancer<sup>16</sup>. It is estimated that CVST may have a higher incidence in patients with cancer, especially in those with hematologic malignancies; However, there is no study with control to confirm this.

Other causes of CVST have been reported by case reports and some small sample studies, such as head trauma, neurosurgery, paroxysmal nocturnal hemoglobinuria, iron deficiency anemia, thrombocytosis, heparin induced thrombocytopenic purpura, nephrotic syndrome, inflammatory bowel disease, connective tissue disease (systemic lupus erythematosus, Behcet's disease), etc<sup>16,153-163</sup>.

### **Recommendation**

1. The risk factors and causes of CVST are complicated and diverse. It is recommended to screen for the risk factors contributed to prothrombotic conditions and exclude the possibility of infections associated with CVST. (Class I, Level of Evidence B)

## **Part 2. Treatment of CVST**

### **Early and standardized anticoagulation**

In 1930s, heparin was firstly used in the treatment of CVST and was controversial in the following decades. In 1990s, two small randomized placebo-controlled trials including 79 patients were conducted. Although the pooled analysis of these two trials revealed no statistical significance of clinical efficacy for intravenous unfractionated heparin (UFH) (OR 0.33, 95%CI 0.08-1.21). Patients treated with heparin had a higher rate of clinical improvement and good prognosis, without new-onset cerebral hemorrhage. By contrast, there were two cases of cerebral hemorrhage and two cases of pulmonary embolism in control group<sup>164-166</sup>. The other trial enrolled 57 females with CVST during puerperal and excluded those with cerebral hemorrhage on CT. Patients were administered heparin subcutaneously and adjusted the dose to activate partial thromboplastin time (APTT). No death or limb

paralysis was found in the treatment group. In contrast, 3 cases died or had limb paralysis in the control group. CVST with cerebral hemorrhage was associated with adverse outcomes, no matter whether anticoagulation was used. In an observational study containing 29 patients with CVST and cerebral hemorrhage, six patients died and the number of deaths was equal in both groups. None of the deaths were attributed to new-onset or enlarged hemorrhage. Most of the studies were single center observational trials, in which intravenous UFH or low-molecular-weight heparin (LMWH) was used initially, followed by vitamin K antagonists. The mortality rate was lower than 10%, mainly attributable to underlying diseases such as cancer rather than CVST or hemorrhage. Most of the patients completely recovered and few of them was disabled<sup>164,167</sup>. The largest study was ISCVST including 624 patients from 89 centers of 21 countries. All patients received anticoagulation treatment in this study. 8.3% of participants died over 16 months, 79% had full recovery, 10.4% had mild to moderate disability, and only 2.2% was severely disabled<sup>16</sup>. Several observational studies revealed the risk of cerebral hemorrhage after anticoagulation for CVST is 0-5.4%<sup>164,168-170</sup>. Overall, previous studies have confirmed the efficacy and safety of anticoagulation treatment for CVST, regardless of the presence of cerebral hemorrhage. Therefore, a new randomized controlled trial may be not reasonable and feasible. The European Federation of Neurological Societies and American Heart association guidelines both recommend anticoagulation treatment as a primary therapy for CVST, which is also applicable to CVST with cerebral hemorrhage<sup>9,44</sup>.

### **1. Heparin and LMWH**

UFH and low molecular-weight heparin (LMWH) are commonly used anticoagulant agents in patients with CVST. Currently, there is no consensus on the use of heparin or LMWH in CVST. A randomized controlled trial containing 66 patients compared the efficacy of LMWH with UFH in patients with CVST<sup>171</sup>. Six cases (19%) died in the UFH group, in contrast to none in the LMWH group. At 3 months, the rate full recovery was higher in patients with LMWH than UFH. Three cases treated with UFH had major hemorrhagic complication but none in the LMWH

arm. Although this trial has a few methodological limitations, it suggests the efficacy and safety of LMWH are superior to UFH. An observational study compared UFH (n = 119) with LMWH (n = 302) in patients with CVST. The rate of functional independency at 6 month was 84% in UFH group and 92% in LMWH group. New-onset cerebral hemorrhages occurred in 16% patients treated with UFH and 10% in LMWH arm<sup>172</sup>. Therefore, these studies suggest a better efficacy of dose adjusted LMWH over UFH, with lower risk of hemorrhage. The 2017 European Stroke Organization guideline also recommends LMWH over UFH in patients with CVST<sup>44</sup>.

## 2. Vitamin K antagonists

Duration of anticoagulation in acute phase is non-uniform and usually lasts for 1 to 4 weeks. After acute phase, oral anticoagulants should be continued<sup>141</sup>. The most commonly used agent is warfarin. The duration of anticoagulation should be based on a comprehensive consideration of individual genetic factors, risk factors, recurrence, follow-up, and bleeding risks. Until now, there are no randomized controlled prospective trials or case-control studies in evaluating the optimal duration of anticoagulation in CVST. A retrospective cohort study enrolled 706 patients and followed up for 40 months. At the end of anticoagulation, 4.4% of CVST and 6.5% of patients with extracranial venous thrombosis had recurrent venous thromboembolism. The overall incidence of recurrence was 23.6 events/1000 patient-years (95%CI: 17.8-28.7) and 35.1 events/1000 patient-years (95%CI: 27.7-44.4)<sup>173</sup>. For a CVST with a primary or mild thrombophilia, anticoagulation should continue for 6 to 12 months. For patients with recurrent CVST or severe thrombophilia, long-term anticoagulant therapy may be considered. In patients with a transient risk factor, such as pregnancy, oral contraceptives, anticoagulation therapy may be used within 3 months<sup>16,165, 174</sup>. The role of recanalization on imaging in guiding the duration of anticoagulation is still unclear. In a study investigating the role of recanalization, 33 patients were initially treated with intravenous heparin, followed by warfarin for 4-12 months. After four months, 94% of superior sagittal sinuses, 80% of straight sinuses, 57% of transverse sinuses, and 41% of sigmoid sinuses have been recanalized. No further recanalization was observed at 12 months. 82% of patients had no

neurological deficits or recurrent CVST, suggesting four-month anticoagulation is sufficient for CVST<sup>175</sup>. In another retrospective cohort study, 91 patients with CVST received heparin and warfarin for at least 4 months, and 74 (81%) patients achieved complete or partial recanalization. However, the recanalization was not associated with the clinical outcomes, indicating that recanalization might not be an imaging marker for guiding the duration of anticoagulation<sup>176</sup>. Therefore, the optimal duration of anticoagulation is still unknown. The EXOCA-CVST(ISRCTN25644448) trial is ongoing to compare the efficacy and safety of short-term (3-6 months) versus long-term (12 months) anticoagulation for preventing CVST<sup>177</sup>.

In order to prevent symptomatic fluctuations during the replacement of anticoagulants, warfarin and heparin should overlap for 3-5 days. After international normalized ratio (INR) reaches 2 to 3, heparin is stopped and the dose of warfarin is regularly adjusted according to INR.

### **3. Novel oral anticoagulants**

The efficacy and safety of novel oral anticoagulants (NOACs), including direct thrombin inhibitor (dabigatran) and Factor Xa inhibitors (rivaroxaban、apixaban and edoxaban) in preventing CVST is uncertain. In patients with lower extremity venous thrombosis or atrial fibrillation (AF), NOACs showed similar therapeutic effects to warfarin and heparin. In contrast, the risk of intracranial hemorrhage of NOACs was greatly reduced, suggesting that the safety of NOACs were superior to conventional anticoagulants. Therefore, NOACs are promising candidates for the treatment of CVST. A retrospective study in 2014 compared warfarin (n = 9) with rivaroxaban (n = 7). The results showed that 7 patients in rivaroxaban group had a full recovery and recanalization and 2 cases had mild epistaxis. By contrast, 8 patients in the warfarin group had full recovery and 9 cases had recanalization, with 1 case having increased menstruation<sup>178</sup>. This observational study demonstrated that the efficacy of Factor Xa inhibitor was comparable to warfarin for CVST. Further systematic prospective studies are warranted to investigate the efficacy and safety of Factor Xa inhibitor. In another retrospective study, 18 patients with CVST were enrolled and treated with dabigatran (11 cases) and warfarin (7 cases). Four patients on warfarin were switched

to dabigatran because of adverse effects at 0.5, 1, 3.5, and 4 months. A total of 15 patients were treated with dabigatran with median follow-up time of 19 months. Good outcomes were observed in 87% of patients and recanalization in 80%<sup>179</sup>. Recently, an exploratory, prospective, randomized trial (RE-SPECT CVT) compared the efficacy and safety of dabigatran with warfarin in patients with CVST for 24 weeks. 120 patients with CVST were randomly assigned to dabigatran (60 cases) and dose-adjusted warfarin group (60 cases). No recurrent venous thrombotic events were observed in either group. One major bleeding event was recorded in the dabigatran group, and 2 (3.3%; 95%CI, 0.4-11.5) in the warfarin group. The result demonstrated both dabigatran and warfarin were safe and effective for preventing recurrent venous thrombotic events in patients with CVST<sup>180</sup>.

### **Recommendation**

1. Anticoagulation therapy should be initiated in patients with CVST immediately. (Class I, Level of Evidence B) The safety and efficacy of LMWH is slightly superior to UFH. (Class IIa, Level of Evidence B) LMWH is recommended for the acute management of CVST. The therapeutic dosage of LMWH is 0.4ml to 0.6 ml, injected subcutaneously twice a day. If UFH is used, the initial treatment should at least double the activated partial thromboplastin time, lasting for 1-4 weeks. CVST with minor intracranial hemorrhage or intracranial hypertension is not an absolute contradiction to anticoagulation therapy. (Class IIb, Level of Evidence B)
2. Oral anticoagulants should be initiated after the acute stage of CVST. The most commonly used agent is warfarin, with a target INR of 2 to 3. The duration of treatment depends on the tendency to thrombosis and the risk of recurrence. (Class IIa, Level of Evidence C). Warfarin is recommended to maintain 3 to 6 months to prevent the recurrence of CVST and other venous thromboembolic events. (Class IIa, Level of Evidence C) It is undetermined whether recanalization of the occluded veins or dural sinuses can be considered as an indication for withdrawal of oral anticoagulants. (Class III, Level of Evidence C),
3. Dabigatran may be considered in patients with CVST unsuitable for warfarin.

(Class IIa, Level of Evidence B) (New recommendation) Further studies are needed to determine the efficacy of other new oral anticoagulants (NOACs) in CVST. (Class IIb, Level of Evidence C)

### **Endovascular treatment**

Endovascular treatment of CVST includes direct catheter thrombolysis, aspiration thrombectomy and stent-assisted mechanical thrombectomy. Direct catheter thrombolysis will be described in the medical treatment section.

#### **1. Aspiration thrombectomy**

A multicenter, prospective, randomized, blinded endpoint trial (Thrombolysis Or Anticoagulation for Cerebral venous Thrombosis---TO-ACT trial)<sup>181</sup> compared endovascular thrombolysis with standard anticoagulant treatment in patients with a severe CVST. This trial recruited patients from 13 centers of 5 countries. The interim results were announced in 2017 European Stroke Organization annual conference and showed no significant difference of functional outcomes between the two treatment groups. There are a number of case reports and cohort study on the efficacy of thrombolysis and thrombectomy in patients with CVST<sup>182-184</sup>. A recent meta-analysis calculated the incidence of major bleeding was 9.8% (95%CI: 5.3-15.6), symptomatic intracranial hemorrhage 7.6%, and death rate 9.2%<sup>185</sup>. Another meta-analysis included a total of 185 patients with CVST and found the rate of recanalization (partial or complete) was as high as 95%. Nevertheless, the level of evidence was judged as very low and all studies were observational with high risk of bias<sup>186</sup>. A non-randomized study compared the efficacy of intrasinus thrombolysis (IST) with mechanical thrombectomy in CVST. In comparison with IST, mechanical thrombectomy was more frequently used in patients with severe CVST and extensive venous sinus thrombosis. No statistical significance of was found in the mortality, neurological dysfunction at discharge, and long-term morbidity between two groups<sup>182</sup>. In a systematic review of 235 patients receiving endovascular mechanical thrombectomy, 40.2% patients presented with encephalopathy or coma. Complete angiographic recanalization of CVST was achieved in 69.0% of patients. At follow-up, 34.7% of patients were neurologically intact and the mortality rate was 14.3%. The recurrence



of CVST was evident in 1.2% of patients. New-onset intracranial hemorrhage occurred in 8.7% of cases. Notably, 87.6% of patients received mechanical thrombectomy, in conjunction with thrombolysis<sup>187</sup>. Acute patients presenting a CVST risk score  $< 3$ <sup>188</sup>, or no coma, mental disorder, deep venous thrombosis and intracranial hemorrhage, had a very low risk of poor prognosis. Therefore, aggressive and potentially harmful treatments, such as thrombolysis or mechanical thrombectomy, are not recommended in these group of patients. The aforementioned TO-ACT study has excluded such low-risk patients<sup>181</sup>.

Although venous sinus mechanical thrombectomy can quickly restore venous blood flow and improve neurological function, some of the patients have recurrence of venous thrombosis or present residual increased intracranial pressure regardless of recanalization ( $>330\text{mmH}_2\text{O}$ ). Additionally, mRS score may be insufficient to represent the clinical outcome of CVST. Therefore, the indications for surgical therapy and evaluation indicators for clinical efficacy need to be further investigated. Studies have showed the time window for endovascular treatment of CVST of around 30 days after onset (acute or subacute phase)<sup>189,190</sup>.

Overall, for patients with severe CVST, intrasinus thrombolysis or mechanical thrombectomy may be considered if anticoagulation is ineffective. For patients with cerebral venous infarction and a significantly space-occupying effect, decompressive craniectomy is recommended before mechanical thrombectomy.

## **2. Intravenous stent treatment**

For patients with idiopathic intracranial hypertension caused by venous sinus stenosis, endovascular stent placement has a good therapeutic effect<sup>191</sup>. The causes of venous sinus stenosis include congenital or thrombosis induced stenosis<sup>192</sup>. Venous sinus stenosis can cause obstruction of venous reflux, and further lead to intracranial hypertension. Studies have shown that stent placement can significantly improve the clinical outcomes in patients with venous sinus stenosis, especially in reducing intracranial pressure and improving symptoms caused by intracranial hypertension, such as headache, papilledema, visual impairment, pulsatile tinnitus etc<sup>193, 194</sup>.

Fargen et al reported a female patient presented an instant reduction of intracranial

pressure after stent placement<sup>195</sup>. This phenomenon was also found in other two prospective studies containing 10 patients with sinus stenting. Venous sinus stenting can improve the symptoms of intracranial hypertension<sup>196</sup>. Systematic review and meta-analysis showed that 78-83% of headaches, 87-97% of papilledema, 74-85% of visual symptoms and 95% of tinnitus can be improved after venous stenting. These studies also showed a low incidence of complication after sinus stenting, approximately 1.4-7.4% in total. Among them, 1.6 to 2.9% were severe complications, and 1.6 to 4.4% were minor complications<sup>186,192</sup>. Catheter venography and manometry should be performed before stent placement. If the pressure gradient across the stenosis is greater than 8-10 mmHg, stent placement may greatly improve the symptoms<sup>130,131</sup>. Currently, there are no systematic trials on the strategy of antithrombotic agents after sinus stenting. It is reasonable to adopt the regimen in arterial stenting, with dual antiplatelets in the first 3-6 months and subsequent single antiplatelet for maintenance.

There are several studies in China using multiple modalities of endovascular treatments in combination, including thrombectomy, intravenous thrombolysis, and sinus stenting. The results showed that all patients achieved venous recanalization and had neurological deficits improved, without any major complications<sup>197</sup>. It was suggested that the modalities of endovascular treatment might be selected according to the course of disease<sup>198</sup>.

### **Recommendation**

1. Current evidence is not sufficient to recommend the application of intrasinus thrombolysis or mechanical thrombectomy in severe CVST. However, mechanical thrombectomy can be considered in patients with severe CVST after adequate anticoagulation has failed and there is a need to prevent or treat brain herniation. (Class IIb, Level of Evidence C)
2. Venous pressure measurements via retrograde venography may be performed in patients with intracranial hypertension and dural venous stenosis. Intrasinus stenting may be considered if the pressure gradient between proximal and distal segment to the stenosis is beyond 8-10 mmHg. (Class IIb, Level of Evidence C)

3. The long-term antithrombotic treatment after the sinus stenting is not clear. According to clinical practice in arterial stenting, it is reasonable to use dual antiplatelet therapy for the first 3 months followed by single antiplatelet therapy for maintenance. (Class IIb, Level of Evidence C)

### **Treatment of CVST during pregnancy**

Vitamin K antagonists, including warfarin, are associated with fetal malformations, intrauterine and neonatal bleeding. Therefore, warfarin is considered to be contraindicated in pregnant patients. Instead, LMWH is the best choice for women during pregnancy and in the early puerperium. In contrast to heparin, LMWH is not associated with teratogenicity or fatal bleeding. The American College of Chest Physicians guidelines recommends LMWH in the prevention and treatment of DVT and pulmonary embolism in pregnant women, rather than heparin<sup>199</sup>. A retrospective study involving 37 high-risk pregnant women treated with LMWH once a day to prevent first or recurrent CVST found that none of 37 patients developed systemic venous thrombosis. Only 1 patient had parietal arterial infarction and 1 had postpartum CVST<sup>200</sup>.

Women with a prior history of venous thrombosis are at increased risk of CVST<sup>146</sup>. Six studies investigated the outcome of pregnancy in 855 women with a prior CVST, and found 83 women subsequently became pregnant. The results showed that the risk of complications was very low, with 88% having a normal birth and the remaining 12% having a voluntary or spontaneous abortion. CVST recurred in only 1 case and DVT in 2 cases. However, a relatively high rate of spontaneous abortion was noted<sup>16,167,201-204</sup>. Therefore, a prior history of CVST is not a contraindication for pregnancy. Considering the potential risk, prophylactic use of LMWH during pregnancy and postpartum may be benefit for women with a prior CVST.

### **Recommendation**

1. LMWH is recommended in women with CVST during pregnancy. The safety of LMWH is superior to UFH. Subcutaneous injection of LMWH is recommended throughout the pregnancy (0.4ml, twice a day), followed by LMWH or warfarin with a target INR of 2 to 3 for at least 6 weeks postpartum. The total duration of

treatment is no less than 6 months. (Class I, Level of Evidence C)

### **Etiological treatment**

CSVST is a rare cerebrovascular disease with high risk of death. An organized management of the disease in stroke unit can significantly reduce the incidence of mortality and complications. The causes of CVST should be investigated and treated promptly, including infection, hypercoagulability, tumors, connective tissue diseases, autoimmune diseases, etc. In cases of infectious thrombus, sufficient and effective antibiotics should be initiated immediately. Multiple or broad-spectrum antibiotics should be used before the pathogens have been identified. In order to control the infection effectively and prevent recurrence, the duration of antibiotic treatment should be sufficient, generally 2-3 months, or continuing 2-4 weeks after symptoms disappear. On the basis of antibiotic therapy, surgical treatment can be performed to completely remove the primary pyogenic lesions. For non-infectious thrombus, it is also important to correct dehydration, reduce blood viscosity and improve regional circulation on the basis of management for primary disease. For patients with prothrombotic status due to congenital factors, including mutations in factor V Leiden gene and deficiency in protein C and protein S, long-term use of oral anticoagulants with INR between 2.0 to 3.0 may be beneficial. However, there is no evidence that aggressive treatment should be taken in patients who have not yet developed CVST but have protein C or protein S deficiency. Given the limited data available, oral contraceptives should be avoided after the first episode of CVST to reduce the risk of recurrence. For women with a prior CVST, it is recommended to inform the patient of the risk of venous thrombosis and abortion and CVST is not the contraindication for pregnancy.

### **Recommendation**

1. It is recommended to seek and treat the potential causes. Administration of appropriate and adequate antibiotics should be initiated immediately in patients with infection and CVST, as well as surgical removal of sources of infection. (Class I, Level of Evidence C)
2. CVST patients with factor V Leiden gene mutation, protein C or protein S

deficiency, may benefit from long-term therapy with oral anticoagulants. (Class IIa, Level of Evidence C)

3. It is recommended to reduce or avoid the use of oral contraceptives, especially in female patients with a previous history of CVST. (Class I, Level of Evidence C)
4. Pregnancy is not contraindicated in female patients with a history of CVST, but patients should be informed of the high risk of recurrent CVST or loss of pregnancy. (Class IIa, Level of Evidence C)

### **Management of complications**

#### **1. Intracranial hypertension and cerebral herniation**

Intracranial hypertension is very common in the acute stage of CVST, usually presenting as headache or papilledema. In patients with intracranial hypertension, the effect of anticoagulation and analgesic is limited. Acetazolamide may lower the intracranial pressure by reducing CSF production, but does not have a sufficient effect in the acute stage of CVST. In a prospective study, 44 of 59 (75%) patients with CVST and isolated intracranial hypertension received therapeutic lumbar puncture. The overall outcome was favorable, but these data were insufficient to determine the efficacy of lumbar puncture<sup>9,205</sup>. There is inadequate evidence to recommend hypertonic solution mannitol and diuretics in patients with CVST, which may lead to hemoconcentration and hypercoagulability, and aggravate development of venous thrombosis. Therefore, dehydrating agents should not be routinely used except for cerebral herniation.

Some patients may have acute vision loss due to intracranial hypertension. In these patients, especially with severe vision impairment, pressure lowering therapy should be done promptly through lumbar puncture or neurosurgical shunt<sup>9,206,207</sup>. In a subgroup of patients, intracranial hypertension may lead to decreased level of consciousness and even coma in the absence of brain parenchymal lesions, which may be caused by the reduction of cerebral perfusion due to severe intracranial hypertension. Evidence-based management is not available for these cases because there is a paucity of literature. In rare cases, emergency shunting or bilateral decompressive surgery was performed<sup>208</sup>. The main cause of death in the early stage

of CVST is transtentorial herniation resulting from the space-occupying effect of lesion<sup>209</sup>. Decompressive surgery (decompressive craniectomy or hematoma evacuation) should be performed in patients with clinical and radiological signs of herniation<sup>206</sup>. Although randomized controlled trials are scarce at present, there are a number of case series, two systematic reviews, and two non-randomized controlled trials comparing decompressive surgery with non-surgical treatment<sup>210-212</sup>. The results showed a mortality rate of 18.5%, death or disability of 32.2%, severe disability of 3.4%, and full recovery of 30.7%. In spite of small sample size, the results of two non-randomized controlled trials confirmed the benefit of decompression in preventing death and did not show any increase in severe disability.

## 2. Epilepsy

Epilepsy may occur in 37% of adults, 48% of children, and 71% of newborns with CVST<sup>15,169</sup>. Results from randomized controlled trials are not yet available to recommend the timing to initiate antiepileptic drugs and guide drug selection. It remains controversial whether anticonvulsants should be given to all patients with CVST or only after the onset of seizure. Studies have found that the incidence of early seizure increased by 2.7 times in patients with parenchymal lesion on CT/MRI, and 6.8 times in those with sensory defects<sup>213</sup>. The use of antiepileptic drugs reduced the incidence of seizure within 2 weeks in seizure-free patients with supratentorial lesions on CT/MRI, though the difference was not statistically significant. A Cochrane systematic review showed a lack of evidence regarding the use of antiepileptic drugs in both primary and secondary prevention of seizure in CVST<sup>214</sup>. Some studies demonstrated an association between seizure and death in acute stage, however, this was not consistently reported. Moreover, none of these studies showed a relationship between antiepileptic treatment and functional outcome of CVST. Since seizure may increase hypoxic injury, the initiation of antiepileptic drugs after the first seizure is reasonable<sup>215</sup>. However, it may be harmful to use antiepileptic drugs in patients without seizures<sup>216-218</sup>.

## 3. Hydrocephalus

Hydrocephalus occurs in 15% of patients with CVST<sup>159,219</sup>. Most of cases are

obstructive hydrocephalus caused by basal ganglia/thalamic edema, or rupture of thalamic hemorrhage into the ventricle, which was described in neonatal whereas might also occur in patients of any age<sup>220,221</sup>. Hydrocephalus increases the risk of poor prognosis, but it remains unclear whether the raise of risk is caused by hydrocephalus or underlying parenchymal lesions. In a systematic review of 15 CVST patients treated with shunt<sup>208</sup>, the mortality rate was 22.2%, death or disability rate was 55.6%, and severe disability rate was 16.7%. Three patients with intracranial hypertension but no parenchymal lesions received a ventriculoperitoneal shunt and had a good outcome. In a recent report involving 14 patients with hydrocephalus, only one patient was treated with shunt and finally died<sup>219</sup>. Considering the uncertainty of outcomes and the need of anticoagulation, shunt is only considered in patients with severe symptoms caused by hydrocephalus<sup>208,219</sup>.

#### 4. Dural arteriovenous fistula

It has been found that patients with CVST might have arteriovenous fistula (AVF) at the end of anticoagulation. For some patients with recurrent papillary edema and headache, the possibility of AVF should be considered. Treatment of AVF secondary to CVST should follow the general guideline of AVF, including complete closure of the fistula, improvement of cerebral venous reflux, reduction of sinus pressure, and relief of clinical symptoms. Comprehensive procedures of AVF consist of catheter embolization, radiation, surgical clamping and other treatments. It should be noted that the blood reflux of fistula mainly depends on the cortical vein due to the occlusion of dural venous sinus. Thus, more attention should be paid to the establishment of cerebral venous reflux in order to prevent the occurrence of complications in AVF<sup>222,223</sup>. Some patients only need embolization of AVF, but others may need several procedures in 8 months, including endovascular embolization, open clipping, and gamma knife radiotherapy, etc.<sup>224</sup>

#### **Recommendation**

1. Patients with severe intracranial hypertension and impending cerebral herniation should be treated immediately. Use of decompressive craniectomy, ventriculoperitoneal shunt, or hematoma evacuation may be considered. (Class IIa,

Level of Evidence C)

2. Patients with increased intracranial pressure and progressive visual loss should be treated early to save the vision. Decompressive surgery includes optic nerve sheath fenestration and ventriculoperitoneal shunt. (Class IIa, Level of Evidence C)
3. It is reasonable to initiate short-term dehydration therapy with mannitol or furosemide, to gain time for surgery in patients with intracranial hypertension, progressive visual loss or cerebral herniation. Excessive dehydration is prohibited as it can lead to blood concentration and aggravation of CVST. Acetazolamide may be considered in certain patients to reduce intracranial pressure by decreasing the secretion of cerebrospinal fluid. (Class IIb, Level of Evidence C)
4. In patients with a first seizure and parenchymal lesion, antiepileptic therapy should be initiated immediately (Class I, Level of Evidence B). In patients with a first seizure without parenchymal lesion, early initiation of antiepileptic drugs may be beneficial. (Class III, Level of Evidence C) Prophylactic use of antiepileptic drugs in patients with CVST is not beneficial. (Class III, Level of Evidence C)
5. The treatment of dural arteriovenous fistula induced by CVST can refer to the general principles of dural arteriovenous fistula. More attention should be given to the establishment and protection of cerebral venous drainage. (Class IIb, Level of Evidence C)

### **Other medical treatments**

#### **1. Thrombolysis**

Currently, there are no randomized controlled trials for thrombolysis in patients with CVST. A study in 2014 summarized 16 reports including a total of 26 patients with CVST. All patients received intravenous systemic thrombolysis (thrombolytic agents include urokinase, streptokinase and rt-PA). The results demonstrated that 80% of patients had a good outcome, two had intracranial hemorrhage. Due to the small sample size and lack of controls in the published literature, the efficacy of systemic thrombolysis in acute CVST remains inconclusive. Nevertheless, a nonnegligible



bleeding risk was reported for thrombolysis in CVST<sup>225</sup>.

Although the efficacy of systemic thrombolysis is uncertain, more and more non-controlled studies have showed the benefit of local thrombolysis in CVST<sup>226-229</sup>. In a retrospective multicenter study from the United States, 27 (15%) of 182 patients received intrasinus thrombolysis, and 10 of them taken concomitant anticoagulation therapy. 26 (96%) patients achieved recanalization, 4 developed intracranial hemorrhage, and 1 patient died. Another systematic review involving 169 CVST patients treated with local thrombolysis showed a benefit of thrombolysis in patients with severe CVST, but the incidence of intracranial hemorrhage was 17%, with 5% having clinical deterioration<sup>230</sup>. A recent study from southern India found that in 29 patients with severe CVST receiving in situ thrombolysis, 24 patients had a good outcome (mRS 0 or 1), 3 patients had mild deficits (mRS 2), and 1 patient had moderate disability (mRS 3). One patient succumbed as a result of increased hematoma and transtentorial herniation. At 3 months follow-up, 26 patients were asymptomatic and two patients had residual minor symptoms<sup>231</sup>. Another study from the Pennsylvania State University reported the efficacy of continuous rt-PA treatment through intravascular catheter in 3 patients with CVST. All patients achieved recanalization without serious bleeding complications. The researchers explored a new methods of drug delivery in this study. 20 mg rt-PA was dissolved in 1L saline, given at 100 ml per hour and lasting for 10 hours<sup>232</sup>. A study from China demonstrated the efficacy of local thrombolytic therapy by placing a micro-catheter in 12 patients with CVST during postpartum period. All patients were treated with low molecular weight heparin in the acute phase. The result showed that superior sagittal sinus was recanalized in 9 cases, and the cortical venues and deep venues were recovered to normal. In addition, three patients achieved partial recanalization. This study suggested that local thrombolytic treatment is safe and effective in patients with severe cerebral venous sinus thrombosis during puerperium<sup>183</sup>.

Compared with anticoagulation, local thrombolysis can rapidly achieve recanalization, but the risk of hemorrhagic complications is high, especially in patients with intracranial hemorrhage before treatment<sup>233</sup>. Most studies regarding

local thrombolysis recruited patients with severe CVST, and treated with LMWH. Currently, there is no control study comparing local thrombolysis with heparin or LMWH, and no trials revealing better clinical outcome in local thrombolysis. Thus, we do not recommend the use of local thrombolysis in patients with CVST, and so as systemic thrombolysis.

## **2. Antiplatelet and defibrase**

Currently, there are no randomized, controlled or noncontrolled trials of antiplatelet or defibrase in CVST, and thus evidence is insufficient to confirm their efficacy and safety. Nevertheless, a particular group of patients may benefit from antiplatelet or defibrase, especially for patients with abnormal blood composition, such as thrombocytosis or hyperfibrinogenemia. In 1993, one patient with CVST and acute ulcerative colitis was treated with antiplatelet purely, and had complete recanalization of venous sinuses<sup>234</sup>. In a study from China, patients also had good outcomes, after being treated with local thrombolysis and subsequent antiplatelet for 6 months. This study concluded that it was safe and effective to use antiplatelets in preventing recurrence of CVST<sup>183</sup>.

## **3. Steroids**

CVST is usually accompanied with vasogenic edema and cytotoxic edema. Theoretically, steroids may be effective in reducing vasogenic edema, and further lower intracranial pressure. However, steroids may promote thrombosis, inhibit thrombolysis, induce hemorrhage, hyperglycemia and infections, and even lead to recurrent CVST<sup>235</sup>. At present, there are no randomized controlled trials regarding steroids in patients with CVST. In an analysis of data based on the ISCVST, 640 patients with CVST were enrolled and 150 patients (24%) were treated with steroids. The result showed no statistical significance of functional outcome between the steroid and control groups at 6 months. Moreover, poor prognosis was observed in the steroid group for patients without parenchymal lesions<sup>236</sup>. Since this study was non-randomized, non-blinded, small sample size, and non-uniform in types and doses of steroids, the indications of steroids in CVST need further investigation. Current evidence does not support the use of steroids in CVST. In a post-hoc analysis of an

international study of cerebral venous and dural sinus thrombosis, no correlation was found between steroids and good outcome. Actually, steroids might be harmful in patients without parenchymal lesions. Therefore, we do not recommend steroids in the treatment of CVST.

#### 4. **Antibiotics**

Local and systemic infections are associated with adjacent or distant venous or sinus thrombosis. Patients with infections and CVST should be treated with antibiotics. A report in 2016 summarized the etiology, diagnosis and treatment of infectious CVST, indicating that antibiotics should be initiated promptly in patients suspected of infectious CVST (even before microbiological reports). Broad-spectrum antibiotics or a combination of cephalosporins, vancomycin and metronidazole are recommended in infectious CVST. Sensitive antibiotics should be given after identifying the pathogenic microorganism, and the duration of treatment should last at least 3-8 weeks<sup>237</sup>.

#### **Recommendation**

1. In patients with clinical deterioration despite adequate anticoagulation therapy, and without severe intracranial hemorrhage, direct intrasinus thrombolysis can be carefully performed under close supervision. (Class IIb, Level of Evidence C). Current evidence does not support the use of systemic thrombolysis in CVST. (Class III, Level of Evidence C)
2. Current evidence does not support the routine use of antiplatelet drugs or de-fibrin therapy in CVST, unless it is indicated for other underlying diseases. (Class III, Level of Evidence C)
3. Routine use of steroid in CVST is not beneficial, unless it is indicated for other underlying diseases. (Class III, Level of Evidence B)
4. It is recommended to use antibiotics in patients with CVST and infection for 3-8 weeks. (Class I, Level of Evidence C)

#### **Part 3. Secondary prevention of CVST**

Currently, there are no clinical trials regarding secondary prevention in patients with CVST. The strategies of prevention are based on observational studies that

evaluate the recurrence of CVST with or without anticoagulation. In a cohort of 154 patients with CVST at Mayo Clinic from 1978 to 2001, 56 patients received both heparin and warfarin, 12 patients received heparin only, and 21 patients received warfarin only<sup>158</sup>. Seventy-seven (50%) were treated with warfarin for an average of 9 months, and 25 patients received lifelong anticoagulation<sup>158</sup>. In the 36-month follow-up (464 patient-years), twenty-three patients (13%) had thromboembolic events, most of which occurred in the first year. Ten patients had recurrent CVST (2.2 per 100 patient-years), and 11 patients had deep vein thrombosis or pulmonary embolism (2.8 per 100 patient-years)<sup>158</sup>. Nine events occurred during warfarin therapy<sup>158</sup>. There was no association between the use of warfarin and recurrence of thromboembolic events<sup>158</sup>.

In another cohort study, 8 out of 54 patients with CVST had recurrent events including deep vein thrombosis, pulmonary embolism, or CVST (1 case) during a mean follow-up of 2.5 years<sup>238</sup>. Only 2 of these 8 patients were taking anticoagulants with an INR of 1.6 and 2.1 respectively, and the other 6 patients were not taking anticoagulants<sup>238</sup>. The median time to recurrence ranged from 2 weeks to 10 months<sup>238</sup>.

In the ISCVT study involving 624 patients, 14 had recurrent CVST, and 27 had other thrombotic events (including 16 deep vein thrombosis, 3 pulmonary embolism, 2 ischemic stroke, 2 transient ischemic attack, and 4 acute limb ischemia) during a mean follow-up of 16 months<sup>16</sup>. Seventeen (41.5%) of these 41 recurrent patients were receiving anticoagulation, but the type of anticoagulants was unclear and whether the therapeutic target had been reached was unknown<sup>16</sup>. The VENOPORT study evaluated the outcome of 142 patients with CVST. 51 cases were retrospectively collected (maximum follow-up of 16 years) and 91 cases were prospectively recruited (a follow-up of 12 months)<sup>201</sup>. In the prospectively-followed cases, the annual risk of thrombotic events was 4% and all of these events occurred within the 12 months of follow-up<sup>201</sup>. Three of the 5 events occurred during anticoagulation therapy, whereas the INR values at that time were unknown<sup>201</sup>. A French study enrolled 77 patients with CVST from 1975 to 1990 and followed up for

63 months<sup>167</sup>. Nine cases had recurrent CVST, 8 occurred within the first 12 months after onset, and all of the 9 cases had stopped anticoagulation therapy at the time of recurrence<sup>167</sup>. Eleven patients had other thrombotic events including deep vein thrombosis, pulmonary embolism and arterial thrombosis<sup>167</sup>. No recurrent thrombotic events were reported during anticoagulation<sup>167</sup>.

Recently, a study followed 145 patients with first-onset CVST. Five patients (3%) had recurrent CVST and 10 patients (7%) had other thrombotic events in a six-year follow-up after discontinuation of anticoagulation therapy<sup>239</sup>. The recurrent rate of all thrombotic events was 3.4% and the recurrence of CVST was 1.3% during the first 16 months<sup>239</sup>. Approximately half of these recurrent events occurred within the first 12 months after discontinuation of anticoagulation therapy<sup>239</sup>. Mild thrombophilia was not associated with recurrent CVST, but severe thrombophilia (including protein C or protein S deficiency, antiphospholipid syndrome, thrombin V Leiden gene mutation) might increase the risk of deep vein thrombosis or pulmonary embolism<sup>237</sup>. The study had similar recurrent rate with the previous Italian and ISCVT studies (1.3% and 2.2% respectively)<sup>16</sup>.

The overall risk of any new-onset thrombotic events after CVST was as high as 4 per 100 person-years, and most of events occurred within the first year<sup>240</sup>. Male and polycythemia/thrombocytopenia are independent risk factor for recurrence<sup>240, 241</sup>. Severe thrombophilia and a prior history of extracerebral venous thromboembolism have been associated with increased risk of recurrence in a certain population<sup>173, 239</sup>. However, the association between thrombotic recurrences and the duration of anticoagulation is controversial<sup>173, 239, 240</sup>. A relevant clinical trial comparing short-term (3 to 6 months) anticoagulation therapy with long-term (12 months) anticoagulation is ongoing<sup>177</sup>.

Oral contraceptives and hormonal treatments containing estrogen increase the risk of thrombosis, thus female should be advised not to use these drugs after CVST. Although pregnancy is associated with increased risk of venous thromboembolism, the absolute incidence of recurrent thrombotic events during future pregnancy is low in women with a history of CVST: the estimated incidence is 9 CVST and 27

extracerebral venous thrombosis out of every 1000 pregnant women<sup>9, 16, 242, 243</sup>. Therefore, a history of CVST should not be a contraindication for future pregnancy. However, women of childbearing age should be informed of the relatively high risk of pregnancy associated thrombosis and the potential benefit if antithrombotic therapy.

The secondary prevention of CVST, deep vein thrombosis and pulmonary embolism shares some common features. Although women are more likely to develop CVST and the severity of thrombophilia may differ, the long-term and short-term risk factors are basically the same<sup>244</sup>. In the ISCVT cohort, the overall recurrent rate (including CVST and other thrombotic events) was 4.1 per 100 person-years<sup>240</sup>. Male and polycythemia/thrombocytopenia are independent risk factors for recurrence<sup>240</sup>. The study also demonstrated that the cumulative risks of thrombotic events increased steadily regardless of the use of anticoagulation therapy. Therefore, randomized controlled trials were warranted to assess the efficacy and safety of short-term and long-term anticoagulation in the prevention of recurrent CVST<sup>240</sup>. Given that the incidence of systemic venous thrombosis after CVST is higher than recurrence of CVST, the secondary prevention of CVST can follow the guidelines in systemic venous thrombosis<sup>199, 240</sup>. However, each individual should undergo risk assessment including thrombophilia and other risk factors. The level of risk, the indication for long-term anticoagulation, the risk of bleeding, and the risk of thrombosis without anticoagulation should be considered carefully.

### **Recommendation**

1. If patients with a history of CVST have a recurrent and constant headache, it is necessary to evaluate the recurrence of CVST and pay attention to intracranial hypertension. (Class I, Level of Evidence C)
2. To prevent recurrence of CVST, it is important to eliminate the root cause. (Class I, Level of Evidence C). It is beneficial to seek and treat prothrombotic conditions, such as protein C, protein S deficiency, antiphospholipid syndrome, and factor V Leiden mutation, for preventing recurrence of CVST in certain patients. (Class IIa, Level of Evidence C)
3. Long-term oral anticoagulants may be considered in patients with recurrent CVT

and severe thrombophilia, with a target INR of 2.0 to 3.0. (Class IIa, Level of Evidence C)

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