INTRODUCTION

Thrombosis of the cranial venous sinuses and the cerebral cortical veins is a common cerebrovascular disorder due to a multitude of causes, which unlike arterial stroke, most often affects even young adults and children. The diagnosis is often missed because the symptoms and clinical course are highly variable, etiological factors are even more heterogeneous making cortical vein thrombosis (CVT) a unique clinical entity. The disorder can occur de novo as the first manifestation, or can overlap on another existing clinical problem. In either case, it is always multifactorial, and is variable in each patient. Each component of the Virchow’s triad (endothelial damage, stasis and hypercoagulability of blood) may in turn have several contributory factors/causes to produce the final manifestation. These factors, which vary from patient to patient, operate together incidentally or accidentally to produce CVT and therefore the patients are often not comparable. This also implies that randomized studies are not reliable in those with CVT, to arrive at logical conclusions on therapeutic guidelines and strategies. The set of actions required to correct the contributory factors will then be different in each patient. Clinical observations based on case series and sharing of such information alone is the alternative to arrive at a consensus. Because of the heterogeneity in the clinical presentation and etiology, the diagnosis of CVT is often missed, and even if a diagnosis is made, the contributory factors which are often subclinical are also missed or overlooked. Most often only one of the etiological factors is prominent enough to be picked up and it is a universal practice to look for rarer causes and some inherited causes of venous thrombosis. Diagnosis is often missed, unless clinicians maintain a high index of suspicion and be aware of the varied clinical presentations to be able to recognize and manage by prompt and proper application of clinical skills, rather than depending heavily on investigations alone.

Depending on the site, size, duration and rapidity of development of thrombus, it can present as seizure alone, space occupying lesion, benign intracranial hypertension, subarachnoid hemorrhage, unexplained altered sensorium or meningoencephalitis. It can be mistaken for metabolic encephalopathy and vertebrobasilar insufficiency. Moreover, the patient may land up with any practitioner or specialist because it can coexist with several medical, surgical and obstetric conditions like pregnancy, eclampsia, postoperative phase, uncontrolled diabetes, pyogenic or other meningitis, disseminated intravascular coagulation (DIC), septicemias, hyperviscosity and thrombophilic states, collagen vascular disorders and vasculitic syndromes. It could also occur while on treatment with certain drugs like L-asparaginase and thalidomide. Cortical vein thrombosis can be the first manifestation of a thrombophilic state like polycythemia, thrombocytosis (both primary and secondary), leukocytosis, sickle-cell disease, hyperhomocysteinemia, hemoconcentration due to a multitude of causes, hypereosinophilia and antiphospholipid antibody (APLA) syndromes. As mentioned already, almost always more than one cause coexists in each patient, which is found out only on good clinical evaluation and not by laboratory studies alone. To compound all this, the new generation doctors forget the importance of proper clinical evaluation and the correlation of important observations in the diet, lifestyle and environment of the patients. Many of them do not bother to find out such information and rather proceed prematurely to laboratory tests for diagnosis. After making a diagnosis of CVT, the clinician should apply clinical skills and common sense with which it is possible to arrive at one or more completely correctable common etiological factors contributing to the development of CVT, even if there is an underlying inherited disorder, which cannot be corrected. Recurrences can be avoided in future if all the other contributory factors are found out by good clinical evaluation. Therefore, CVT almost always has a good prognosis compared to other cerebrovascular accidents (CVAs). In many patients with the so called idiopathic CVT, nutritional deficiencies and lifestyle issues are more important basic etiological factors in pathogenesis, at least in some epidemiological settings such as strict vegetarians and those who consume an unbalanced diet. Study by observation of patients regarding their diet, lifestyle and environment might give the answer to the several etiological factors in cerebral CVT, as in all other clinical problems, rather than depending on the costly laboratory investigations alone.

PATHOGENESIS

The dural sinuses that are most frequently thrombosed are the superior sagittal sinus, the lateral sinus (transverse sinus and sigmoid sinus) and cavernous sinus. Less frequently affected are the straight sinus and the vein of Galen. Still rarely, smaller cortical veins may be the primary site of thrombus formation without evidence of thrombus in the major sinuses or the thrombus in the major sinus would have resolved by the time, the patient comes to clinical attention. This is one reason for the misdiagnosis in computed tomography (CT) and magnetic resonance imaging (MRI). Occlusion of a venous sinus and/or cortical vein is usually caused by a partial thrombus or an extrinsic compression that subsequently progresses to complete occlusion. Once the sinus is occluded, the thrombus may extend to the cerebral cortical veins draining into that sinus (Figure 1). Thrombosis and complete occlusion result in cortical venous infarction, with petechial hemorrhages or overt hemorrhagic infarction. There are
different mechanisms for the signs and symptoms in patients with cerebral venous thrombosis:

- Local effects caused by the venous obstruction, consequent ischemia, infarction or hemorrhage and the neuronal dysfunction
- The mass effect behaving like an intracranial space occupying lesion (ICSOL)
- Venous obstruction leading to sudden development of edema inside the closed compartment of the cranial cavity, which varies depending on the size and site of thrombus, causing rapid development of intracranial hypertension and its consequences
- Sudden development of edema and ischemia in the cortex corresponding to the territory involved, causing hyperexcitability with seizure discharges and neuronal dysfunction later on
- Symptoms and signs due to the underlying disorder/disorders responsible for a thrombophilic state.

In the majority of patients, all these happen suddenly and simultaneously or sequentially and one of the symptoms may dominate the clinical picture. Unlike in arterial obstruction, early development of intracranial hypertension (especially when one of the major venous sinuses is obstructed), is very common. Cytotoxic edema is caused by ischemia, which damages the energy-dependent cellular membrane pumps, leading to intracellular swelling. Vasogenic edema is caused by a disruption in the blood-brain barrier and leakage of blood plasma into the interstitial space, which is reversible if the underlying condition is treated promptly. Besides the severe cerebral edema of sudden onset, there is another mechanism for the development of intracranial hypertention, especially when the thrombus does not resolve or gets organized. Normally, the cerebrospinal fluid (CSF) is transported from the cerebral ventricles through the subarachnoid spaces at the base and surface of the brain to the arachnoid villi, where it is absorbed and drained into the venous sinuses. Thrombosis of these venous sinuses leads to impaired absorption of CSF, and consequently, increased intracranial pressure. Pathological examination shows enlarged, swollen veins, edema, ischemic neuronal damage and petechial hemorrhages, which can merge and become large hematomas.1,2

CAUSES AND RISK FACTORS

Why Does the Thrombus Develop?

Venous thrombosis anywhere in the body results from exaggerated activity of one more mechanisms of hemostasis or reduced activity of one or more natural antithrombotic mechanisms or a combination of both. In reality, thrombosis is almost never due to a single etiological factor, it occurs only when several etiological factors come together accidentally or incidentally. In normal state, the fluidity of blood is maintained by: normal intact endothelium, prostacyclin, antithrombin III, heparin sulfate, thrombomodulin, Proteins C and S, fibrinolytic system, normal flow of blood and the absence of a prethrombotic/hypercoagulable state (thrombophilic state). The common conditions with a tendency for thrombophilic states to be routinely looked for are dehydration (even subclinical), unusual postures in travel or sleep, prolonged immobilization, surgery or trauma, focus of infection/inflammation/abscess adjacent to the sinuses or in its drainage areas, pregnancy/postpartum period, hyperhomocysteinemia, polycythemia, thrombocytosis, obesity, diabetes, oral contraceptives, hormone replacement therapies, antiphospholipid antibodies, paroxysmal nocturnal hemoglobinuria (PNH), Behcet's and other vasculitis, congestive cardiac failure, nephrotic syndrome, smoking, inflammation, liver disease [acquired Protein C and S, antithrombin III (ATIII) deficiency], increasing age, dyslipidemia, atherosclerosis and malignancies. Rarely only one of the contributory causes is an underlying hereditary thrombophilia-like Factor V Leiden activated Protein C resistance (APCR),

1,2
prothrombin gene mutation, hereditary hyperhomocysteinemia, deficiency of Proteins C and S, antithrombin deficiency, increased Factor VIII and dysfibrinogenemia. But in practice, these hereditary thrombophilias are not the primary cause in any patient with thrombosis. One or more of the acquired causes are the real culprits even when they have an underlying hereditary thrombophilia. A clinically obvious prothrombotic risk factor or a direct cause is identified in about 85% of patients with cerebral venous thrombosis. Even in these situations, there are several other coexisting subclinical factors, which need to be corrected to prevent recurrence. Most often, a precipitating factor, such as head injury or obstetrical cause, results in cerebral venous thrombosis in a person with another acquired or genetically increased risk. One example is hyperhomocysteinemia, which is very common due to poor intake of folic acid containing diet, which is almost universal, along with and B₁₂ deficiency, in some strict vegetarians who do not take a balanced vegetarian diet due to curvy, isyrian or during such women become pregnant, several other thrombophilic states are added on to the existing ones and therefore deep vein thrombosis or cerebral CVT occur. Deficiency of folic acid, vitamins B₁₂ and B₉ are the most common cause of hyperhomocysteinemia rather than inherited causes of it. Besides, hyperhomocysteinemia is also seen in many other conditions like renal failure/liver disease, hypothyroidism, smoking, excessive coffee intake, inflammatory bowel diseases, psoriasis and rheumatoid arthritis. Similarly, the most common cause for Protein C and S deficiency is liver disease, which often goes unrecognized, because subclinical liver disease is very common due to alcohol and nonalcoholic fatty liver disease. Acquired Protein S deficiency can also be due to oral contraceptives or hormone replacement therapy, pregnancy, oral anticoagulants, DIC, nephrotic syndrome, inflammatory conditions, after an acute thromboembolism, autoantibodies to Protein S following varicella and other infections. Antithrombin deficiency, when it is severe, can cause severe arterial and venous thrombosis and resistance to heparin therapy. But after an acute thrombosis or while on heparin therapy, ATIII levels decrease to less than 50%, leading to wrong diagnosis. Acquired causes of ATIII deficiency are seen in liver disease, DIC, nephrotic syndrome (loss in urine), chemotherapy with L-asparaginase and preeclampsia. Elevated factor VIII levels can also contribute to thrombosis, and is seen in increasing age, obesity, pregnancy, surgery, chronic inflammation, liver disease, hyperthyroidism, diabetes and in non-O blood groups. Pregnancy and postpartum period are important considerations in women of childbearing age. Pregnancy itself is a thrombophilic state due to the changes in blood composition like increased factor VIII, fibrinogen, decreased Protein S, decreased fibrinolysis (increased plasminogen activator inhibitor (PAI)), obesity, cesarean section, immobilization and other mechanical and hemodynamic factors due to pregnant state. Coexisting hyperhomocysteinemia is very common due to malnutrition and consequent deficiency of folic acid. Besides the chance of tissue thromboplastin entering blood due to placental injury, ischemia or during delivery, the fetus, coexisting reactive thrombocytosis due to hemorrhage or iron deficiency state may all contribute to increased thrombotic tendency. During the last trimester of pregnancy and after delivery, the risk of CVT is increased. The frequency of peripartum and postpartum CVT is about 12 cases per 100,000 deliveries. Inflammatory bowel diseases such as Crohn’s disease and ulcerative colitis are described as risk factors. Corticosteroids used in treatment of these conditions may play a causative role. Collagen vascular diseases such as systemic lupus erythematosus, Wegener granulomatosis and Behçet’s syndrome have been reported to be associated with CVT. Trauma in the form of head injury, direct injury to the sinuses or to the jugular veins (from jugular catheterization) and neurosurgical procedures can trigger the onset of CVT. Lumbar puncture is postulated to produce CVT sometimes, and some of the postlumbar puncture headaches could be due to CVT. A plausible reason is that low CSF pressure after a lumbar puncture (LP) causes a downward shift of the brain, with traction on the cortical veins and sinuses. Deformation of the venous walls by any mechanism may induce thrombosis. The diagnosis of sinus thrombosis after a lumbar puncture is difficult, because the headache that follows is attributed not to sinus thrombosis but to the lumbar puncture itself. The classical post-LP headache typically disappears when the patient lies down, and resolves within a few days. Headache in patients with cerebral venous sinus thrombosis does not change with a shift in posture and it worsens during the early stages, and could be more in the early mornings. Infections like otitis and mastoiditis can be complicated by thrombosis of the adjacent sigmoid and transverse sinuses. If the contralateral transverse sinus is hypoplastic (a frequent anatomical variant), absorption of CSF becomes impaired and hydrocephalus can result (ie thrombophlebitic states). The most common cause of infection into the cerebral venous sinuses may occur by extension from the paramanal sinuses. These cases may also be associated with subdural empyma. Bacterial meningitis as a coexistent condition should be considered in these cases. Frontal sinuses are the most common source of infection. A special case is thrombosis of the cavernous sinuses, which is nearly always caused by an infection of the paranasal (ethmoid and sphenoid) sinuses, the orbit or the face. Multiple organisms are to be considered, Staphylococcus aureus being the most common. In chronic infections, Gram-negative organisms and fungi such as Aspergillus species may be found. The frequency of infectious sinus thrombosis has declined in adults. Higher frequencies of both systemic infections (e.g. neonatal sepsis) and local infections (e.g. otitis) are reported in children. Though lateral sinus (transverse and sigmoid) and cavernous sinus thrombosis are usually secondary to infections in the adjacent areas like otitis media, mastoiditis and sinusitis, the superior sagittal sinus thrombosis is most often due to noninfective processes. But infection may reach superior sagittal sinus from the nasal sinuses or as an extension from the lateral or cavernous sinuses or from an epidural or subdural focus. Any of the cerebral venous sinuses or the cerebral veins, which drain into the sinuses may be occluded partially or completely by trauma or tumors. The coexisting thrombophilic states like malnutrition or dehydration, hyperhomocysteinemia can accelerate the process of thrombosis. The thrombus can then grow into the sinus or vice-versa. Transverse sinus and sigmoid sinus thrombosis cause headache and vomiting without fever and features of raised intracranial pressure. Papilledema develops, which is usually bilateral but can be unilateral. Drowsiness, coma and seizures can occur. Cavernous sinus thrombosis, usually originates from infections in the orbit, nasal sinuses or upper half of the face. The infection commonly involves only one sinus at the onset but rapidly spreads through the circular sinus to the other side. One or both of these can be involved by spread of infection or spread of thrombus from the other dural sinuses. Thus CVT or any venous or arterial thrombosis is just a manifestation of multiple thrombophilic states, which vary from patient to patient and a highly individualized approach is essential for the effective management and prevention.

CLINICAL FEATURES

Most common venous sinus to develop thrombosis (or probably detected commonly) is the superior sagittal sinus. Irrespective of the sinus affected, there is overlapping of clinical features, except when it is confined to cavernous sinus or one of the smaller cerebral veins. Headache is the most frequent but least specific symptom; severe headache is present in more than 90% of adult patients. Usually the headache mimics migraine, but is persistently unilateral or diffuse, and is not relieved after sleep, increases gradually over
Hematology

a couple of days, but can also start in a split second, mimicking intracerebral or subarachnoid hemorrhage. Nausea and vomiting may be associated. Cortical vein thrombosis can present as isolated intracranial hypertension syndrome, which is often misdiagnosed as benign intracranial hypertension. Focal syndromes (focal deficits, seizures or both) mimicking and often mistaken for intracranial space occupying lesion is not uncommon; even on CT and MRI, the venous infarct is mistaken for glioma or even focal demyelination.1,2,4,8 Encephalopathy with multifocal signs, mental status changes, stupor or coma can occur suddenly over hours or days. Cerebral lesions and neurologic signs develop in half of them. Unilateral hemispheric symptoms such as hemiparesis or aphasia, followed within days by symptoms due to involvement of the other hemisphere, caused by the development of cortical lesions on both sides of the superior sagittal sinus are characteristic, but rare. Superior sagittal sinus thrombosis may also present as an unilateral lower extremity weakness or paraplegia.1,2 Venous infarct has a notorious high risk of hemorrhage into the cortical white and grey matter. Convulsions is almost always accompanied by dramatic signs and symptoms due to hemorrhage into the cortical white and grey matter. Convulsions may cause even permanent blindness. Besides all these, the clinical examination may show papilledema. Severe papilledema can cause even permanent blindness. Especially with increased intracranial pressure as the only presenting sign with paralysis of eye movements due to involvement of the oculomotor, ocular nerve syndromes are seen with lateral venous sinus (sigmoid and transverse sinus) thrombosis. These include vestibular neuronopathy, pulsatile tinnitus, unilateral deafness, double vision, facial weakness and obscuration of vision. If the thrombosis in lateral sinus extends to the jugular vein, the patient may develop involvement of cranial nerves IX, X, XI and XII due to jugular foramen syndrome. If it is secondary to a septic focus, there could be fever and chills, and other features of septicemia. The classic symptoms of lateral sinus thrombosis are fever, headache, nausea and vomiting. Seizures occur in about 40%, of which it is focal in 50%, but may generalize to a life-threatening status epilepticus.9 Thrombosis of the deep venous system (straight sinus and its branches) often causes bilateral thalamic lesions, with behavioral symptoms such as delirium, amnesia and mutism, which may be the only manifestation. If large unilateral infarcts or hemorrhages compress the diencephalon and brain stem, patients may become comatose or die from cerebral herniation.1,2 Other causes of coma are diffuse involvement and generalized seizures followed by postictal coma. Infectious cavernous sinus thrombosis is characterized by headache, fever and eye symptoms such as periorbital edema, proptosis, chemosis and paralysis of eye movements due to involvement of the oculomotor, abducens or trochlear nerves. Lateral sinus thrombosis may present with increased intracranial pressure as the only presenting sign with associated headache and a pseudotumor cerebri-like picture.1,2 Patients with isolated intracranial hypertension have headache but no other neurologic symptoms, with the exception of diplopia due to VIth nerve palsy when the intracranial pressure is very high. Fundus examination may show papilledema. Severe papilledema can cause transient visual impairment, or if it is persistent and left untreated can cause even permanent blindness. Besides all these, the clinical picture will usually be associated with the underlying disorder/s, which contributed to the thrombotic state. If the thrombus occurs in the setting of meningitis, brain abscess or uncontrolled diabetes, the clinical picture will be even more confusing. Extension of the thrombus from the sagittal or lateral sinus into the cerebral veins is almost always accompanied by dramatic signs and symptoms due to hemorrhage into the cortical white and grey matter. Convulsions often are focal, hemiplegia, aphasia or hemianopia can occur.1,2

DIAGNOSIS

A high index of suspicion is absolutely essential to diagnose cerebral venous thrombosis. Diagnosis of CVT should be considered in all young and middle-aged patients with recent onset unusual headache, with stroke-like symptoms, especially with seizures.1,2,3,8

Diagnosis is basically clinical, one should be aware of the varied clinical presentations and if the clinical picture is also consistent with CVT, besides the usual differential diagnosis, the next step is to get a CT or MRI to look for supportive evidence of CVT and to rule out other mimickers. Computed tomography may show multiple lesions, some hemorrhagic others radiolucent, which could often be bilateral. After ruling out other causes for the clinical presentation, or after getting definite proof of diagnosis, all the contributory factors of CVT should be looked for. A common mistake is to depend entirely on the radiologist to give a definite diagnosis and on the laboratory to give an etiological diagnosis. If the clinical picture is highly suggestive, is consistent with, or at least not against the diagnosis of CVT and if there is no other definite etiological diagnosis on CT or MRI, the patient should be managed as CVT. This is to avoid delay in initiating the specific treatment directed at the thrombus and its precipitating factors. Clinical presentation is highly variable, and the clinical picture may be developing while under treatment or observation for another disorder.1,3,6,7 Usually, there is a delay in diagnosis, especially in patients with unexplained intracranial hypertension, or in those with CT evidence of hemorrhagic infarcts, especially if the infarcts are multiple and in those presenting like ICSOL or demyelination on CT. The clinical suspicion of CVT based on sound clinical reasoning is the most important starting point in the diagnosis and the suspicion of CVT should be indicated in the request form when referring for CT or MRI studies. The most sensitive investigation technique to confirm the diagnosis is MRI in combination with magnetic resonance venography.9 T1- and T2-weighted MRI may show a hyperintense signal from the thrombosed sinuses if the clot is recently formed. The combination of an abnormal signal in a venous sinus and a corresponding absence of flow on magnetic resonance venography confirm the diagnosis of thrombosis.9 But it may not be possible to demonstrate the thrombus in the smaller cortical veins on CT or MRI and their effects on the brain may be mistaken for ICSOL or demyelination. Thrombus in the major sinus alone is picked up by the imaging studies and we cannot expect it to be present at the site when we do the imaging, since it could be resolving or even completely resolved by the time, the imaging is done. Computed tomography scanning is a useful technique for the initial evaluation, basically to rule out other acute cerebral disorders that mimic CVT and occasionally to show lesions, which suggest venous infarcts or hemorrhages. Many times, CT scan is reported as normal in patients with CVT. Empty delta sign on contrast enhanced CT (CECT)—that is enhancement of the collateral veins in the superior sagittal sinus walls surrounding a nonenhanced thrombus in the sinus is suggestive.2,8 Dense triangle sign is formed by fresh coagulated blood in the superior sagittal sinus. High resolution CT (HRCT) may show the thrombus as a hyper intense signal in a sinus or even in the cortical veins (the “cord sign”). Computed tomography venography is a promising new technique for creating images of the cerebral venous system.9 If the diagnosis is still uncertain after MRI or CT angiography, cerebral angiography may be indicated. Angiography may provide better details of the cerebral veins, and hence, is useful in the diagnosis of rare cases of isolated thrombosis of the cortical veins without sinus thrombosis. It also shows dilated and tortuous (“corkscrew”) veins, which are evidence of thrombosis downstream in the sinuses.8 But depending too much on radiological studies alone for making the diagnosis will result in wrong diagnosis and over investigation. The posterior ischemic leukoencephalopathy reported by the radiologists appears to be one such instance because on clinical evaluation, these patients have all the features of CVT involving the posterior circulation and they also have the clinical setting to develop venous thrombosis. But if the clinical diagnosis is not asserted by the referring clinician, when there is no radiologic proof of the thrombus in the lateral sinus, it is reported as posterior
Recognize Cerebral Vein Thrombosis

1. Appropriate clinical setting is the most important; sudden onset of severe headache, seizure or a neurologic deficit, which is difficult to be attributed to one vascular territory or unexplained vascular headache, which is persistently unilateral or sometimes diffuse

2. Computed tomography is reported as normal or reported as ICSOL/gloma/infarct/hemorrhage—not confined to any specific vascular territory

3. No other diagnosis or if there is confusion in diagnosis or the radiologist reports as posterior ischemic leukoencephalopathy or demyelinating plaque in the above clinical setting

4. Risk factors or clinical settings to develop venous thrombosis.

If all the above four are present it is almost always CVT (unless otherwise proved beyond doubt by evaluation, investigation and follow-up) and hence it is wiser to be managed as CVT. Once CVT is suspected MR and MR venogram may help to confirm but difficult to rule out. Basically, the imaging is to look for an alternative cause rather than to confirm CVT.

The diagnostic steps should involve:

- • Recognize: Cortical vein thrombosis by applying good clinical skill and a high index of suspicion; this is the most important step
- • Rule out other possible diagnosis: By supporting investigations like CT and MRI, or sometimes only MR/MR venogram helps to rule in CVT
- • Good clinical evaluation to the identify all possible acquired causes of thrombophelia by history and physical examination and supporting laboratory tests—even if there is no documented thrombus in one of the venous sinuses
- • Look also for possible hereditary causes: If identified or strongly suspected consider prolonged anticoagulation and avoid all acquired risk factors for thrombosis.

One can suspect hereditary causes of thrombophilia in the following settings: absence of acquired causes, documented venous thromboembolism in first-degree relatives, early age of onset (< 45 years), spontaneous and unprovoked thrombosis, recurrent episodes of venous thromboembolism, thrombus in unusual locations, thrombosis on OCP, recurrent fetal loss.1,2,6

Laboratory Studies

After making the diagnosis of CVT, laboratory studies are to look for the prothrombotic state. Complete blood count might give evidence of polycythemia, thrombocytosis, vitamin B12 deficiency; very high erythrocyte sedimentation rate (ESR) might favor a collagen vascular disorder, antinuclear antibody (ANA) and anti-ds deoxyribonucleic acid (DNA) are important in suspected collagen vascular disorders.

Antiphospholipid and anticardiolipin antibodies are to be done when primary or secondary APLA syndrome is suspected. Elevated serum glutamic pyruvic transaminase (SGPT) and serum proteins may help to screen for liver disease. Decreased albumin: globulin ratio, with hypergammaglobulinemia can suggest hyperviscosity states. Sickle-cell preparation or hemoglobin electrophoresis may be required in relevant cases. Urine protein is to be done to screen for nephrotic syndrome. D-dimer values may be beneficial in screening patients for venous thrombosis. Evaluation for Proteins S and C, antithrombin III, lupus anticoagulant and Factor V Leiden mutation should not be made soon after the event and while the patient is on anticoagulant therapy since they are likely to be low, and as such these disorders are rare as compared to several other acquired disorders, which are easily managed.

Diagnostic Guidelines

Recognize Cerebral Vein Thrombosis

1. Appropriate clinical setting is the most important; sudden onset of severe headache, seizure or a neurologic deficit, which is difficult to be attributed to one specific arterial territory, clinically or by radiological methods. During evaluation, one should take a detailed history to look for any of the clinical settings for an increased risk of venous thrombosis, like history of decreased fluid intake or increased fluid loss like excessive sweating, diarrhea or vomiting, drug intake including oral contraceptive pill (OCP), travel, injury, constitutional symptoms, fever, weight loss, chemotherapy with l-asparaginase or thalidomide, etc. A detailed dietary history for any features to suggest vitamin B12 or folic acid deficiency is absolutely essential.

Look also for physical signs of vitamin B12 deficiency (like knuckle hyperpigmentation, premature greying of hair, neurological findings), signs of polycythemia, (congested conjunctiva, ruddy complexion, palmar erythema), liver disease including nonalcoholic fatty liver disease (NAFLD) and features of vasculitic disorder or any findings to suggest malignancy.
Serum homocysteine was elevated in cases of severe neurological deterioration, open clinical features and the predisposing factors help in diagnosis potentially lethal disease. High index of suspicion and awareness of the understanding of the pathophysiology of it. Even then cerebral venous thrombosis is now being diagnosed and important advances have been made in our knowledge of subclinical thrombophilic states or rarely with a genetically increased risk. During the last trimester of pregnancy and after delivery, the risk of venous sinus thrombosis is increased many times.

**CASE HISTORY 1**

A 30-year-old mechanic came with sudden onset of headache of 4-day duration; the headache was more on the left side. This was associated with several episodes of vomiting. There was no history of seizures, altered sensorium, loss of consciousness, weakness, bowel or bladder symptoms, neck pain, visual blurring. There was no head injury/trauma/ear discharge/leukocytes cough, breathlessness, chest pain. He was a strict vegetarian and did not consume adequate green leafy vegetables and fruits. He had left leg swelling 2 years back diagnosed as deep vein thrombosis. He was on warfarin for several months, which was stopped only 2 months back. There was no history of hypertension, diabetes, ischemic heart disease or similar illness in the past. He did not smoke or drink alcohol, and did not have any addictions. From the history, a diagnosis of cerebral vein thrombosis/subarachnoid hemorrhage or vascular headache was considered. On examination, he was conscious, oriented and cooperative. His body mass index (BMI) was 22, pulse rate 64 beats per minute, blood pressure (BP) 140/90 mm Hg. No pallor/jaundice/ cyanosis/clubbing/lymphadenopathy/edema was noted. Skin showed knuckle hyperpigmentation and premature greying of hair suggesting vitamin B_{12} deficiency. Abdomen, cardiovascular system and respiratory system were normal. Pupils were equal and reacting. There was no cranial nerve palsy, no motor/sensory involvement, no neck stiffness, no cerebellar signs. Skull and spine were normal, fundus—no evidence of papilledema. Investigations, hemoglobin (Hb): 11.6 g/dL, total leukocyte count (TLC): 12,000/mm³, differential leukocyte count (DLC): P 71 L 21 E 8, mean corpuscular volume (MCV): 97.2 fL, mean corpuscular Hb (MCH): 32.3, mean corpuscular hemoglobin concentration (MCHC): 33.2, red blood cell distribution width (RDW): 16.1% and platelet count was 2,78,000/mm³, ESR: 15 mm in the 1st hour. Computed tomography of head was normal. Since the clinical diagnosis was CVT, we proceeded with MRI and MR venogram, which confirmed the diagnosis of sagittal sinus thrombosis (Figures 1 and 2A). Serum homocysteine was elevated to 16.61 μmol/L (normal 5-15 μmol/L). All other investigations including screening for collagen vascular disease, APLA and vasculitis did not yield any positive result. The final diagnosis was CVT due to hyperhomocysteinemia of vitamin B_{12} deficiency. He was treated with injection heparin 5,000 international unit (IU) IV quarterly (Q) 6 hours, injection mannitol, injection vitamin B_{12} and injection dexamethasone. Later warfarin was added and titrated according to international normalized ratio (INR). Folic acid and multivitamin tablets were given from day 1.

The case history illustrates that if CVT was not suspected by history, the diagnosis could have been be missed, and if a detailed history of diet and lifestyle was not asked, vitamin B_{12} deficiency could have been missed.

**CASE HISTORY 2**

A 20-year-old female who was asymptomatic till 4 months back, went to her doctor with recurrent episodes of persistent left sided headache of 4 months duration, subsiding with analgesics. It was not associated with any sensory or motor complaints and there should be treated with appropriate anticonvulsants. The priority of treatment in the acute phase is to stabilize the patient’s condition and to prevent or reverse cerebral herniation.1,2,5,9,10

**Issue of Anticoagulation**11-13

The most important treatment option is anticoagulation with heparin to arrest the thrombotic process and also to prevent pulmonary embolism, which may complicate venous sinus thrombosis. Anticoagulant treatment has raised much controversy because of the tendency of venous infarcts to become hemorrhagic; about 40% of all patients with sinus thrombosis have a hemorrhagic infarct even before anticoagulant treatment is started. The main reason to avoid heparin has been “the concern” about its safety. But clinical trials show no increased or new cerebral hemorrhages developing after treatment with heparin. Most physicians now start treatment with heparin as soon as the diagnosis is confirmed, even in the presence of hemorrhagic infarcts. No studies have compared the effect of fractionated heparin with that of unfractionated heparin. Conventional unfractionated heparin is enough for all practical purposes. After 3–4 days of heparin therapy or after the patient has shown steady improvement, warfarin is started at minimally effective doses, both are overlapped for 2 days and then heparin is withdrawn. But the optimal duration of oral anticoagulant after the acute phase is decided by the individual patient’s profile. Usually, oral anticoagulants are given for 6 months after a first episode of venous sinus thrombosis, or longer when there is persistence of the predisposing factors.

**Thrombolysis**11

Endovascular thrombolysis can be attempted with the administration of a thrombolytic enzyme, usually urokinase, into the sinus, sometimes in combination with mechanical thrombectomy. Published reports are limited to case reports and uncontrolled studies from which it is not possible to conclude that the results associated with endovascular thrombolysis are superior to those with systemic heparin. Until better evidence is available, endovascular thrombolysis may be applied at centers where the staff has experience in interventional radiology and this treatment method should be restricted only to patients with a poor prognosis.11-16

**Surgical care**: In cases of severe neurological deterioration, open thrombectomy and local thrombolytic therapy have been described as beneficial in patients with subdural empyema or brain abscess.

**Persistent Intracranial Hypertension**

In patients who have symptoms only of chronic intracranial hypertension, the first priority is to rule out an intracranial space occupying lesion and to see whether venous sinus thrombosis could be the cause for it. If there are no contraindications such as large infarcts or hemorrhages, a lumbar puncture is then performed to measure the CSF pressure and also as a therapeutic measure. Oral acetazolamide may reduce the intracranial pressure, which may be continued for weeks to months. If repeated, lumbar punctures and treatment with acetazolamide do not control the intracranial pressure within about 2 weeks, surgical drainage of the CSF is indicated, usually by a LP shunt.15,16

**SUMMARY**

More and more cases of cerebral venous thrombosis are now being diagnosed and important advances have been made in our understanding of the pathophysiology of it. Even then cerebral venous sinus thrombosis remains a diagnostic challenge, and is a potentially lethal disease. High index of suspicion and awareness of the clinical features and the predisposing factors help in diagnosis as illustrated by the two case histories below. With improved diagnosis and prompt treatment, it is possible to achieve an excellent outcome for most patients. An acquired prothrombotic risk factor or a thrombophilic state can be identified in most patients with sinus thrombosis. Often, one obvious precipitating factor such as pregnancy, delivery or postpartum state, head injury or trauma cause sinus thrombosis in a person with one or more acquired and often subclinical thrombophilic states or rarely with a genetically increased risk. During the last trimester of pregnancy and after delivery, the risk of venous sinus thrombosis is increased many times.3-5
was no history of early morning headache. Two months after the onset of headache, she developed generalized tonic-clonic seizures, while watching television. Computed tomography head showed isodense to hypodense nonenhancing lesion with peripheral hypodense zone in the upper posterior part of the left temporal lobe and adjacent parietal lobe with minimal mass effect (Figures 2A and B). A differential diagnosis of low-grade glioma/granuloma/focal infarction/resolving hematoma were considered. Magnetic resonance imaging showed hypodense lesion in T1-weighted images and hyperdense lesion in T2-weighted images in left temporal lobe, which supported the diagnosis of low-grade glioma (Figures 3 and 4). Then patient was referred from the local hospital for surgery to another higher center. Prior to surgery at the higher center, she underwent a repeat MRI, which showed focal gyral hyperintensity in the region of left posterior temporal gyrus on T1-weighted images. Corresponding areas showed signal intensification on T2-weighted images. Hyperintensity was also noted along the course of the vein of Labbe in F1 three-dimensional (3D) images suggesting vein of Labbe thrombosis (Figures 5A and B). Magnetic resonance venogram subsequently confirmed the CVT. She was further evaluated at that center: the physical examination was unremarkable according to them, except for the pallor. The Hb was 9.2 g/dL, with macrocytosis (MCV 110 fl), MCH 33.8 and MCHC 36. Total leukocyte count and DLC were normal with mild thrombocytosis (5.1 lakh/cmm), RDW of 18%, with a normal ESR and reticulocyte count (0.6%). Antinuclear antibody, anti-ds DNA, antiphospholipid antibody were negative. The CSF study showed opening pressure of 110 mm of CSF with total of 2 cells/cmm, which were lymphocytes and the protein was 41 mg/dL with sugar of 70 mg/dL (corresponding blood sugar of 99 mg/dL). The echocardiogram (ECG) and chest skiagram were normal as well as the two-dimensional (2D) echocardiogram. Sleep EEG showed mild-degree of focal nonspecific electrophysiological abnormalities over the left posterior temporal region. No epileptiform abnormalities were seen. The striking abnormality was the serum homocysteine of...
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65 µmol/L (normal 5–15 µmol/L). She was treated with antiepileptics and was supplemented with folate for the macrocytic anemia and for hyperhomocysteinemia. She was referred to us for evaluation of anemia and the procoagulant state.

A detailed review of history showed that she was on a strict vegetarian diet with no consumption of egg or dairy products. The vegetarian diet she took was erratic and totally unbalanced without adequate intake of green leafy vegetables. She was moderately built and nourished with mild pallor, and striking premature graying of the hair and knuckle hyperpigmentation. She had by then features suggestive of mild Subacute Combined Degeneration of the spinal cord as evidenced by Romberg’s sign positivity. Folate supplementation alone, which she received prior to coming to our center, in the presence of severe vitamin B₁₂ deficiency might have precipitated the neurological signs. Thus a clinical diagnosis of vitamin B₁₂ deficiency was made. The following investigations were done: peripheral smear showed moderate anisopoikilocytes with normochromic normocytic cells, macroovalocytes, tear drop cells and a few microcytes suggestive of dimorphic anemia. Serum vitamin B₁₂ was 293 pg/mL (211–911 pg/mL) and the serum ferritin was decreased. Peripheral smear report and lower limit of vitamin B₁₂ in spite of partial supplementation earlier, supported the diagnosis of vitamin B₁₂ deficiency with iron-deficiency. Hyperhomocysteinemia was secondary to vitamin B₁₂ deficiency, which resulted in hypercoagulable state. Patient was treated with vitamin B₁₂ and folate, and she improved dramatically over the next few weeks. Currently

Figures 4A and B: Hyperdense lesion in T2-weighted magnetic resonance imaging (MRI) scan suggesting glioma (Case 2)

Figures 5A and B: Magnetic resonance imaging (MRI) scan showing hyperintensity along the course of vein of Labbe (Case 2)
she is asymptomatic, is adhering to balanced diet, and is not on anticoagulants for the last 2 years.

This case history illustrates that if we do not elicit the dietary history and if we fail to notice the physical signs of vitamin B₁₂ deficiency, it will prolong the agony even after the diagnosis of CVT is made. It also tells that the thrombus may not be demonstrable in major sinuses at the time of evaluation. Therefore, clinical suspicion, proper clinical evaluation, supporting investigations and clinical judgment should be the most important methods in arriving at the conclusions.

REFERENCES