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UNCOMMON AND/OR UNUSUAL HEADACHES AND SYNDROMES (J AILANI, SECTION EDITOR)

Cerebral Venous Thrombosis Headache

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Abstract

Purpose of Review Cerebral venous thrombosis (CVT) is a neurovascular disease caused by a thrombotic occlusion of either a dural sinus or cerebral vein. CVT results in a variety of neurological symptoms with the most common being headache. The purpose of this review is to characterize CVT, describe the headache pattern, and, finally, provide an update to date review of diagnostic and treatment options for this condition.

Recent Findings CVT is a very difficult disease to diagnose due to the variability in both patient presentation and imaging findings. Recent literature has attempted to standardize its risk factors, diagnosis, and treatment modalities. Additionally, new laboratory studies are being investigated for CVT patients who present with isolated headaches.

Summary CVT is a debilitating disease requiring immediate medical or surgical intervention. Because the disease can mask as a multitude of neurological deficits, patients are not properly diagnosed. Headache is the most common patient presentation. The quality of this headache is highly variable with no specific location or pattern. New literature has provided insight into potential diagnostic and treatment options for CVT patients. However, further large-scale cohort studies are necessary to standardize the care for this disease.

Keywords Cerebral venous thrombosis · Cerebral venous thrombosis headache · Thunderclap headache · Thrombosis, isolated headache, headache in young

Introduction

Cerebral venous thrombosis (CVT) is a thrombotic disorder of the brain venous sinuses. The first documented case of CVT was in 1825 by French physician Ribes [1]. Autopsy confirmed that this 45-year-old man's headache and seizures were due to a thrombosis of the superior sagittal and lateral sinuses [1]. In 1828, the first case of puerperal CVT was documented by John Abercrombie [2]. Dr. Abercrombie documented a 24-year-old female presenting 2 weeks post-delivery with headache and seizures [2]. On post mortem examination, she was found to have thromboses of the superior sagittal sinus and cortical vein [2]. There was very little CVT research up until the late twentieth century with the introduction of catheter cerebral angiography and later with computed tomography (CT) venography and magnetic resonance (MR) venography. Both single- and multi-center international studies emerged after these advancements, which reshaped our understanding CVT [3–6].

It is well documented that headache is the first and most common presentation of CVT [7•, 8, 9]. Approximately 60–90% of these patients present to a physician complaining of severe headache [7•]. However, the description and location of this headache are extremely variable with no identifiable or recognizable pattern [8]. This may lead to misdiagnosis and increased morbidity and mortality. This review article will first discuss the clinical and radiologic features of CVT; then, we will further discuss the headache presentation of CVT, along with current and new diagnostic and treatment options for the disease.

Epidemiology

CVT affects approximately 5 people per million annually and accounts for less than 1% of all strokes [10, 11]. It affects women more than men, notably women aged 20 to 50. The International Study on Cerebral Venous Thrombosis (ISCVT), one of the largest multi-center cohort studies for CVT,

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reported 487 of the 624 (78%) patients with CVT were less than 50 years old [4, 10]. Additionally, 465 out of the 624 patients (74.5%) were women [4]. The gender discrepancy in CVT is likely due to estrogen fluctuations, oral contraceptive use, and pregnancy/puerperium. Silvis et al. [12] pooled data from several studies to estimate the prevalence of specific risk factors for CVT. Between 54 and 71% of female patients on oral contraceptives and between 11 and 59% of pregnant/puerperium patients were diagnosed with CVT [12].

Other risk factors to consider can be seen in Table 1 [4, 12–17, 18, 19–22].

Pathophysiology

The pathophysiology of CVT requires an understanding of both cerebral vein anatomy and physiology. A venous thrombus forms due to an imbalance of prothrombotic and thrombolytic factors. Eventual propagation into the cerebral veins/sinuses forces a back flow increasing capillary and venous pressure [23]. High pressures in combination with this backflow result in a breakdown of the blood-brain barrier and decreased cerebral perfusion, leading to either local cerebral ischemia, edema, or intracerebral hemorrhage [23, 24]. The cerebral veins can be divided into two entities: dural venous sinuses and cerebral veins. Venous sinuses play a role in both venous drainage and cerebrospinal (CSF) absorption via arachnoid granulations [25]. Therefore, a sinus thrombus can lead to a dysfunction in CSF absorption and intracranial hypertension [25]. The most common location for a CVT is the superior sagittal sinus and lateral sinuses. In the ISCVT study, 62% of CVTs were in the superior sagittal sinus, with 44.7% and 41.2% in the left and right lateral sinuses, respectively [4].

Cortical vein thrombosis can result in damage of brain parenchyma. Damage to parenchymal tissue after an occlusion of these veins will depend on the size of the thrombus, capillary pressure, breakdown of the blood-brain barrier, and number of robust collaterals [26]. Parenchymal lesions occur in approximately 50–60% of patients with a CVT, and surprisingly, literature from animal models suggests parenchymal lesions can also occur in occlusions of dural venous sinuses [26, 27].

Table 1 CVT risk factors

Sex-specific risk factors	Oral contraceptives Pregnancy Hormone replacement therapy
Hereditary thrombophilia	Factor V Leiden Prothrombin G20210A mutation Antithrombin deficiency Protein S deficiency Protein C deficiency
Other	Infections
Systemic diseases	Cancer Myeloproliferative neoplasms Inflammatory bowel disease Behçet disease Thyroid disorders Systemic lupus erythematosus Antiphospholipid antibodies Nephrotic syndrome Sarcoidosis Wegener granulomatosis
Hematologic conditions	Anemia Paroxysmal nocturnal hemoglobinuria
Iatrogenic	Obesity Head trauma Dural arteriovenous fistula Spontaneous intracranial hypotension Dehydration

Clinical Presentation

The most common clinical presentation for CVT is headache. The second most common is seizure, with approximately 80% of acute symptomatic seizures occurring even before the diagnosis [28]. Further details regarding the clinical presentation of CVT depend on the anatomical locations of the thrombus and affected brain parenchyma. Patients with dural venous sinus thrombosis without parenchymal involvement typically have a clinical presentation of intracranial hypertension syndrome: headache, papilledema, and decreased visual acuity. A thrombosis of the deep venous system leads to mental status disorders, diffuse encephalopathy, or coma. Patients with a cavernous sinus thrombosis present with ophthalmoplegia, orbital pain, proptosis, or chemosis [11]. Brain parenchymal lesions can occur in either scenario leading to various focal neurological deficits corresponding to the anatomical location of the damage.

CVT Headache

While there is evidence explaining the pathophysiology of CVT, there is limited literature on why it is associated with headache [29, 30]. Some theories exist to explain this association. Mechanical stretching of nerve fibers in the walls of occluded venous sinuses is thought to be one possible cause. This blockage in the venous sinus can lead to venous volume expansion and dilatation of the sinus and cortical and spinal veins. A compression of the nerve fibers within the veins is thought to cause a headache [31, 32]. Since the dura surrounding the sinuses is innervated by the trigeminal nerve, the trigeminovascular system may be activated and cause a migrainous headache.

A cortical infarct, due to limited blood reflux, can cause cortical irritation and inflammation which may also

exacerbate pain [33••, 34••]. It is also proposed that the headache could simply be caused by increased intracranial pressure [35]. Infection must also be considered as an underlying cause for CVT and in turn headache [1].

This criterion is useful in diagnosing a CVT headache but should be used with caution (Table 2). CVT headache has a highly variable presentation without an obvious pattern and should be identified as soon as possible in the patient's presentation. Headache is the most prevalent symptom in CVT and usually the one manifesting first. The ISCVT cohort which is the largest study, observing symptoms associated with CVT, reported that 89% of patients with CVT presented with headache. Other studies have reported headache as being the most common symptom in CVT, ranging from 62 to 95% [36–38]. Rarely, headache will be the only symptom at presentation (6–23%) [2, 39]. Typically, patients presenting with headache are younger compared with those that are headache free; ISCVT reported average age of 35 and 42 respectively. This is likely related to cerebral atrophy in the elderly being protective against intracranial hypertension as well as possible diminished pain reactivity in the elderly [16, 18, 40]. Although there is some evidence that headache can be ipsilateral to the sinus involved, other studies showed no consistent pattern [2]. The headache characteristics of CVT can mimic several primary headache disorders with migraine appearing to be the major differential diagnosis, particularly when considering the high prevalence of migraine in the general population. While variable numbers of CVT headache patients report throbbing, the majority describe nausea, vomiting, and/or phono/photophobia [17, 41, 42]. CVT headache differs from migraine in several aspects. CVT headache is often exacerbated by the Valsalva maneuver and recumbence [43]. Headache onset in 64–88% of CVT patients is reported as sub-acute and the pain is more often diffuse rather than unilateral [15, 35, 44]. In a large study of 200 patients with proven CVT, patients reported their headache was acute in 60%, sub-acute in 24%, and chronic in 10%. In this study, however, acute was defined as 1–3 days, sub-acute as 4–14 days, and chronic as over 14 days [16]. The majority of CVT headaches typically appear over a 1–14-day period. Rarely, CVT headache can also present as a thunderclap headache. It is important to identify subarachnoid hemorrhage since the treatment is different and making a misdiagnosis is potentially fatal [15].

Table 2 ICHD-3 classification of CVT headache

A. Any new headache, fulfilling criterion C
B. Cerebral venous thrombosis (CVT) has been diagnosed
C. Evidence of causation demonstrated by both of the following:
1. headache has developed in close temporal relation to other symptoms and/or clinical signs of CVT, or has led to the discovery of CVT
2. either or both of the following:
a) headache has significantly worsened in parallel with clinical or radiological signs of extension of the CVT
b) headache has significantly improved or resolved after improvement of the CVT
D. Not better accounted for by another ICHD-3 diagnosis.

The neurological exam is abnormal in 68% of patients. The most common findings are focal neurological deficits, altered mental status, and papilledema in 5–22%, 15–20%, and 15–30% respectively [4, 5, 18].

Although CVT headache can be difficult to differentiate from primary headache disorders, some clues include a subacute onset; pain is often diffuse and throbbing with concurrent phono-photophobia, neurological deficits, worsening with Valsalva maneuvers and can have signs of intracranial hypertension such as papilledema.

Diagnostic Studies

Imaging is crucial for the diagnosis and localization of CVT. The three most important imaging techniques are as follows: CT scan of the head, CT venography, magnetic resonance imaging (MRI) of the brain with MR venography and catheter angiography [10]. Catheter angiography has significant complications and is only used if CT or MRI is inconclusive, if a dural arteriovenous fistula is considered, or if endovascular intervention is needed [7•]. MRI with MR venography is the most common imaging modality, specifically recommended are the T2*-weighted gradient recall echo, susceptibility-weighted imaging, and contrast-enhanced MR venography [45]. MRI signal intensities of a thrombus depend on its age: an early thrombus will appear hypointense caused by increased amounts of deoxyhemoglobin, and a late thrombus as hyperintense because of methemoglobin [45, 46]. CT scan is inferior to MRI and is mostly used in acute cases to look for hemorrhage. Location of the thrombus and type of CT scan (with or without contrast) are important when diagnosing a CVT. In an acute CVT, the occluded sinus will appear hyperdense on CT without contrast [47]. Furthermore, if a clot is in the superior sagittal sinus or cerebral vein, the hyperdense vessel is termed a "dense triangle" or "cord sign," respectively [48, 49]. Contrast-enhanced CT scans typically display an "empty delta sign" signifying contrast enhancement of the wall of the thrombosed sinus due to collateral circulation. Lastly, contrast-enhanced CT venography is considered a reliable alternative to MR venography, particularly in patients with contraindications for MRI. Approximately 99% of sinus thromboses and 88% of cortical vein thromboses were correctly diagnosed by CT venography [50]. Other than venous occlusions, there are specific signs on imaging that are important in diagnosing parenchymal lesions secondary to a CVT. The most common secondary lesion is an intracerebral hemorrhage

(ICH), which can display various patterns on CT such as scattered subcortical foci to lobar hematomas [7•]. Additionally, small juxtacortical hemorrhages are pathognomonic for a superior sagittal sinus thrombosis [51].

CVT Treatment and Diagnostic Advancements

CVT is a medical emergency and should be triaged to an appropriate unit such as a stroke unit or neurological intensive care unit (NICU) [10]. The mainstay treatment option is heparin or low molecular weight heparin (LMWH) with a bridge to warfarin [10]. Patients who are unsuccessful with the above treatment are considered for endovascular treatment and/or decompressive craniectomy [10, 52]. New oral anticoagulants (NOACs) have emerged as potential treatment options for CVT. Patel et al. [52] reviews the literature for successful treatment of CVTs with NOACs. A case study conducted by Hon et al. [53] treated two CVT patients with dabigatran, an oral direct thrombin inhibitor. Initially, these patients were started off with LMWH for 2 weeks followed by 6 months of dabigatran [53]. Ultimately, MRI and MRV findings showed complete resolution of the clot and normal venous flow [53]. Furthermore, Geisbuch et al. [54] compared seven CVT patients on rivaroxaban, an oral factor Xa inhibitor, with nine CVT patients on a vitamin K antagonist. Patients who received rivaroxaban had a mean survival rate of 93.8% [55]. Lastly, apixaban, which has been rigorously studied in the treatment of venous thromboembolism, has not been formally studied for CVT patients [53].

Patients presenting with only a headache make it quite challenging to diagnose a CVT. The current literature has recommended two laboratory tests which may be helpful in diagnosing CVT in headache patients. Alons et al. [54] conducted a study with a combined total of 636 consecutive patients complaining solely of headache and were not pregnant/in puerperium. Forty-five (7.1%) were diagnosed with CVT, one of which had a negative D-dimer (1.6%) [54]. Sensitivity for diagnosing CVT with D-dimer was 97.8% (95% CI 25.2–41.7%), specificity was 84.9% (95% CI 81.8–87.7%), and negative predictive value was 99.8% (95% CI 98.9–100%) [54]. Moreover, Demir et al. [56] proposed the use of red cell distribution width (RDW) as a useful diagnostic tool for cerebral venous sinus thrombosis (CVST) in isolated headache patients. A retrospective cross-sectional study determined the RDW ratio of patients diagnosed with CVT was higher than that of patients with a primary headache (15.3 ± 1.4 vs $13.3 \pm .5$; $p < .0001$) [56]. Furthermore, it was concluded that an appropriate RDW cutoff of 14.1% (sensitivity 91.9%, specificity 99%, positive predictive value 92.8, negative predictive value 0.082) along with clinical symptoms was enough to consider a CVT [56]. D-dimer and RDW require further studies before they are used to diagnose CVT.

For patients with persistent CVT headache, we have found it helpful to first rule out recurrent CVT and other secondary causes for headache and then treat the patient based on which headache type they most closely resemble. In a study looking at 3-year clinical outcomes in CVT patients, around 60% had persistent headache. Out of a sample of 29 patients, the headache resembled migraine in 14, tension headache in 13, and other headache disorders in 2 [57, 58].

CVT can cause persistent fluctuations in intracranial pressure. Case reports have shown chronic paroxysmal intracranial hypertension especially when acetazolamide is tapered off. The EFNS (European Federation of Neurological Societies) advises the following for the acute treatment of CVT: (1) analgesics for the treatment of headache, (2) lumbar puncture (if there are no parenchymal lesions and prior to considering anticoagulation), and (3) acetazolamide, a carbonic anhydrase inhibitor which reduces intracranial pressure. For the chronic phase of CVT, EFNS recommends paracetamol for pain management, acetazolamide, and lumbar puncture(s) and/or lumbar peritoneal shunt if needed [59]. In patients with elevated blood pressure, acetazolamide 500 mg or furosemide can be considered. It is however unclear how effective this is in alleviating headache [60]. One case study revealed that intravenous dihydroergotamine (DHE) 0.5 mg three times a day was effective in a CVT patient with refractory headache. Additional studies have suggested possible benefit with repeat lumbar punctures and lumbar peritoneal shunt. The efficacy of these is unproven [60]. Previously, steroids were used for CVT headache; however, these have shown to have no benefit [61]. The American Heart Association and American Stroke Association published a joint statement about diagnosis and management for CVT which advised that for severe and persistent headache, a recurrent CVT should be ruled out [60].

Much research is still needed to characterize CVT headache and possible treatment approaches.

Conclusion

The symptomatology, diagnostic criteria, and treatment options for CVT are complex, requiring a multidisciplinary approach to provide successful treatment for this potentially debilitating disease. With recent advancements in both medicine and imaging techniques, researchers can further investigate CVT and standardize its care. However, with its numerous risk factors and diverse patient presentations, CVT continues to cause much morbidity and mortality.

Compliance with Ethical Standards

Conflict of Interest Amit Mehta, Julius Danesh, and Deena Kuruvilla declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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