Review

Pathogenesis and Management in Cerebrovenous Outflow Disorders

Chaobo Bai[1,2,3,#], Zhongao Wang[1,2,3,#], Christopher Stone[4], Da Zhou[1,2,3], Jiayue Ding[1,2,3], Yuchuan Ding[3,4], Xunming Ji[2,3,5], Ran Meng[1,2,3*]

[1]Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China. [2]Advanced Center of Stroke, Beijing Institute for Brain Disorders, Beijing, China. [3]Department of China-America Institute of Neuroscience, Xuanwu Hospital, Capital Medical University, Beijing, China. [4]Department of Neurosurgery, Wayne State University School of Medicine, Detroit, Michigan, USA. [5]Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing, China

ABSTRACT: In keeping with its status as one of the major causes of disability and mortality worldwide, brain damage induced by cerebral arterial disease has been the subject of several decades of scientific investigation, which has resulted in a vastly improved understanding of its pathogenesis. Brain injury mediated by venous etiologies, however, such as cerebral, jugular, and vertebral venous outflow disturbance, have been largely ignored by clinicians. Unfortunately, this inattention is not proportional to the severity of cerebral venous diseases, as the impact they exact on the quality of life of affected patients may be no less than that of arterial diseases. This is evident in disease sequelae such as cerebral venous thrombosis (CVT)-mediated visual impairment, epilepsy, and intracranial hypertension; and the long-term unbearable head noise, tinnitus, headache, dizziness, sleeping disorder, and even severe intracranial hypertension induced by non-thrombotic cerebral venous sinus (CVS) stenosis and/or internal jugular venous (IJV) stenosis. In addition, the vertebral venous system (VVS), a large volume, valveless vascular network that stretches from the brain to the pelvis, provides a conduit for diffuse transmission of tumors, infections, or emboli, with potentially devastating clinical consequences. Moreover, the lack of specific features and focal neurologic signs seen with arterial etiologies render cerebral venous disease prone to both to misdiagnoses and missed diagnoses. It is therefore imperative that awareness be raised, and that as comprehensive an understanding as possible of these issues be cultivated. In this review, we attempt to facilitate these goals by systematically summarizing recent advances in the diagnosis and treatment of these entities, including CVT, CVS stenosis, and IJV stenosis, with the aim of providing a valid, practical reference for clinicians.

In recent years, long-term brain dysfunction caused by cerebral and internal jugular venous outflow disorders has become increasingly well-understood. Despite this, it has not received attention in proportion to its elucidation, as has been the case for cerebral arterial diseases. Experimental and clinical research investigating cerebral and internal jugular venous outflow disturbance and other related entities is consequently still limited in comparison with arterial etiologies. Nevertheless, the impact exacted on the quality of life of affected patients may be no less than that of arterial diseases. Examples of severe sequelae of venous disorders abound, including CVT-mediated

*Correspondence should be addressed to: Dr. Ran Meng, Xuanwu Hospital, Capital Medical University, Beijing, 100053, China. E-mail: victor65@126.com. #These authors contributed equally to this work.

visual impairment, epilepsy, and intracranial hypertension [1-5]; and non-thrombotic CVS stenosis and/or IJV stenosis-induced long-term unbearable head noise, tinnitus, headache, dizziness, sleeping disorder, and severe intracranial hypertension [6-20].

In addition, the vertebral venous system (VVS), a large-volume, valveless vascular network that stretches from the brain to the pelvis and facilitates bilateral communication into and throughout the central nervous system, provides a conduit for diffuse transmission of tumors, infections, or emboli, with potentially devastating clinical consequences. Moreover, the lack of specific features and focal neurologic signs seen with arterial etiologies render cerebral venous disease prone to both to misdiagnoses and missed diagnoses. Whereby, it is imperative to raise awareness and make a comprehensive understanding of these issues.

In this review, we attempt to facilitate these goals by systematically summarizing recent advances in the diagnosis and treatment of these entities, including CVT, CVS stenosis, and IJV stenosis, with the aim of providing a valid, practical reference for clinicians.

1. Cerebral venous thrombosis

1.1 Etiology

Cerebral venous thrombosis (CVT) is a subtype of stroke that mainly affects young individuals. The pathological mechanism of CVT has not yet been fully elucidated, but vessel wall dysfunction, alterations in hemodynamics, and changes in blood composition are all recognized as potential contributors. A variety of risk factors may predispose patients to CVT; risk factors are classified as either non-genetic, as in pregnancy and malignancy, or genetic, as in the hereditary thrombophilias.

1.1.1 Non-genetic risk factors

Pregnancy and the postpartum period

Both pregnancy and the postpartum period have been widely considered to be common risk factors for CVT; however, recent studies have shown that a higher risk of CVT is associated with the postpartum period, and that pregnancy is not as significant. A multicenter, case-control study from the Netherlands in 2019, for instance, indicated that pregnancy did not increase the risk of CVT compared with the control group, while the risk of CVT was increased 10-fold during the postpartum period [21]. In addition, a large, multicenter clinical study (VENOST study) in Turkey involving 1144 patients in 2017 showed both that gynecologic risk factors constituted the largest group of causes of CVT, and that the postpartum period was the most prevalent of all gynecologic risk factors

[22]. A real-world cohort study from China yielded similar results, showing that the top risk factor for CVT in females was the postpartum period [23].

Oral contraceptive use

Oral contraceptive use is also a common risk factor for CVT. A meta-analysis by Dentali F et al. suggested that patients with oral contraceptives had a high risk of developing CVT (odds ratio (OR) 5.59; 95% confidence interval [CI] 3.95 to 7.91; $p<0.001$) [24]. These results were replicated in another meta-analysis conducted by Amoozegar F et al., which found that women aged 15-50 who had taken oral contraceptives had a CVT risk 7.59 times higher than that possessed by women not taking oral contraceptives. (OR = 7.59, 95% CI 3.82-15.09) [25].

Tumors

As CVT is essentially a deep vein thrombosis (DVT) that impacts the cerebral circulation, it is not surprising that it shares with DVT an association with tumors, especially when the tumors are malignant. Potential mechanisms underlying this association include direct compression, invasion of the cerebral venous sinus by malignant tumors, and malignant tumor-mediated hypercoagulable states [1].

Strong clinical evidence has confirmed that tumors in general, and hematological malignancies in particular, are risk factors for CVT. The findings from a case-control study by Silvis SM et al. involving 594 patients with CVT and 6278 controls suggested that patients with tumors had a 5-fold higher risk of CVT. Notably, the risk of CVT reached nearly 90-fold within 1 year after the diagnosis of hematological malignancies [26].

Obesity

A case-control study from the Netherlands in 2016 reported that obesity is significantly associated with CVT in women. Obese women were nearly 3.5 times more likely to develop CVT than non-obese patients, and the use of oral contraceptives further increased the risk of overweight and obese women by 11 and 29 times, respectively [27].

Other risk factors

Other risk factors, including systemic immune diseases, brain trauma, arteriovenous malformations, infections, head and neck surgery, spontaneous low intracranial pressure, anemia, dehydration, thyroid dysfunction, and hyperhomocysteinemia, etc., all may also contribute to the occurrence of CVT [28, 29].

1.1.2 Genetic thrombophilia

Anti-thrombin, protein C, and protein S deficiencies

Screening for genetic thrombophilia is an integral part of the CVT risk factor assessment. A number of common etiologies have been described, including deficiencies of anti-thrombin, protein C, and protein S [30]. The results of Martinelli et al. indicated that the prevalence of anti-thrombin, protein C, and protein S deficiency in patients with CVT are 2.5, 5.2, and 3.1%, respectively [31]. Two high-quality studies investigated the role of anti-thrombin, protein C, and protein S deficiency as risk factors for CVT. The combined ORs of these studies were 2.69 (95% CI, 0.66–10.96; $p<0.19$) for anti-thrombin, 11.10 (95% CI, 1.87–66.05; $p<0.009$) for protein C deficiency, and 12.49 for protein S deficiency (95% CI, 1.45–107.29; $p<0.03$) [24, 28-30].

Prothrombin G20210A and factor V Leiden

Prothrombin G20210A and factor V Leiden are regarded as common risk factors for arterial ischemic stroke as well as CVT [32]. In a meta-analysis conducted by Green M et al. in 2018, however, it was reported that Prothrombin G20210A and factor V Leiden polymorphisms had a greater effect on CVT than on arterial ischemic stroke [33]. In addition, the meta-analysis results reported by Dentali F et al. suggested that factor V Leiden (OR 3.38; 95% CI 2.27 to 5.05; $p<0.001$) combined with the prothrombin G20210A mutation (OR 9.27; 95% CI 5.85 to 14.67; $p<0.001$) significantly increases the risk of CVT [24].

FVIII

A matched case-control study in 2018 that included 116 patients and 116 controls by Vecht L et al. reported that elevated FVIII was frequently observed in CVT patients (CVT vs. control was 83.6% vs. 28.4%, $p<0.001$). Patients with elevated FVIII had a nearly 15-fold increased risk of developing CVT (OR 15.3, 95% CI 7.8-30.1) compared with controls. Interestingly, the association between FVIII and CVT was more prominent in male patients than in females [34].

FXII

In 2008, Reuner KH et al. analyzed 78 consecutive patients with CVT and 201 healthy members of the general population of southern Germany, finding that the TT genotype of the FXII C46T gene may be a new independent risk factor for CVT (OR 4.57; 95% CI 1.55-13.41; $p=0.006$) [35]. Similarly, a study by Prabhakar P et al. from India in 2012 showed that this FXII mutation disrupts the vital role played by FXII in the fibrinolytic pathway, resulting in a 2.9-fold increase in the risk of CVT [36].

JAK2 V617F mutation

There is currently controversy over the advisability of routine JAK2 gene screenings for CVT patients. A study from France in 2008 found that the likelihood of a positive screen for JAK2 mutations in CVT patients without myeloproliferative disorders was as low as 1.1%, and therefore concluded that routine testing is not recommended [37]. However, during the same period, an Italian study found a higher mutation rate of about 6.2%, leading the authors to suggest that JAK2 mutations should be sought in the interest of developing a more rational early management protocol for patients carrying the mutation [38]. Another retrospective cohort study from Italy in 2012 agreed, finding a 6.6% mutation rate and proposing that the JAK2 V617F mutation should be considered as a screening option [39].

1.2 Clinical subtypes

1.2.1   Cerebral venous sinus thrombosis (CVST)

Cerebral venous sinuses include the superior sagittal sinus, inferior sinus, transverse sinus, straight sinus, sigmoid sinus, and cavernous sinus. CVST is the most common subtype of CVT, the clinical manifestations of which include headache, visual impairment, epilepsy, focal neurological deficits, and altered consciousness.

1.2.2   Cortical venous thrombosis

Isolated cortical venous thrombosis is not common and has only been reported in individual cases. The clinical manifestations of isolated cortical venous thrombosis are similar to those of venous sinus thrombosis, either alone or in combination with other symptoms such as papilledema, epilepsy, and focal neurological deficits. Of these symptoms, it has been reported in the literature that focal neurological impairment and epilepsy were more common in patients with isolated cortical venous thrombosis [40-42].

1.2.3   Cerebral deep venous thrombosis

Cerebral deep venous thrombosis is a relatively rare and potentially lethal subtype of CVT. The vein of Galen and the basal vein are the principal conduits of deep venous outflow responsible for drainage of the cerebral hemispheric white matter, basal ganglia, thalamus, and diencephalon. Because cerebral deep venous thrombosis affects venous outflow in this territory, it may cause mental status alterations, gaze palsy, and diffuse encephalopathy or coma [43-46].

1.3 Clinical manifestations

1.3.1   Headache

The symptoms with which CVT presents are highly variable between individuals. Headache is usually the first, and is also the most common symptom of CVT [47, 48]. It frequently accompanies other clinical symptoms but may also present in isolation, and only 10% of CVT patients do not report it [49]. In CVT, most headaches present acutely or sub-acutely; only a few are chronic. The location of the headache has no significant correlation with the lesion, unless the lateral sinus is involved, in which case patients are prone to neck or occipital pain [50]. The properties of CVT headaches are diverse, including thunderclap, migraine-like, cluster, post-dural puncture, band-like, and others [2]. This headache variability and lack of specificity can result in diagnostic delay. Therefore, clinicians should be aware that some types, such as aggravated headaches, thunderclap-like headaches, or headaches while lying down or during the Valsalva maneuver, should prompt concern for CVT [51, 52].

1.3.2   Seizure

Epileptic seizures are a feature of the presentation in nearly 40% of severely acute CVT cases, a higher rate than that seen in either acute arterial stroke or intracranial hemorrhage [48, 53]. Seizures may be generalized or focal, and some patients may experience both. Patients with epilepsy generally manifest sensorimotor deficits, hemorrhagic infarcts, frontal lobe lesions, or superior sagittal sinus or cortical venous thrombosis [3, 54, 55]. Status epilepticus, which is considered a neurological emergency, occurs in 5.6%-7% of CVT [3, 55]. The impact of epilepsy on CVT mortality is still controversial. It was reported that status epilepticus is one of the factors leading to the death in CVT patients, and that mortality with status epilepticus is three times higher than that seen with non-sustained seizures [55]. On the other hand, findings from another study suggested that there is no significant association between seizures and mortality or 90-day prognosis [56]. Still, it is worth noting that early identification and management of epilepsy may help minimize neurological impairment.

1.3.3   Focal neurological deficits

About 40% of CVT patients present with focal neurological deficits, including motor or sensory impairment, aphasia, and cranial nerve palsies [57]. In CVT, brain parenchymal impairment may result from insufficient compensatory venous outflow, precipitating focal neurological deficits affecting the obstructed region. Because of the extensive anastomoses and physiological variation that characterize the intracranial veins, however, the connection between focal neurological deficits and

impaired vessels may be inconsistent. Unlike in ischemic stroke, most of these deficits are caused by vasogenic edema secondary to blood-brain barrier impairment, which resolves relatively readily [58]. Focal deficits are more common in non-inflammatory CVT, while cavernous sinus syndrome is more commonly observed in infection-associated CVT.

1.3.4   Altered consciousness

Approximately 14% of CVT cases feature severely altered consciousness in the early phase [1]. The presence of altered consciousness in CVT is usually thought to be associated with involvement of the deep venous system [59]. Although CVT patients with altered consciousness are more likely to get an early diagnosis, coma is a strong predictor of poor prognosis: it is reported that nearly 25% of patients still have progressive coma despite aggressive anticoagulation [60]. Therefore, the establishment of a rapid diagnostic protocol and more effective intervention strategies for patients with severely altered consciousness are priorities in the effort to improve the prognosis of severe CVT.

1.3.5   Visual manifestations

CVT can cause neuro-ophthalmological symptoms, including visual impairment and papilledema. Visual impairment, including vision loss and visual field defects, may be linked pathogenically to papilledema induced by elevated intracranial pressure or focal lesions. Papilledema can be found in most CVT patients, suggesting the presence of increased intracranial pressure. Fortunately, the majority of visual impairment induced by CVT is restorable, although persistent papilledema may ultimately cause permanent optic atrophy. In addition, it has been reported that CVT can manifest as psychiatric symptoms and transient global amnesia [1, 2, 61-64].

1.4 Diagnosis

1.4.1   CT/ CT venography (CTV)

CT is the most commonly used initial examination tool for sudden, new-onset presentations suggesting CVT, such as headache, epilepsy, changes in consciousness, and focal neurological signs. However, only about one-third of patients exhibit the direct CVT signs of high attenuation in the cortical veins or cerebral venous sinuses. Indirect signs, such as cerebral hemorrhage and subarachnoid hemorrhage, occur infrequently. CVT may also appear as a filling defect of the cerebral venous sinus on contrast-enhanced CT [65, 66].

CTV can provide fast and reliable results, exhibiting a diagnostic efficacy at least equal to that of MRV. The main drawbacks of this modality are the radiation exposure it entails and the limitations of its application imposed by allergies to iodinated contrast material [53, 67, 68].

1.4.2 MRI/Time-of-Flight (TOF)-MRV/Contrast-enhanced (CE)-MRV/Phase Contrast (PC)-MRV

MRI and MRV, owing to the high accuracy they confer, have gradually become standard diagnostic tools for CVT [69]. The primary problem posed by their use is a scanning speed that is inadequate to meet the demand faced by the emergency department. Another issue concerns the inferiority of MRV to DSA in diagnostic accuracy for stenosis, due to which it may generate false-positives and false-negatives for this entity [70]. Finally, while conventional MR sequences are impaired by limited resolution for solitary cortical venous thrombosis, advances in MRI scanning and imaging technology have mitigated this concern. For instance, while 2D-TOF-MRV is the most commonly applied tool for diagnosing CVT in clinical practice, its diagnostic accuracy is inferior to that of 3D-CE-MRV, which provides better image quality and resolution of intracranial veins, as well as superior inter-operator consistency due to a short scanning time. However, it is worth noting that CE-MRV is prone to false-negative results in chronic thrombosis or in cases of partially recanalized thrombi[71], and that contrast injection and the presence of poor renal function limit its application [72]. Another promising novel imaging modality is 3D-PC-MRV, which offers the advantage of flow quantification to assist in distinguishing between thrombi and venous blood flow. 3D-PC-MRV also provides a realistic velocity map that supports the assessment of venous flow and the degree of stenosis. The disadvantages of this method relate to the long scanning time it requires, and the ideal velocity encoding that may generate motion artifacts and inconsistencies between operators [73] (Fig.1).
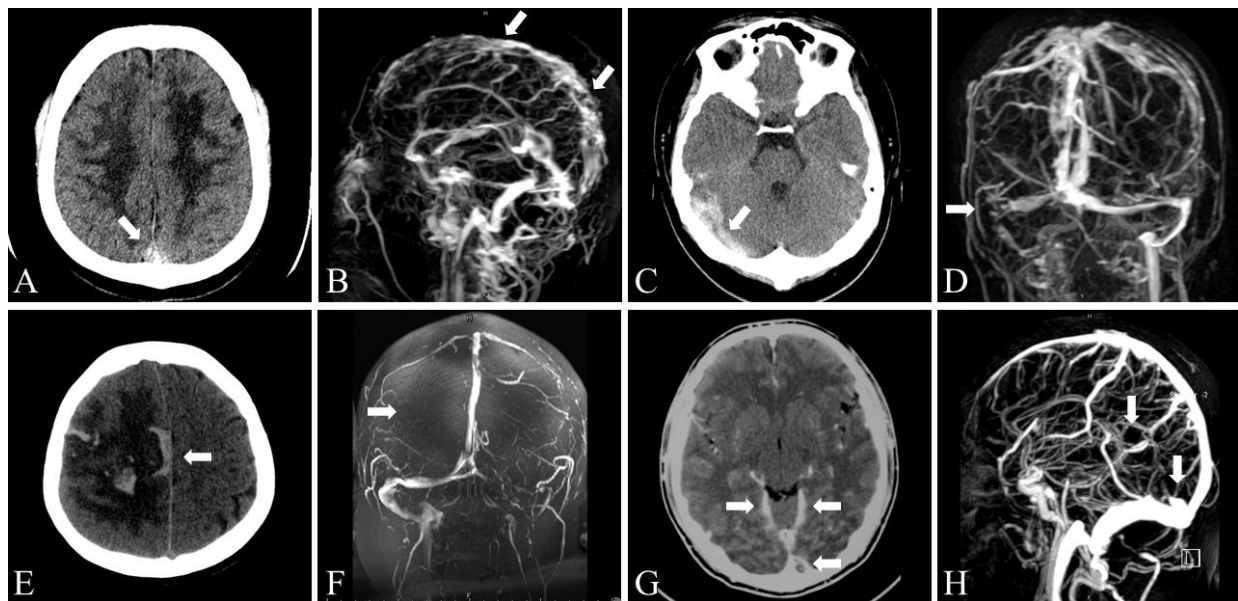
Figure 1. Imaging findings using CT and MRV in patients with CVT. (A-B) Superior sagittal sinus thrombosis. Axial CT demonstrated hyperintense signal intensity of the superior sagittal sinus (A). Sagittal CE-MRV confirmed thrombosis in the superior sagittal sinus (B). **(C-D)** Right transverse sinus and sigmoid sinus thrombosis. Axial CT demonstrated hyperintense signal intensity of the right transverse sinus (C). MRV confirmed thrombosis in the right transverse sinus and sigmoid sinus (D). **(E-F)** Cortical venous thrombosis. Axial CT scan of a patient with cortical venous thrombosis showed a venous hemorrhagic infarct in the right parietal lobe (E). TOF-MRV showed disappearance of the right cortical veins. The white arrow indicates that this right cortical venous disappearance was caused by a thrombus (F). **(G-H)** Cerebral deep venous thrombosis. Hyperintense signal intensity of the straight sinus and bilateral deep cerebral veins was observed using axial CT (G). With sagittal CE-MRV, the straight sinus and bilateral deep cerebral veins were not observed. The white arrows indicate filling defects that were caused by the thrombus (H).

1.4.3   Invasive diagnostic procedures

Cerebral angiography

Cerebral angiography is generally appropriate when the diagnosis cannot be determined after MRV and CTV, or when an endovascular treatment procedure is under consideration. Aplasia or malformations of cerebral veins or venous sinuses can be clarified during the venous phase of cerebral angiography. If a cerebral vein or venous sinus is not visualized with angiography, the suspicion for acute CVT should be high [74, 75].

Cerebral venography

Direct cerebral venography involves injection of contrast material using micro-catheters into the cerebral vein or venous sinus after introduction through the internal jugular vein. When this is done, CVT with partial obstruction manifests as a filling defect, while fully obstructed venous vessels show no filling. Direct cerebral venography is also capable of measuring venous pressure, rendering it useful in cases when intracranial venous hypertension is suspected [74, 75].
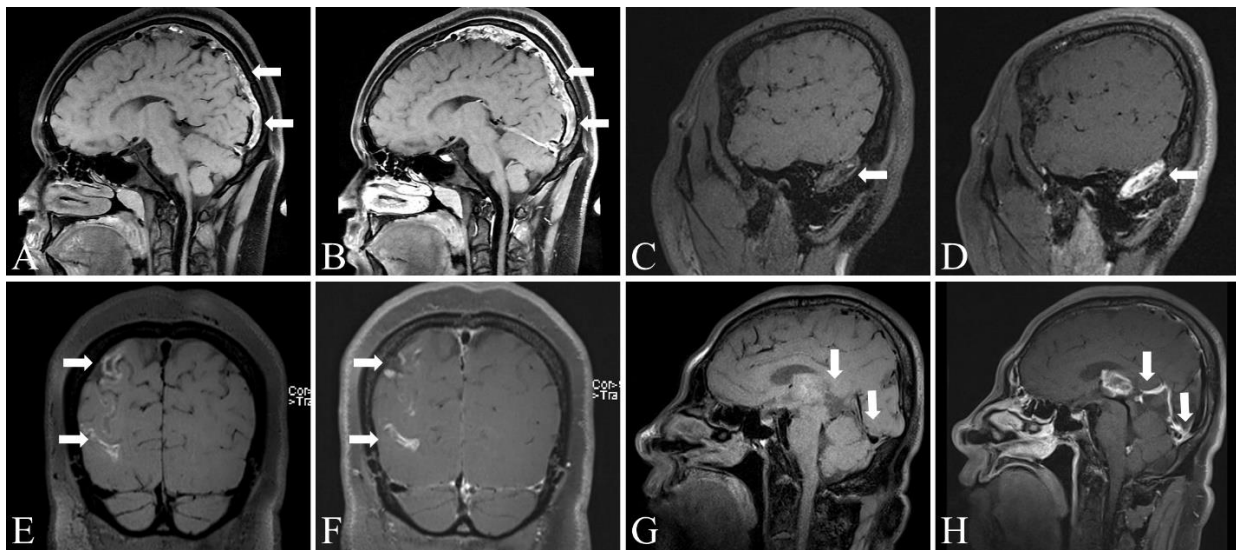
Figure 2. Imaging findings using MRBTI in patients with CVT. (A-B) Subacute superior sagittal sinus thrombosis. Sagittal MRBTI and MRBTI enhancement showed significant hyperintense signal in the superior sagittal sinus, suggesting intraluminal subacute thrombus formation. **(C-D)** Chronic right transverse sinus and sigmoid sinus thrombus. Sagittal MRBTI showed significant isointense and hyperintense signal in the right transverse sinus and sigmoid sinus, suggesting intraluminal chronic thrombus formation (C). Sagittal MRBTI enhancement showed that the lumen in the right transverse sinus and sigmoid sinus was enhanced. The white arrows indicate that new blood vessels appeared inside the thrombus (D). **(E-F)** Subacute cortical venous thrombosis. Coronal MRBTI and MRBTI enhancement demonstrated hyperintense signal in the cortical veins of the right parietal and occipital lobes, suggesting subacute intraluminal thrombus formation. **(G-H)** Chronic straight sinus thrombosis. Sagittal MRBTI showed significant isointense and hypointense signal in the straight sinus and the deep cerebral veins (G). Sagittal MRBTI enhancement showed that the lumen in the straight sinus and the deep cerebral veins was enhanced. The white arrows indicate that new blood vessels appeared inside the thrombus (H).

1.4.4   Advanced diagnostic modalities

Transcranial Doppler

Transcranial Doppler may support the diagnosis of CVT and is useful for its capacity to detect the venous blood flow velocity and hemodynamic pattern. Its main drawback is susceptibility to interference from bony structures [76, 77].

4D flow MRI

4D-flow-MRI allows visualization and quantification of physiological cerebral venous hemodynamics; the quantitative analysis of cerebral venous blood flow by 4D-flow-MRV demonstrates high reliability and accuracy. 4D-flow-MRV is limited by an imperfect ability to visualize cerebral venules [78].

*T2*gradient-echo sequence*

Although MRV supplies high resolution when tasked with imaging major venous thromboses, the T2*gradient-echo sequence demonstrates a diagnostic value superior to traditional MRV for the variable, superficial cortical veins [79].

Magnetic resonance black-blood thrombus imaging technique (MRBTI)

Traditional imaging techniques detect thrombi primarily indirectly, through changes in venous blood flow. This renders them susceptible to interference, resulting in a mismatch between the image and the actual thrombus. In 2016, Yang Q et al. established MRBTI as a potential solution to this problem, and thus as a potential first-line diagnostic tool for CVT. MRBTI can effectively suppress the blood flow signal to black in order to directly detect the thrombus itself, which then appears with high signal intensity. Furthermore, MRBTI can quantify the volume of thrombus using software assistance. Accordingly, the occurrence of false-positives may be diminished compared to conventional MRV, thereby improving the accuracy of CVT detection [80]. In addition, this sequence has been shown to yield good sensitivity in both acute and non-acute CVT patients, thus contributing value both to the early identification of CVT and further observation over time [81]. MRBTI does not require contrast agents, and its capacity to directly quantify volume variation of the thrombus renders it useful for CVT follow-up. Despite these promising features, however, larger and multicenter studies are required to generate more evidence to validate the application of this emerging technology for use in CVT **(Fig.2)**.

1.4.5   D-Dimer and NSE measurement

Measurement of the fibrin degradation product D-dimer can be performed easily in the emergency room, exhibits high sensitivity for the initial diagnosis of CVT, and is also, given its high negative predictive value, a reliable way to exclude it. Normal D-dimer levels measured by sensitive immunoassay or rapid ELISA predict a low probability of CVT [82-84]. However, several studies have offered evidence that negative D-dimers may have a limited efficacy for ruling out CVT in the context of a recently isolated headache [85, 86].

Serum neuron-specific enolase (NSE), located in neurons and neuroendocrine-derived cells, is a sensitive laboratory biomarker for brain injury. Although there is currently little research designed to evaluate the value of NSE levels in the workup of CVT, a recent retrospective study found that baseline NSE levels were associated with CVT severity, and had the potential to predict prognosis [87].

1.5 Treatment

1.5.1   Anticoagulation

Anticoagulation is the first-line therapy for initial CVT treatment. It may be achieved using traditional anticoagulants such as unfractionated heparin, low molecular weight heparin, and warfarin; as well as with new anticoagulants, such as dabigatran and rivaroxaban. Anticoagulant therapy functions by halting the growth of existing thrombi, promoting recanalization, and preventing deep vein thrombosis and pulmonary embolism. The new anticoagulants offer the advantages of requiring infrequent blood testing and conferring low risks of thrombus recurrence and bleeding, while their main drawback has historically been the unavailability of antagonists; this has recently changed, however, with the advent of the reversal agents idarucizumab and andexanet alfa [88-91].

1.5.2   Fibrinolytic Therapy

The rate of partial or complete recanalization following anticoagulant therapy alone has been estimated to fall between 47%-100%, and 9%-13% of CVT has been shown to carry a poor clinical prognosis despite sufficient anticoagulant therapy. Thus, simple anticoagulation may insufficient for some patients, particularly when large and extensive thromboses are present. In these cases, fibrinolytic therapy may be added as a supplementary treatment. Fibrinolytic therapy may be delivered non-invasively with novel drug therapies such as batroxobin, or using invasive therapeutic strategies such as direct catheter thrombolysis and mechanical thrombectomy /thrombolysis [53].

Batroxobin is a non-invasive drug therapy that may promote CVT recanalization. Ding et al. analyzed the safety and efficacy of batroxobin in combination with anticoagulants on CVT and found a higher recanalization rate in the batroxobin group compared with the control group, especially in CVT patients with a high level of fibrinogen. Severe hemorrhagic events were not observed [92, 93].

Endovascular therapy may be considered when disease exhibits rapid progression, resulting in sequelae such as severe neurological impairment or altered consciousness [94]. Early recanalization of CVT generally predicts a better prognosis [95]. Regardless of drug therapy or endovascular treatment, however, it is difficult to achieve ideal recanalization in some patients. In 2018, a study from the United States assessed these refractory patients, showing that, in CVT patients with a poor response to endovascular therapy, using "microcatheter contact with alteplase perfusion" may effectively achieve recanalization without adverse outcomes, rendering this a promising alternative to be pursued after failure of standard treatment [96]. Currently, prioritization between the various endovascular methods for CVT therapy cannot be conducted due to insufficient clinical evidence [97].

1.5.3 Surgery

Given the availability of both standardized anticoagulation and endovascular therapies for CVT, surgical treatment plays a limited role. Life-saving surgical interventions such as decompressive craniotomy should be considered, however, if the patient's neurological symptoms continue to deteriorate or if imaging confirms severe brain tissue compression despite maximal non-surgical treatment [98-101].

2. Non-thrombotic cerebral venous sinus (CVS) stenosis

2.1 Proposed etiology

Although neither the origin nor the pathogenesis of non-thrombotic CVS stenosis is well-defined, a number of factors are believed to contribute to its onset. These etiologies are classified as either extrinsic or intrinsic.

2.1.1 Extrinsic anomalies

Broadly speaking, any extraluminal anomalies that impinge on the venous wall may cause CVS stenosis. Due to the present lack of research designed to investigate CVS stenosis, current etiologic theory is mainly derived from clinical experience. A few case reports have produced evidence for extrinsic impingement by describing an association between meningiomas and CVS stenosis. In such cases, an intracranial mass occupying the vicinity of the intracranial venous sinuses may directly invade the venous walls, leading to venous stenosis and outflow obstruction. If involvement of the cerebral venous sinuses is sufficiency extensive, this can cause severe, life-threatening cerebral edema [102-105].

Another potential, though controversial, impingement-based etiology is intracranial hypertension. Compelling evidence has been produced for a close association between isolated intracranial hypertension and transverse sinus stenosis: elevated intracranial hypertension may cause the collapse of cerebral venous sinus walls, resulting in CVS stenosis and outflow obstruction [11, 106, 107]. Nevertheless, Peng et al. proposed that the effects of intracranial hypertension and CVS stenosis may, rather than the former giving rise to the latter, be better conceived as mutually reinforcing [61].

2.1.2 Intrinsic anomalies

The other category of CVS stenosis etiologies is intrinsic anomalies, which refers to proposed intraluminal causes. Arachnoid granulations represent this category. These are normal intracranial structures that protrude into the dural sinus lumen and function to facilitate drainage of cerebrospinal fluid into the cerebral venous system. Generally, arachnoid granulations larger than 1cm are considered giant, and may appear as local dilatations or filling defects within the cerebral venous sinus. Most giant arachnoid granulations are discovered incidentally and only rarely cause clinical symptoms, but may narrow or obstruct the lumen of the dural sinuses, leading to intracranial venous hypertension [108-110]. Notably, multiple consecutive giant arachnoid granulations appear similar to CVT on MRV, and may therefore be misdiagnosed as such [111].

2.2 Clinical manifestations

2.2.1 Intracranial hypertension

Isolated intracranial hypertension is a syndrome characterized by elevated intracranial pressure of an uncertain etiology. Various etiological hypotheses have been proposed, including intracranial venous stenosis, increased secretion or decreased absorption of cerebrospinal fluid, and the effects of hormones [61]. Nevertheless, despite evidence that intracranial sinus stenosis is closely related to intracranial hypertension, the causal relationship between these entities remains, as mentioned above, uncertain [106]. It has been shown, however, that intracranial venous stenting was effective in relieving medically refractory isolated intracranial hypertension, suggesting that intracranial venous outflow disorders may promote the development of intracranial hypertension [6-10]. The common intracranial hypertension-related clinical manifestations such as headache, visual impairment, and papilledema may occur in the setting of CVS stenosis, but vary among individuals [11-13].

2.2.2 Tinnitus

Unilateral or bilateral pulsatile tinnitus is another common symptom of CVS stenosis. When it presents in isolation most patients tolerate this symptom, resulting in treatment delays or misdiagnoses due to the lack of accompanying focal neurological signs. Accordingly, pulsatile tinnitus may last for many years before the affected patient is finally diagnosed with CVS stenosis. Although the mechanism of tinnitus in this context is unknown, it has been shown to respond exceptionally well to endovascular stenting, which may imply an etiologic relationship to changes in intracranial venous blood flow [14-20].

2.3 Diagnosis

2.3.1 MRV

MRV is a widely accepted, non-invasive method for assessing the cerebral venous system. It has several advantages, including avoidance of ionizing radiation exposure, no need to use a contrast agent, non-invasiveness, and suitability for long-term follow-up and pregnant women. One area in which MRV falls short is in the display of veins with slow flow velocity [67, 112].

Time-of-Flight magnetic resonance venography (TOF-MRV) is the most used modality for the diagnosis of CVS stenosis, and the two-dimensional TOF MRV has good sensitivity compared with three-dimensional TOF MRV for demonstrating slow flow. Disadvantages of TOF MRV include a limited capacity to display intracranial venules, as well as susceptibility to interference from tissue signals (e.g., from fat), resulting in errors in image interpretation [43, 79, 113-118].

Compared to TOF-MRV, CE-MRV enhances visualization of the intracranial venous system. This visual superiority comes at the expense of requiring the use of a contrast agent, however, rendering CE-MRV unsuitable for patients who are allergic to the contrast agent and for pregnant women.
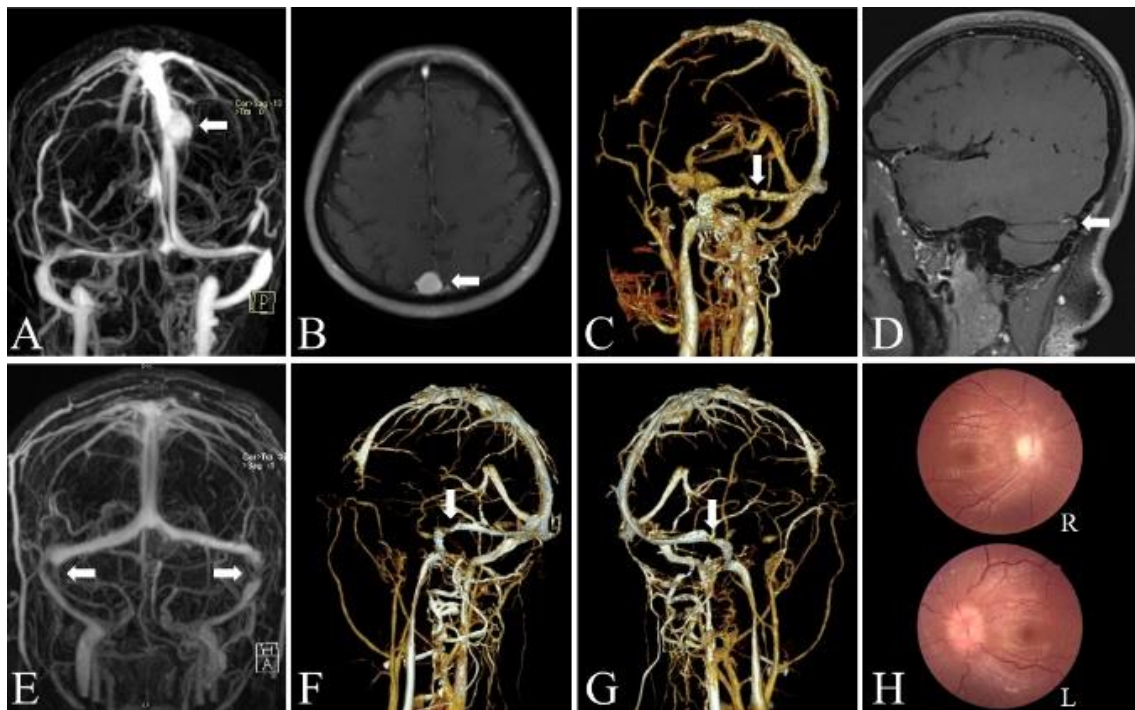
Figure 3. Imaging findings in patients with CVS stenosis. (A-B) Large meningioma-induced superior sagittal sinus stenosis seen with CE-MRV and with MRI enhancement. In CE-MRV, a well-defined meningioma caused confined stenosis of the superior sagittal sinus (A). The meningioma demonstrated hyperintense signal intensity with MRI enhancement, and caused significant compression of the superior sagittal sinus (B). **(C-D)** Large arachnoid granulation-induced transverse sinus stenosis seen with CTV and MRBTI. Severe stenosis of the left transverse sinus was observed with CTV (C). MRBTI showed a large arachnoid granulation in the left transverse sinus (D). **(E-H)** Severe bilateral transverse sinus stenosis seen with MRV and CTV. Severe stenosis of the bilateral transverse sinuses was observed using MRV (E) and CTV (F-G). Fundus examination showed bilateral papilledema (Frisen grade IV in the left eye and Frisen grade II in the right eye) (H).

2.3.1 CT venography (CTV)

The term "CT-venography" was first described by Casey et al. as a technique capable of rapid generation of high-quality images of the cerebral venous circulation [119]. CTV is a non-invasive and relatively inexpensive detection method characterized by fast scanning time and convenient operation. For patients with ferromagnetic implants or cardiac pacemakers on the body, it is more suitable than MRV. In addition, the immediacy with which CTV can be carried out makes it superior to MRV in the management of critically ill patients.

In a study involving 24 patients, CTV was shown to be superior to MRV in showing the details of small veins,

and was more reliable in revealing the basal veins, the thalamostriate veins, and the inferior sagittal sinus [120]. These researchers then concluded that the diagnostic value of CTV is equal to that of MRV. Similarly, Casey et al. showed that CTV is preferable to MRV in displaying vein details and venous collateral circulation. The use of CTV has been limited, however, by the exposure to ionizing radiation and injection of contrast agents it entails, and its unsuitability for pregnant women or repeated follow-up [67, 121, 122] (Fig.3).

2.3.2 Digital subtraction angiography (DSA) and Direct Cerebral Venography (CV)

DSA is well-known as the gold standard for evaluating intracranial venous anatomy, showing features such as hypoplasia or atresia of the intracranial veins and dural sinuses, and is also capable of providing detailed information on the flow dynamics of contrast media. CV is invariably performed during endovascular therapy and is accomplished first by insertion of microcatheters directly into the internal jugular vein, after which contrast media is injected into the dural sinus or cerebral vein. Because these methods are invasive and require exposure to radiation and contrast media, both are considered suboptimal diagnostic techniques [74, 75, 124].

2.3.3 Transcranial Doppler (TCD)/Transcranial color-coded duplex sonography (TCCS)

Ultrasound examination of CVS is a technique developed in recent years that effectively assesses cerebral blood flow velocity and abnormalities of the venous lumen. TCD recognizes venous blood vessels by relying on fragments of the circle of Willis as markers, and thus is limited in the scope of examinations it permits. The advantage of TCCS over TCD is that it can depict venous structures using blood flow information independently of the need for an arterial marker. In addition, TCCS may be used to study the collateral circulation of intracranial veins. Given its inexpensiveness and non-invasiveness, TCCS can also be used as a detection method in follow-up patients. However, TCCS does have some drawbacks. First, it cannot detect all intracranial venous structures: for older patients, thickening of the bony structures affects the reflection of sound waves, resulting in interference that impedes detection of intracranial veins. In addition, increased intracranial pressure affects hemodynamics, thus affecting detection with TCCS. Finally, there are a large number of variations in the intracranial veins, especially among smaller vessels, that are not supported by uniform norm data and therefore difficult to evaluate with TCCS [125-128].

2.3.4 Four-dimensional flow magnetic resonance imaging (4D-MRI)

Despite its advantages, one drawback of MRV is its lack of capacity to collect quantitative hemodynamic information; 4-dimensional (4D) flow MRI, by contrast, offers the potential to visualize and quantify the hemodynamics of the entire cerebral venous system. 4D-MRI provides unique and detailed insights, including changes in hemodynamics, recruitment of collateral pathways, and normalization of blood flow conditions after recanalization. Thus, this technique overcomes the limitations of standard MRV and CTV with respect to detecting hemodynamic information, as well as the limitations of ultrasound regarding bony windows that may hinder the detection of intracranial veins [78, 129-132].

2.3.5 Four-dimensional CT angiography (4D-CTA)

4D-CTA is a convenient non-invasive alternative to DSA that can both identify cerebral venous abnormalities such as CVT or CVS stenosis, and is sufficiently sensitive to differentiate between them. In comparison with angiographic information obtained with DSA and MRV, however, its ability to image subependymal and deep medullary veins is suboptimal [133].

2.3.6 Intravascular ultrasound (IVUS)

IVUS is an effective diagnostic tool in coronary and carotid angiography as well as in endovascular stenting that has also been applied in recent years to cerebral venous diseases. As an auxiliary tool for conventional venoplasty or stenting, IVUS appears to possess potential to augment diagnostic accuracy and to provide management guidance [134, 135].

2.4 Treatment

Currently, endovascular stenting is the most widely applied treatment for CVS stenosis. Although stenting has been shown to effectively alleviate CVS stenosis-related symptoms such as intracranial hypertension and tinnitus [6-10, 18-20, 136], assessment of its overall safety and efficacy will require larger, multicenter clinical trials. As more patients with CVS stenosis undergo this procedure, specification of the ideal candidate profile for stenting, as well as a comprehensive account of its risks, benefits, and potential complications, will serve as objectives for future research.

As for intracranial mass lesions such as meningiomas, optimization of surgical strategy may improve clinical results and minimize complications such as the need for

sinus reconstruction [102-105]. One apparently promising surgical technique for patients with CVS stenosis is cerebrospinal fluid shunt placement. Levitt et al. reported that a patient with intracranial hypertension had a significant improvement in bilateral transverse sinus stenosis after installation of a cerebrospinal fluid shunt, leading the authors to speculate that intracranial hypertension may cause collapse of the transverse sinus wall, resulting in stenosis. Reduction of intracranial pressure using a cerebrospinal fluid shunt may reduce the pressure gradient to which the venous wall is exposed, allowing the sinus to re-expand [137].

3. Internal jugular vein (IJV) stenosis
3.1 Proposed etiology

Unlike the internal carotid artery, the internal jugular vein lacks smooth muscle, rendering it vulnerable to extrinsic impingement. Thus, as was the case for CVS stenosis, the etiology of IJV stenosis can be divided into extrinsic and intrinsic anomalies.

3.1.1 Extrinsic anomalies

Structural abnormalities adjacent to the IJV may manifest as bony compression, arterial compression, enlarged lymph nodes, or an enlarged thyroid, and may therefore impinge on the venous wall, causing venous outflow obstruction [123, 138]. Compression of the IJV lumen may produce a spectrum of consequences ranging from local stenosis to complete occlusion. The etiology of compressive insults to the IJV varies along its different segments. In general, the upper IJV is susceptible to compression by the lateral mass of cervical vertebrae at the C1 segment and by the styloid processes, while the middle and lower IJV are more susceptible to compression by the adjacent carotid artery, lymph nodes, and aberrant muscles. Of all these potentially impinging structures, bone appears to be the most common culprit, with previous studies showing that about 40% of extrinsic anomalies are bony in origin [14, 15]. A recent study showed that the incidence of IJV stenosis secondary to external compression reached 41.9% in a Chinese cohort [139].

3.1.2 Intrinsic anomalies

Intrinsic anomalies include thrombi, vessel wall abnormalities, and malformed venous valves. IJV thrombosis is a rare entity, mentioned only in a few case reports [140-142]. Intraluminal defects (such as flaps, webs, septa, membranes, and malformed valves) may hinder normal blood flow drainage from the brain, resulting in hemodynamic alterations, including reflux, reduced flow, or no flow. Doppler and intravascular ultrasound are effective tools for visualizing malformed valves, of which a variety of types have been reported, including fused, elongated, ectopic, accessory leaflet-containing, inverted, and double valves [143, 144].

3.1.3 The vertebral venous system (VVS)

The VVS is a valveless, interconnected venous system with abundant side branch anastomoses that extends longitudinally down the entire length of the spinal canal. It can be partitioned into three distinct divisions: an internal plexus, an external plexus, and the basivertebral veins. Postural changes between the supine and erect positions affect the drainage of the VVS. In the erect position, venous outflow from the brain mainly relies on VVS, and the IJVs only drain approximately 10% of outflow. Thus, the VVS provides free venous communication between the brain and spinal cord, and could potentially serve as an alternative circulatory route in patient with IJV stenosis. However, it also increases the risk of tumor metastasis, infection and embolism [145-147].

3.1.4 IJV stenosis and CNS disorders

It has been reported that IJV stenosis may be associated with various CNS disorders, such as multiple sclerosis, Alzheimer's disease, Parkinson's disease, and Meniere's disease [148-152]. In the case of MS, the link with IJV stenosis has, since it was proposed by Zamboni P et al. in 2009 along with the concept of chronic cerebrospinal venous insufficiency (CCVSI), triggered a wide-ranging debate. One of the outcomes of his conception, according to which abnormalities in cerebrospinal venous flow may contribute to the pathogenesis of MS, was that an increasing number of MS patients undergo endovascular treatment in an attempt to improve neurological function and quality of life. Unfortunately, recent multicenter randomized controlled trials have concluded that endovascular treatment does not improve the outcome of MS, and suggested that endovascular treatment for MS patients should be discouraged until appropriate high-quality trials confirm safety and efficacy [153]. Another perspective on CCVSI was provided by Thibault et al., who proposed that chronic persistent venulitis caused by Chlamydophila pneumoniae, an obligate intracellular bacterium, may play a role in CCVSI and other vascular diseases; their non-randomized cohort study found that extracranial blood flow improved after treatment with a combined antibiotic protocol [154-156]. In summary, although some CNS disorders appear to be associated with IJV stenosis, causal relationships between these entities and IJV stenosis have not been firmly established.

To further evaluate this issue, comprehensive consideration of precipitating risks such as age, sex, race, comorbidities, etc., should be incorporated into future safe and ethical observational studies.

3.2 Clinical manifestations

The clinical manifestations of IJV outflow disturbance may differ among patients due to anatomical variation and variable compensatory capacity of collaterals. Clinical manifestations such as headache, head noises, tinnitus, visual disorders, hearing loss, sleep disturbances, cognitive decline, and neck discomfort are common in IJV stenosis. Of these, head noises and tinnitus may be the typical clinical manifestations of IJV stenosis and are suggestive of IJV blood flow alterations. IJV stenosis can also precipitate intracranial hypertension, which can be effectively relieved by stenting [14, 15, 19].
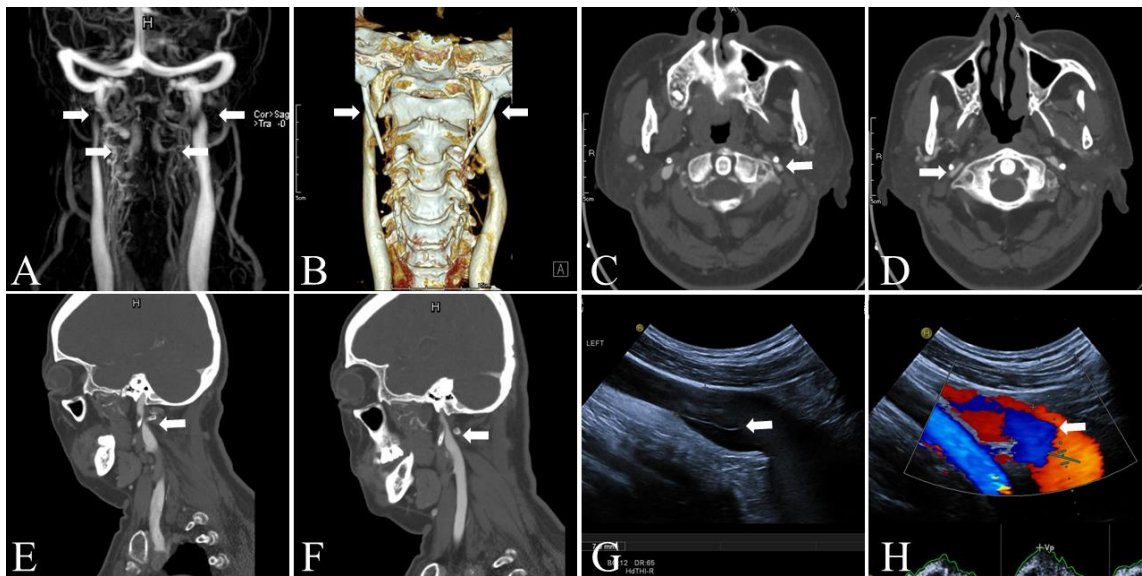
Figure 4. Imaging findings in patients with IJV stenosis. (A-F) Bony compression-induced bilateral IJV stenosis seen with MRV and CTV. Bilateral internal jugular vein stenosis with abnormally tortuous vertebral venous plexus compensation seen with MRV (A). CTV showed that the bilateral internal jugular veins were significantly compressed by elongated styloid processes, as well as the transverse processes of C1 (B-F). **(G-H)** Lengthy internal jugular vein valve that induced IJV reflux. Jugular venous ultrasound showed a lengthy venous valve (G) and the blood reflux it precipitated (H).

3.3 Diagnosis

3.3.1 MRV

MRV is the most commonly used technique for assessing extracranial vessels and provides the advantage of non-invasiveness as well as of less operator dependence. TOF-MRV can be performed quickly to directly visualize IJV morphology and is more sensitive in the presence of slow blood flow. CE-MRV, however can visualize IJV anatomy in more detail. In addition, 4D-MRI and Phase-Contrast (PC)-MRV have the potential to assess IJV blood flow velocity and pattern [157-159].

3.3.2 Doppler ultrasonography

Doppler ultrasonography is the primary screening tool used in the evaluation for IJV stenosis. Its benefits include its non-invasiveness, low cost, and freedom from radiation; it is also useful for providing information on IJV flow velocity and assessing for the presence of any abnormal intravascular structures. Its use is hindered, however, by operator dependence, which may result in variable measurements [160, 161]. Another potential application for this technology was proposed by Thibault et al., who described the efficacy of extracranial duplex ultrasonography for the postoperative assessment of venoplasty. They found that ultrasonography provided reliable information about IJV and vertebral vein stenoses and could, with the help of venous blood volume flow detection technology, quantify the degree of stenosis [162].

Ultrasound may also be used in tandem with venography in a technique referred to as intravascular ultrasound (IVUS). Compared with conventional venography, IVUS provided higher resolution and measurement accuracy to better distinguish true stenotic lesions, while venography yielded some false positives. In

addition, IVUS was found to be superior to conventional venography in displaying intravascular abnormalities, resulting in higher diagnostic accuracy [163, 164] **(Fig.4).**

3.3.3   Catheter venography

Catheter venography is still considered the gold standard for assessment of the degree of IJV stenosis and pressure gradients in patients scheduled for endovascular surgery. However, as discussed above, it is inferior to IVUS in reflecting intravascular anomalies. Moreover, the contrast injection and exposure to radiation it requires limit the desirability of catheter venography as a method for evaluating IJV stenosis [163-167].

3.4   Treatment

To date, a deficiency of strong clinical evidence has impaired the production of a consensus with respect to the treatment of IJV stenosis. Current treatments mainly attempt to address etiologies and symptoms, with the aim of restoring normal IJV hemodynamics.

3.4.1   IJV thrombosis

Although IJV thrombosis is not common, timely anticoagulation or endovascular treatment appears, in the interest of avoiding serious complications, to be advisable. Standard anticoagulant therapy, consisting of subcutaneous injections of low molecular weight heparin or intravenous heparin for several days with a subsequent transition to oral anticoagulants, is recommended [141, 142, 168, 169]. It should be understood that these treatment recommendations are not limited to simple IJV thrombosis: other applicable situations include planning IJV reconstruction surgery, IJV venous valve malformations and other hemodynamic abnormalities related to IJV stenosis that predispose to thrombosis and coexisting hypercoagulable states.

3.4.2   Extrinsic abnormalities

Extrinsic impingement-mediated IJV stenosis may require a different treatment approach. Given the large proportion of such cases that appear to be caused by bony compression, it is important to evaluate for this etiology in patients with non-thrombotic IJV stenosis. Multidisciplinary cooperation is gradually emerging as important in this context in the interest of successfully restoring IJV hemodynamics. For example, in cases caused by bony compression from the styloid process and the lateral mass of the C1 cervical vertebral segment, endovascular stenting alone appears to be ineffective secondary to an inability to expand. Thus, modified styloidectomy is considered as a potential adjunct

approach to alleviate the compression. In addition, external compression of the IJV by aberrant muscular elements has also been reported, and may similarly require adjunctive approaches in addition to stenting to avoid frustrated expansion [170, 171].

3.4.3   Intraluminal defects

Intraluminal defects leading to impaired IJV blood flow may be managed with percutaneous angioplasty techniques such as endophlebectomy and autologous vein patch angioplasty, which appear to alleviate blood flow problems within the IJV,[172, 173] but are currently in need of stronger clinical evidence to support their safety and efficacy.

3.4.4   Endovascular treatment

Zamboni P et al. reported in 2009 that chronic cerebrospinal venous insufficiency might, as mentioned above, be responsible for multiple sclerosis [148], but the endovascular stenting and balloon angioplasty that have since emerged as therapies are controversial [173-176]. Large, multicenter randomized controlled trials have concluded that endovascular treatment might be safe but ineffective for patients with multiple sclerosis [177-179]; moreover, significant adverse events and complications of stenting performed for this purpose have been recorded [180]. On the other hand, one study performed on a Chinese cohort revealed the encouraging result that IJV stenosis-induced intracranial hypertension can be corrected by stenting [19]. Therefore, the development of more rigorous inclusion criteria and careful assessment of potential complications for patients with IJV stenosis who may benefit from stenting is urgently needed.

3.4.5   Other treatments

Because of sufficient collateral circulation, a considerable number of patients with IJV stenosis have normal or only mildly elevated intracranial pressure [15]. By contrast, some patients with IJV stenosis may present with severe intracranial hypertension resulting in serious visual damage. For these patients, optic nerve sheath fenestration may be an effective method of alleviating risk of visual deterioration in cases when the causative IJV stenosis cannot be corrected immediately [61, 181].

4.   Summary

In conclusion, intra- and/or extra-cranial venous outflow disturbances merit more scientific attention than they have received up to this point. This is due, in addition to the intrinsic desirability of further characterizing these

important categories of cerebrovascular pathology, to the avoidance of misdiagnosis and treatment delay that a comprehensive understanding of these entities could help achieve. Currently, multicenter, case-control studies designed to assess treatment of cerebrovenous outflow disorders are limited, and research regarding etiologies and pathophysiological mechanisms is, similarly, far from sufficient. It is therefore essential that large, multi-center, well-designed randomized and controlled clinical trials be designed as soon as possible to rectify these gaps in understanding, as they may make a substantial difference to the treatment of our future patients.

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Disclosure of conflicts of interest

The authors report no conflicts of interest.

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