Topic: Current practices , guidelines in management of CVT and the indian scenario of CVT

BACKGROUND:

Thrombosis of the dural sinus and/or cerebral veins (CVT) is an uncommon form of stroke, usually affecting young individuals. CVT represents 0.5% to 1% of all strokes. The current incidence of CVT is estimated to be 1.32/100,000/year in Western Europe.Due to the lack of any population based study or nationwide multicentric hospital based studies, the exact incidence of CVT in India is still not known. The incidence is higher in developing countries. Mean age in most larger studies was between 37 and 38 years though all ages can be affected. CVT is slightly more common in women, particularly in the age group of 20 to 35, due to pregnancy, puerperium and oral contraceptive use. In contrast to this, the recent case series from India do not show this trend of female dominance. In a study of 428 patients of CVT recruited from a tertiary care hospital of Hyderabad, there was larger proportion of males than females.Showing a similar trend, a large prospective study which recruited 612 consecutive patients of CVT from various hospitals of Mumbai had a male to female ratio of 3:2.The plausible reason for this change in gender trends over the last two decades could be the improvement in obstetric care.

Since the possible causal factors and clinical manifestations of thrombosis are many and varied, diagnosis remains a challenge for the clinician and requires a high suspicioun index. Imaging plays a primary role in the diagnosis. A wide range of cross-sectional imaging methods and venographic techniques may be used to detect abnormalities in the brain parenchyma as well as the cerebral veins and venous sinuses. Accurate and prompt diagnosis of cerebral venous thrombosis is crucial, because timely and appropriate therapy can reverse the disease process and significantly reduce the risk of acute complications and longterm sequelae. Currently, CVT is diagnosed with increased frequency due to higher awareness and easier access to cross-sectional imaging.

Cause and Pathogenesis: Underlying Risk Factors for CVT

Predisposing causes of CVT are multiple. The risk factors for venous thrombosis in general are linked classically to the Virchow triad of stasis of the blood, changes in the vessel wall, and changes in the composition of the blood. Risk factors are usually divided into acquired risks (eg, surgery, trauma, pregnancy, puerperium, antiphospholipid syndrome, cancer, exogenous hormones) and genetic risks (inherited thrombophilia). Drugs like oral contraceptives (OCs), steroids, hormone

replacement therapy, and oncological treatments have been implicated in the causation of CVT.

Prothrombotic conditions : Most common risk factor identified for CVT throughout the world is often a prothrombotic condition like **Protein C, Protein S, Antithrombin III Deficiency, Antiphospholipid and Anticardiolipin, AntibodiesFactor V Leiden Gene Mutation and Resistance to Activated Protein C, Prothrombin G20210A Mutation and hyperhomocysteinemia.** In the ISCVT cohort, a prothrombotic condition was found in 34% of all patients, and a genetic prothrombotic condition was found in 22% of all patients. Almost all the large series from the western literature have a large proportion of patients having a prothrombotic condition as a risk factor. Most of the earlier published studies from India did not have information regarding these inherited prothrombotic states due to lack of laboratory facilities and resources to conduct these tests. But in recent times, Pai et al. recruited 612 consecutive patients from various hospitals of Bombay over a period of 9 years and tested them for the common thrombophilia markers (protein C [PC], protein S, antithrombin [AT], and factor V Leiden [FVL] mutation).18% of the patients were positive for the thrombophilia markers studied. PC deficiency was the most common thrombophilia marker followed by a deficiency of protein S, FVL mutation, and AT deficiency. This study had a similar proportion of patients with a genetic prothrombotic state when compared to that reported from developed countries. The proportion of CVT patients with a prothrombotic condition in India is also similar to that of Western countries and has been probably underreported in the earlier studies (due to lack of laboratory facilities).

Pregnancy and Puerperium: are common causes of transient prothrombotic states. During pregnancy especially in 3rd trimester and for 6 to 8 weeks after birth, women are at increased risk of venous thromboembolic events. Hypercoagulability worsens after delivery as a result of volume depletion and trauma. During the puerperium, additional risk factors include infection and instrumental delivery or cesarean section. Most of the earlier case series of CVT reported from India have very high proportions of puerperal CVT. In the recent times, a change in this trend has been noted. The improvement in obstetric care could be the possible cause for this change.

Oral Contraceptives: It is clear that the use of oral contraceptives is associated with an increased risk of CVT, that the great majority of younger nonpregnant women with CVT are oral contraceptive users, and that the risk of CVT with oral contraceptive use in women is greater among those with a hereditary prothrombotic factor.In developed countries, OC as a risk factor for CVT has been more commonly reported compared to the developing countries making it the third most important risk factor; All the large series from India have shown a much

lower proportion of OC usage as a risk factor for CVT compared to the series from west.This could be due to the different sociocultural milieu of our patients compared to the western countries.

Cancer: It has been speculated that CVT could be more frequent in cancer patients, particularly in patients with hematologic malignancies. Potential mechanisms for an association of cancer with CVT include direct tumor compression, tumor invasion of cerebral sinuses or the hypercoagulable state associated with cancer. Chemotherapeutic and hormonal agents used for cancer treatment may also play a role.

The Although infective causes of CVT were frequently reported in the earlier series, they account for a very small percentage of patients in the recent studies.This could be due to the availability of potent broad spectrum antibiotics in today's era

Other Uncommon Causes:

Other conditions have been associated with CVT in case reports or small series, including paroxysmal nocturnal hemoglobinuria,iron deficiency anemia thrombocythemia, heparin-induced thrombocytopenia,thrombotic thrombocytopenic purpura, nephrotic syndrome,inflammatory bowel disease,systemic lupus erythematosus, Behçcet disease,mechanical precipitants, epidural blood patch,spontaneous intracranial hypotension and lumbar puncture.

When we compare the etiological factors of CVT in the western series with the recently published Indian series, there are a similar proportion of patients with prothrombotic conditions and pregnancy and puerperium in both. Despite the continuous description of new causes, in about 13% of patients, no etiology can be found, as has been seen in the recent series. Therefore, the search for an etiology remains a difficult problem in CVT. It requires an extensive initial workup and when no cause is found, a long term followup with repeated investigations. Cerebral venous thrombosis is multifactorial, and identification of one risk factor should not deter the clinician from searching for more causes.

Clinical Diagnosis of CVT:

The diagnosis of CVT is typically based on clinical suspicion and imaging confirmation. Clinical findings in CVT usually fall into 2 major categories, depending on the mechanism of neurological dysfunction: Those that are related to increased intracranial pressure attributable to impaired venous drainage and those related to focal brain injury from venous ischemia/infarction or haemorrhage

Headache, generally indicative of an increase in intracranial pressure, is the most common symptom in CVT and was present in nearly 90% of patients in the ISCVT.1 The headache of CVT is typically described as diffuse and often progresses in severity over days to weeks. A minority of patients may present with thunderclap headache, suggestive of subarachnoid haemorrhage. CVT is an important diagnostic consideration in patients with headache and papilledema or diplopia (caused by sixth nerve palsy) even without other neurological focal signs suggestive of idiopathic intracranial hypertension. When focal brain injury occurs because of venous ischemia or hemorrhage, neurological signs and symptoms referable to the affected region are often present; most common are hemiparesis and aphasia, but other cortical signs and sensory symptoms may occur. Psychosis, in conjunction with focal neurological signs, has also been reported.

Nausea and vomiting may also be associated with CVT. In some cases, seizures, which can be recurrent, occur. The mental status may be quite variable, with patients showing no change in alertness, developing mild confusion or progressing to coma. Earlier case series from India reported that 43% to 93% of patients had an altered sensorium at presentation.Recent studies show a lower proportion of patients having changes in sensorium at presentation.The reason for this decrease is probably due to patients seeking medical help earlier in the recent times.

Clinical manifestations of CVT may also depend on the location of the thrombosis. The superior sagittal sinus is most commonly involved, which may lead to headache, increased intracranial pressure, and papilledema. A motor deficit, sometimes with seizures, can also occur. For lateral sinus thromboses, symptoms related to an underlying condition (middle ear infection) may be noted, including constitutional symptoms, fever, pain and ear discharge. Hemianopia, contralateral weakness, and aphasia may sometimes be seen owing to cortical involvement.

An important clinical correlate to the anatomy of cerebral venous drainage is that bilateral brain involvement is not infrequent. This is particularly notable in cases that involve the deep venous drainage system, when bilateral thalamic involvement may occur, causing alterations in level of consciousness without focal neurological findings. Most patients present with rapid neurological deterioration.

Delays in diagnosis of CVT are common and significant. In the ISCVT, symptom onset was acute (48 hours) in 37% of patients, subacute (48 hours to 30 days) in 56% of patients, and chronic (30 days) in 7% of patients. The median delay from onset of symptoms to hospital admission was 4 days, and from symptom onset to diagnosis, it was 7 days.

Investigations should focus on establishing the diagnosis and searching for underlying causes.

Imaging in the Diagnosis of CVT:

Magnetic resonance imaging (MRI) combined with magnetic resonance venography (MRV) have largely replaced invasive cerebral angiography and conventional computed tomography (CT). The latter will, however, often remain the first imaging modality to be used simply due to availability and also to exclude other conditions such as intracerebral haemorrhage or abscess. The 'empty delta sign' on CT, reflecting the opacification of collateral veins in the wall of the superior sagittal sinus after contrast injection is present in only 10–20% of cases.[1]CT is entirely normal in 10–20% of cases with proven CVST. The most commonly used venographic techniques currently include unenhanced TOF MR venography, contrast-enhanced MR venography, and CT venography. **MRI combined with MRV** is reliable as the sole examination for this condition. It can show the consequences of thrombosis such as cerebral oedema, infarction and haemorrhage as well as the anatomy of the disturbed venous circulation. TOF MR venography is the method most commonly used for the diagnosis of cerebral venous thrombosis. Two-dimensional TOF techniques are used to evaluate the intracranial venous system because of their excellent sensitivity to slow flow and their diminished sensitivity to signal loss from saturation effects compared with the sensitivities of three-dimensional TOF techniques . A close assessment of the source images is mandatory to accurately evaluate venous morphologic features and reduce the potential for diagnostic error . Small-vessel visualization is improved at contrast-enhanced MR venography, compared with that at TOF MR venography . There are, however, pitfalls of this technique which may, in doubtful cases, make cerebral angiography necessary. One of the common problems is the absence or hypoplasia of the anterior portion of the superior sagittal sinus, a normal variant that can simulate thrombosis on MRV. Also, contrast enhancement along the edge of the thrombus can be mistaken for normal contrast material accumulating within a patient's sinus. **CT venography** is a rapid, readily available, and accurate technique for detecting cerebral venous thrombosis. CT venography provides a highly detailed depiction of the cerebral venous system, superior to that available with conventional TOF MR venography, and has at least equivalent accuracy for the detection of cerebral venous thrombosis. Drawbacks of CT venography include the difficulty of reconstructing maximum intensity projection (MIP) images from the source image data sets, a process that requires the subtraction of bone adjacent to the venous sinus; it is very difficult to subtract all of the adjacent bone without also subtracting part of the sinus. However, source images and multiplanar reformatted images can be displayed quickly for evaluation. Because the technique involves the use of ionizing radiation, CT venography may have limited use in pregnant patients and children, in whom the radiation dose may be a cause

for particular concern, as well as in patients with renal failure, contrast material allergy, or another contraindication to the use of iodinated contrast material. More recently, CT venography has been shown in at least one series to be superior to MRV in visualising sinuses or smaller cerebral veins or cortical veins with low flow. This technique is not used routinely at present.

According to the Indian guidelines for stroke management, patients suspected to be having a stroke due to CVT should be investigated by MRI/MRV/CTV only if the CVT is not diagnosed by a CT scan.n a statement issued by the American Heart Association/American Stroke Association in 2011, a negative plain CT or MRI does not rule out the presence of a CVT. They recommend a venographic study (either CTV or MRV) in suspected CVT if the plain CT or MRI is negative. The venography was also recommended in order to define the extent of CVT if the plain CT or MRI suggests the presence of a CVT (Class I; Level of Evidence C).

All other investigations are directed towards demonstrating the underlying cause. Coagulation studies are important particularly in patients with a family or past medical history of thrombotic episodes in addition to the unexplained cases. The investigations should include a search for the Factor V Leiden mutation if resistance to activated protein C is abnormal, activities of proteins C and S and antithrombin III, plasminogen, fibrinogen and anticardiolipin antibodies.All these investigations should probably be performed twice, ie, before starting anticoagulation and 6 months later after finishing treatment. Many of the above parameters can be transiently influenced by a number of factors, including antithrombotic treatment, pregnancy, oral contraceptives and acute thrombosis.

Management and Treatment:

Anticoagulation: The immediate goals of anticoagulant (AC) therapy are to recanalize the occluded sinus, prevent propagation of the thrombus and to treat the underlying prothrombotic state.

Guidelines from India, Europe and America recommend that patients with CVT without contraindications for AC should be treated either with activated partial thromboplastin time adjusted IV heparin or body weight adjusted LMWH. In the special situation of CVT with cerebral hemorrhage on presentation, even in the absence of anticoagulation, hemorrhage is associated with adverse outcomes. In conclusion, limited data from randomized controlled clinical trials in combination with observational data on outcomes and bleeding complications of anticoagulation support a role for anticoagulation in treatment of CVT, regardless of the presence of pretreatment ICH. The optimal duration of heparin is not established. Warfarin is usually adjusted to obtain an International Normalized Ratio between 2 and 3. The usually recommended duration of treatment is 3–6

months, particularly when there is a known acute cause for CVT. In contrast, prolonged treatment is warranted whenever there is a continuing risk of thrombosis, such as lengthy immobilization, malignant disease, inflammatory disease such as systemic lupus erythematosus or Behcet's disease, inherited thrombophilia or recurrent venous thrombosis.

Interventional/Surgical Considerations:

Endovascular thrombolysis:

The aim of direct thrombolysis is to dissolve the venous clot by delivering a thrombolytic substance(Urokinase, rtpA) within the occluded sinus through an intrasinus catheter. The benefit of direct in-situ thrombolysis is

- Rapid recanalization of the sinus
- Restoration of normal venous outflow
- Reduction of venular pressure
- Reduction of ICP
- Improvement in sensorium

Indication:

- Worsening or not responding to Heparin
- Fulminant venous strokes

The use of direct intrasinus thrombolytic techniques and mechanical therapies was only supported by case reports and small case series. It was difficult to define fulminant stroke in order to decide about Endovascular thrombolysis.

A hospital based randomized controlled trial was performed at KEM Hospital, Mumbai by the Department of Neuroradiology and Intensive Care unit, using a well defined protocol which helped in evaluating and establishing the role of In-situ thrombolysis in Cerebral Venous thrombosis. It is the largest randomised study from India.The aim was to identify which subgroup of patients will benefit with Local Thrombolysis. A Clinical Grading and DSA grading Criteria was initially devised.

Table 1 **KEM INR Criteria for local thrombolysis for cerebral venous sinus thrombosis. (Based on clinical and DSA grades).**

Grade	Clinical Grading	DSA Grading
Grade 1	symptom free	Partial thrombosis of dural sinus with no restrictive venous outflow
Grade 2	minor symptoms (headache,vomiting, diplopia, seizures)	Dural sinus occlusion with no restrictive venous outflow.
Grade 3	major neurological deficit but fully responsive	Dural sinus occlusion with restrictivevenous outflow.
Grade 4	impaired state of alertness but capable of protectiveor adaptive responses to noxious stimuli. (GCS 8-10)	Deep venous system occlusion.
Grade 5	poorly responsive, but with vital signs. (GCS 5-7)	Dural sinus and deep vein occlusion with restrictive venous outflow.
Grade 6	not responsive to shaking, non-adaptive response to stimuli and progressive instability of vital signs. (GCS 3-4)	

Mild Clinical Grade: Clinical status 1 to 3 - Severe Clinical grade: Clinical status 4 to 6

The salient observations were:

•There was significant improvement in survival of patients in thrombolyzed group in cases of severe or fulminant CVT

•In severe clinical grade- mortality was 35% against 100% in non thrombolysed group

•Categorical Comments could be made about lateral sinus thrombosis ,deep venous thrombosis and pediatric age group patients

Based on this experience, the indication for In situ Thrombolysis were defined as:

- Patients in CLINICAL GRADE 4, 5, 6 - (this was considered severe grade - GCS 10 or below)with restricted venous outflow on DSA
- Patients in CLINICAL GRADE 3 - worsening on heparin therapy with restricted venous outflow.

Mechanical thrombectomy may be the preferred option in patients with ICH. It can also be used as an Adjunct with chemical catheter based thrombolysis. The Thromboaspiration catheters devised for Acute stroke therapy has a promising role in future.

Decompressive hemicraniectomy and hematoma evacuation: The leading cause of death is the hemorrhagic conversion of large venous infarcts resulting in brain herniation. In these situations, emergency decompressive hemicraniectomy can prevent death.

Antibiotics: The management of patients with a suspected infection and CVT should include administration of the appropriate antibiotics and the surgical drainage of infectious sources (ie, subdural empyemas or purulent collections within the paranasal sinuses).

Management and Prevention of Early Complications (Hydrocephalus, Intracranial Hypertension, Seizures)

Seizures: Because seizures increase the risk of anoxic damage, anticonvulsant treatment after even a single seizure is reasonable. In the absence of seizures, the prophylactic use of antiepileptic drugs may be harmful (the risk of side effects may outweigh its benefits).

Hydrocephalus: In CVT, the function of the arachnoid granulations may be impaired, potentially resulting in failure of CSF absorption and communicating hydrocephalus.

Obstructive hydrocephalus is a less common complication of CVT and results from hemorrhage into the ventricular system. This is typically associated with thrombosis that involves the internal cerebral veins and may be associated with thalamic hemorrhage. This syndrome is well described in term neonates but occurs at all ages. Neurosurgical evacuation of CSF with ventriculostomy, or in persistent cases, ventriculoperitoneal shunt, is necessary.

Intracranial Hypertension: Up to 40% of patients with CVT present with isolated intracranial hypertension.1 Clinical features include progressive headache, papilledema, and third or sixth nerve palsies. Intracranial hypertension is primarily caused by venous outflow obstruction and tissue congestion compounded by CSF malabsorption. First, measures to reduce the thrombotic occlusion of venous.

outflow, such as anticoagulation and possibly thrombolytic treatment, may result in resolution of intracranial hypertension. Second, reduction of increased intracranial pressure can be accomplished immediately by lumbar puncture with removal of CSF until a normal closing pressure is achieved. Unfortunately, lumbar puncture requires temporary cessation of anticoagulants, with an attendant risk of thrombus propagation. Serial lumbar punctures may be necessary when hypertension is persistent. In refractory cases, a lumboperitoneal shunt may be required.199 Because prolonged pressure on the optic nerves can result in permanent blindness, it is of paramount importance to closely monitor visual fields and the severity of papilledema during the period of increased pressure. Acetazolamide, a carbonic anhydrase inhibitor, is a weak diuretic and decreases production of CSF

Cerebral Venous Thrombosis and Pregnancy:

Pregnancy induces several prothrombotic changes in the coagulation system that persists at least during early puerperium. Hypercoagulability worsens after delivery as a result of volume depletion and trauma. The greatest risk period for the occurrence of CVT is in the third trimester and the first 4 postpartum weeks. [45] In patients who have had an occurrence of CVT in the prior pregnancy, the risk of recurrence in the future pregnancy is low. On the basis of the available evidence, CVT is not a contraindication for future pregnancies. Patients who have had CVT and also possess a transient risk factor are advised to use LMWH prophylaxis during the postpartum period only (4–6 weeks). In patients who have a history of recurrent CVT, venous thromboembolism after CVT, or the first CVT with severe thrombophilia (i.e. homozygous prothrombin G20210A; homozygous factor V Leiden thrombophilia; deficiencies of protein C, protein S, or antithrombin; combined thrombophilia defects; or antiphospholipid syndrome) longterm ACs have to be given. If these patients conceive, then they cannot be given vitamin K antagonists (e.g. warfarin) as it is associated with fetal dysgenesis and bleeding in the fetus and neonate. The choice of AC during pregnancy would be low molecular weight heparin over unfractionated heparin, as it is not associated with teratogenicity or increased risk of fetal bleeding.

Management of CVT in the Pediatric Population:

No randomized clinical trials have been conducted in pediatric CVT. Therefore, treatment practices have been extrapolated primarily from adult studies. In children, and increasingly in neonates, the mainstay of CVT treatment is anticoagulation, including LMWH, UFH, and warfarin for 3 to 6 months, even in the presence of ICH. Individual and regional practices vary widely in pediatric CVT and particularly in neonatal CVT. Seizures were observed in 50% of the pediatric population with CVT. Given the higher frequency of epileptic seizures in children,

continuous electroencephalography monitoring may be considered for unconscious or mechanically ventilated children. Consideration of endovascular treatment for neonates and children with CVT is driven by the high rates of adverse outcomes.