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Review Article

Cerebral venous sinus thrombosis: An underdiagnosed red flag disease in Ophthalmology

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ABSTRACT

Cerebral venous sinus thrombosis is a disease characterised by thrombosis of the cerebral veins and the dural sinuses. It has a variable presentation. It is common in any condition that leads to a prothrombotic state. It leads to cerebrospinal fluid outflow obstruction, thus leading to raised intra-cranial pressure. Management requires a multi-disciplinary approach. Mainstay therapy is with anticoagulants, fibrinolytics. Ophthalmologist play a vital role in the diagnosis and management of this life-threatening condition.

1. Introduction

Cerebral venous sinus thrombosis (CVST), includes thrombosis of the cerebral veins and the dural sinuses. It is a rare disorder that can lead to significant morbidity and mortality. CVST can present with variable signs and symptoms that include a headache, benign intracranial hypertension, subarachnoid hemorrhage, focal neurological deficit including non-localising cranial nerve six palsy, seizures, unexplained altered sensorium, and meningoencephalitis.[1,2] Clinical features as headache and diplopia, many a times brings the patient to ophthalmology department at first. The diversity of risk factors and variable presentation present challenges in diagnosing cerebral vein thrombosis. Delay in diagnosis is common. Thus, having a high index of suspicion for this disorder is crucial to ensure timely diagnosis and treatment.[3,4]

The aim of the article is to get a brief knowledge of CVST and to enlighten ophthalmologist role in this disease entity.

1.1. Epidemiology

Cerebral venous thrombosis is a rare disorder with an annual incidence estimated to be three to four cases per million. The frequency of peripartum and post-partum cerebral venous thrombosis is about 12 cases per 100,000 deliveries in pregnant women, which is only slightly lower than that of peripartum and post-partum arterial stroke. Cerebral venous thrombosis occurs three times more frequently in women than in men. This is thought to be due to gender-specific risk factors, for example, oral contraceptive use and, less frequently, pregnancy, puerperium, and hormone replacement therapy. More recently, there has been a significant female predominance among young adults, with the majority of cases (70% to 80%) being in women of childbearing age, but not among children or elderly persons.

1.2. Etiology

There are many risk factors that contribute to the development of cerebral venous thrombosis. A literature has quoted that, at least one risk factor was identified in more than 85% of patients with cerebral venous thrombosis, and multiple risk factors are found in more than 50%

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of patients with cerebral venous thrombosis.[5] In general, cerebral venous thrombosis is common in any condition that leads to a prothrombotic state. Common conditions leading to prothrombotic state include pregnancy, the post-partum state, or those on oral contraceptives, genetic and acquired thrombophilic states. In the International Study on Cerebral Vein and Dural Sinus Thrombosis, genetic and acquired thrombophilia were present in 34% of patients with cerebral venous thrombosis. Inherited thrombophilic disorders includes protein C and protein S deficiencies, antithrombin deficiency, factor V Leiden mutation, prothrombin gene mutation 20210, as well as hyperhomocysteinemia.[6,7] Acquired thrombophilia should be suspected in patients with a history of nephrotic syndrome or antiphospholipid antibodies. Additional causes and risk factors associated with cerebral venous thrombosis include chronic inflammatory disease states such as systemic lupus erythematosus, malignancy, inflammatory bowel disease and vasculitis like Wegener's granulomatosis. It can also be iatrogenic, after certain neurosurgical procedures, direct injury to the sinuses or jugular veins, such as jugular vein catheterization, and even after a lumbar puncture.[8,9]

1.3. Pathophysiology

Normally cerebrospinal fluid (CSF) in the cerebral ventricles drains out from the subarchnoid space to the dural venous sinuses of the brain, which finally return to the internal jugular vein and heart.

Any obstruction of the cerebral sinuses or vein, particularly when there is thrombus and does not resolve will result in impaired cerebrospinal fluid absorption, ultimately leading to increased intracranial pressure. Increased intracranial pressure leads to several manifestations like papilledema, cytotoxic and vasogenic edema of the brain, and may even lead to hemorrhage.

1.4. Clinical presentation

Diagnosis of cerebral venous sinus thrombosis many a times is delayed due to its variable presentation and low annual incidence. Signs and symptoms may be acute, subacute, or chronic, and the majority of patients present with headache. A headache presents in up to 90% of patients.[5] Many a times, a patient with headache presents to ophthalmology department with a suspected refractive error.

Headaches may be generalized or diffuse and may even mimic migraines. Sometimes, it can present as thunderclap variety of headache, starting suddenly and maximal in intensity at onset, thus mimicking as subarachnoid haemorrhage. The headache may get worsened with Valsalva or coughing, indicative of increased intracranial pressure. The patient may also present with diplopia caused by a sixth cranial nerve palsy when the intracranial pressure is too high. The funduscopic examination will reveal papilledema, which, depending on the severity, can cause visual impairment and even permanent blindness if left untreated for a longer duration.

Focal neurologic signs are also common and motor weakness, including hemiparesis, is the most common focal finding. However, unlike arterial thrombosis as the cause of cerebrovascular accidents, localization to one vascular territory is often absent. Seizures are seen in about 40% of patients with cerebral venous thrombosis. Focal seizures account for 50% of those who experience a seizure in the setting of cerebral venous thrombosis but have the potential to generalize to a status epilepticus. Thus, cerebral venous thrombosis should be considered in any patient who presents with a headache with or without some combination of either focal neurologic deficit or new-onset seizures.

2. Evaluation

2.1. Clinical suspicion

Diagnosis of cerebral venous thrombosis is both clinical and neuroradiological. Given its varied presentation and manifesting as papilledema lately and myriad of symptoms, one must have a high index of suspicion to identify and diagnose this rare and potentially life-threatening condition correctly. It should be always suspected in young and middle-aged patients, with cerebral venous thrombosis risk factors, such as postpartum women, those with genetic or acquired thrombophilia, and patients with focal neurological findings. It should also be suspected in the following in any patient who present with atypical headaches and have undergone multiple repeat evaluations for a non-resolving headache. Refractive error should be excluded at first for any type of headache. CVST comes into differential also in the cases of any focal neurological deficit with stroke-like symptoms, especially in the absence of vascular risk factors that would predispose to cerebral vascular accidents (carotid atherosclerosis), seizures (focal, generalized, or status-epilepticus).

2.2. Laboratory investigation

Laboratory evaluation should include a complete blood count, coagulation panel, chemistry panel. Sedimentation rate and C-reactive protein is done to rule out proinflammatory states. The D-dimer assay is a good tool to assess clotting, but unfortunately, it has been shown to have an unacceptable false-negative rate of up to 26% in one study. However, for ruling out deep venous thrombosis (DVT), it has shown good association. This low sensitivity of the D-dimer assay for CVST may be due to the lower thrombotic burden of cerebral venous thrombosis compared to DVT.[10,11]

Based on recent American Heart Association/American Stroke Association guidelines, a negative D-dimer does

not effectively rule out cerebral venous thrombosis and neuroimaging is indicated, if there is clinical suspicion for cerebral venous thrombosis. [12,13]

3. Neuroimaging

3.1. Non-contrast computed tomography (CT)

The speed and accessibility with which this test can be obtained make it the first go test that should be obtained in any patient presenting with an atypical headache, focal neurologic deficit, seizures, altered mental status, or coma in the emergency setting. Radiologist look for a direct sign of cerebral venous thrombosis i.e., the cord sign, a curvilinear hyperdensity within a cortical vein in the presence of thrombosis which can be seen for up two weeks following thrombus formation. Another sign includes a triangular shape hyperdensity in the superior sagittal sinus, also known as the dense triangle sign.

3.2. Magnetic resonance imaging (MRI) and magnetic resonance venography (MRV)

For any patient presenting with headache and papilledema, ophthalmologist first aim should be to exclude any intracranial space occupying lesion. For this, contrast enhanced MRI (CEMRI) is the investigation of choice. CVST is generally missed in CEMRI. So, the investigation of choice for diagnosing CVST is magnetic resonance venography (MRV). MRI is superior to CT when evaluating for parenchymal oedema as a result of cerebral venous thrombosis. MRI findings are thrombus age dependent. An acutely formed thrombus (0 to 7 days) is harder to detect, but by week 2, abnormalities are easier to detect, with both T1 and T2-weighted images showing a hyperdense signal. The combination of an abnormal signal in a venous sinus along with the absence of flow on MRV confirms the diagnosis of CVST. 2-dimensional lumen-based TOF, multiscale entropy (MSE) of haemoglobin products within the thrombus, DWI abnormality within the involved veins or sinus are other diagnostic tests. [14,15]

3.3. CT Venography (CTV)

Present new advanced helical CT scanners can produce CT venography images superior to MR venography in the identification of cerebral veins. Many a times CTV becomes go to investigation of choice in the emergency setting because it can be rapidly performed following a non-contrast head CT while the patient is still in the CT scanner. Also, in the emergency setting when access to MRI imaging may be limited or unavailable, CTV becomes a good diagnostic tool. Radiologist look for the empty delta sign, representing contrast enhancement flowing around the comparatively hypodense region of the thrombosed superior sagittal sinus.

3.4. Cerebral angiography

If the diagnosis is still in question after using MRI and MRV, the last resort is intra-arterial angiography. Angiography best visualizes the cerebral veins and help us to identify anatomical variants of normal venous anatomy that mimic cerebral venous thrombosis. Its use is limited due to its invasive procedure and morbidity. It is useful in rare cases like isolated cortical vein thrombosis without sinus thrombosis. It can very well highlight dilated and tortuous "corkscrew" collateral veins, evidence that there may be thrombosis further downstream of the sinuses.

Most frequently involved sinus is superior sagittal sinus, followed by transverse sinus. [5]

3.5. Differential diagnosis

1. Abducens nerve palsy
2. Cavernous sinus syndrome
3. Head injury
4. Intracranial abscess
5. Neurosarcoidosis
6. Staphylococcal meningitis
7. Subdural empyema

4. Treatment / Management

Management initially focuses on identifying and addressing life-threatening complications of cerebral venous thrombosis, including increased intracranial pressure (ICP), seizures, and coma. Many a times, an Ophthalmologist becomes the first person to diagnose and treat the patient. Ophthalmologist concern is to diagnose and treat raised intracranial pressure (ICP). In the case of increased ICP, the head of the bed should be elevated, and administration of dexamethasone and mannitol should be done promptly to reduce increased ICP. This is followed by admission to the intensive care unit or stroke unit for close ICP monitoring, with a neurosurgical consultation if the patient decompensates and requires surgical decompression. Next, attention should be shifted to specific therapy, including anticoagulation and, in certain cases, catheter-directed fibrinolysis and surgical thrombectomy. If a patient manifests seizures and has a lesion such as a hemorrhage or infarction on neuroimaging, then specific anticonvulsant therapy, as well as seizure prophylaxis, should be initiated. If a seizure does not occur, then seizure prophylaxis is not indicated.

4.1. To decrease ICP

Any patient diagnosed with CVST with papilledema can be promptly started with either oral acetazolamide or injection mannitol to decrease ICP. Duration and dose of the drug should be properly adjusted as per the need.

After diagnosis and start of ICP lowering drug, the patient should be referred to neurologist/ neurosurgeon for further management.

4.2. Anticoagulation

Anticoagulation is the first line therapy in CVST. The goal of anticoagulation is to prevent thrombus propagation, help to recanalize the occluded cerebral veins, and to prevent the complications of pulmonary embolism. It is started after proper expert advice by neurologist and neurosurgeon.

Based on randomized controlled trials and other observational studies, anticoagulation is recommended as a safe and effective treatment of CVST. It should be started immediately upon diagnosis of CVST. Anticoagulation is done with intravenous unfractionated heparin or subcutaneously administered low-molecular-weight heparin or oral anticoagulation with a vitamin K antagonist. The European stroke organization (ESO) guidelines recommend unfractionated heparin in patients with renal insufficiency or the probability of requiring emergent reversal.[5]

The target goal of treatment is an international normalized ratio (INR) of 2.0 to 3.0 in cerebral venous thrombosis 3 to 6 months in patients with provoked cerebral venous thrombosis and 6 to 12 months in patients with unprovoked cerebral venous thrombosis.[5] Sometimes, indefinite anticoagulation is considered in patients with recurrent cerebral venous thrombosis, those who develop deep vein thrombosis and pulmonary embolism in addition to cerebral venous thrombosis, or those with first-time cerebral venous thrombosis in the setting of severe thrombophilia.

4.3. Thrombolysis

Most patients see clinical improvement with anticoagulation therapy. However, few patients clinically deteriorate despite anticoagulation. In these cases, where anticoagulation fails and the prognosis is poor, systemic and catheter-directed thrombolysis is indicated in patients with large and extensive cerebral venous thrombi. However, there is an increased risk of intracranial haemorrhage with the use of thrombolytics. Based on a systemic review conducted in 2003, which looked at 72 studies and 169 patients with cerebral venous thrombosis, there seems to be a possible clinical benefit due to the use of fibrinolytics in patients with a severe presentation. Intracranial hemorrhage occurred in 17% of patients treated with fibrinolytics and was associated with clinical deterioration in 5% of cases. Overall, endovascular thrombolytics should be used at centers with staff experienced in interventional radiology and should be reserved for patients who are clinically deteriorating and despite treatment with anticoagulation.

4.4. Surgical Intervention

Surgical thrombectomy is reserved for cases of severe neurological deterioration despite maximal medical therapy. In the case of large venous infarcts and hemorrhages causing a mass effect with risk of herniation, decompressive surgery has been thought to improve clinical outcomes, especially if done early. Decompressive surgery has shown favourable outcomes observed in more than 50% of patients.[5]

5. Supportive Care

It is important to identify the underlying contributory factors of cerebral venous thrombosis and plan a treatment strategy to correct them. Any reversible pathology that is leading to unwanted thrombosis should be corrected immediately. In addition to clinical follow-up, the American Heart Association and American Stroke Association has recommended follow-up imaging after 3 to 6 months post-diagnosis to assess for recanalization.

6. Enhancing Healthcare Team Outcomes

The diagnosis and management of cerebral venous thrombosis needs a multi-disciplinary approach that includes an ophthalmologist, neurologist, neurosurgeon, radiologist, hematologist, anesthesiologist. The prognosis of these patients is guarded. Even those who survive are sometimes left with permanent neurological deficits.[16,17]

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8. Conflict of Interest

None.

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