A Dissertation on

"A STUDY ON EVALUATION OF PLASMA D-DIMER AS AN INITIAL DIAGNOSTIC BIOMARKER IN CEREBRAL VENOUS THROMBOSIS"

Dissertation submitted to

THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY

CHENNAI – 600 032

With partial fulfillment of the regulations

For the award of the degree of

M.D. GENERAL MEDICINE

BRANCH – I

Department of General Medicine

Coimbatore Medical College Hospital

Coimbatore – 641 018

CERTIFICATE

This is to certify that the dissertation **"A STUDY ON EVALUATION OF PLASMA D-DIMER AS AN INITIAL DIAGNOSTIC BIOMARKER IN CEREBRAL VENOUS THROMBOSIS"** is a bonafide research work done by **Dr.M.Ananthi** Post graduate in M.D. General Medicine under my direct guidance and supervision to my satisfaction , in partial fulfillment of the requirements for the degree of M.D. General Medicine.

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I hereby declare that this dissertation entitled **"A STUDY ON EVALUATION OF PLASMA D-DIMER AS AN INITIAL DIAGNOSTIC BIOMARKER IN CEREBRAL VENOUS THROMBOSIS"** is a bonafide and genuine research work carried out by me under the guidance of Prof. Dr. Isaac Christian Moses M.D., Department of Medicine ,Coimbatore medical college, Coimbatore .

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ACKNOWLEDGEMENT

With great reverence, first of all ,I would like to express my deep sense of gratitude to my guide and teacher, Prof. **DR.ISAAC CHRISTIAN MOSES M.D.,** Professor of Medicine, Coimbatore Medical College, Coimbatore .He has been more than a guide, a good mentor and a source of constant inspiration throughout my course. I also thank him for his able guidance, suggestion and supervision throughout the making of this dissertation.

I would consider it my privilege to extend my respect and gratitude to Prof.**DR.KUMAR NATARAJAN M.D.,** Professor and Head of the Department of Medicine, Coimbatore Medical College, Coimbatore, for all the encouragement and guidance throughout the course and for this dissertation .

I also take this opportunity to thank **Prof.Dr.S.Chandrasekaran M.D., Prof. Dr.M.Raveendran M.D., Prof.Dr.N.Sundar M.D.,** for their moral support and guidance.

I also sincerely express my thanks to all my Assistant Professor **DR.V.Uvaraj Muruganandham M.D., DR.P.S.Manshur M.D. , DR.A.Akila M.D.,** in the Department of Medicine, Coimbatore Medical College, Coimbatore, for all their effort and guidance throughout the course, for which words fall short of i am indeed indebted to them.

I would also like to express my thanks to THE DEAN, Prof.**DR.S.REVWATHY M.D.,DGO.,DNB.,** for her able guidance and encouragement throughout, I am also thankful to the administration and other allied departments of the Coimbatore Medical College for their support in helping me carrying out this study.

I also express my heartfelt sincere thanks to all my fellow postgraduates, for their unconditional support and guidance, and for just being there. No words can express the support extended by my family in all these years; thank you.

My biggest gratitude will always be towards my patients, without whose cooperation this study would have been incomplete. I thank the Almighty for his abundant blessings.

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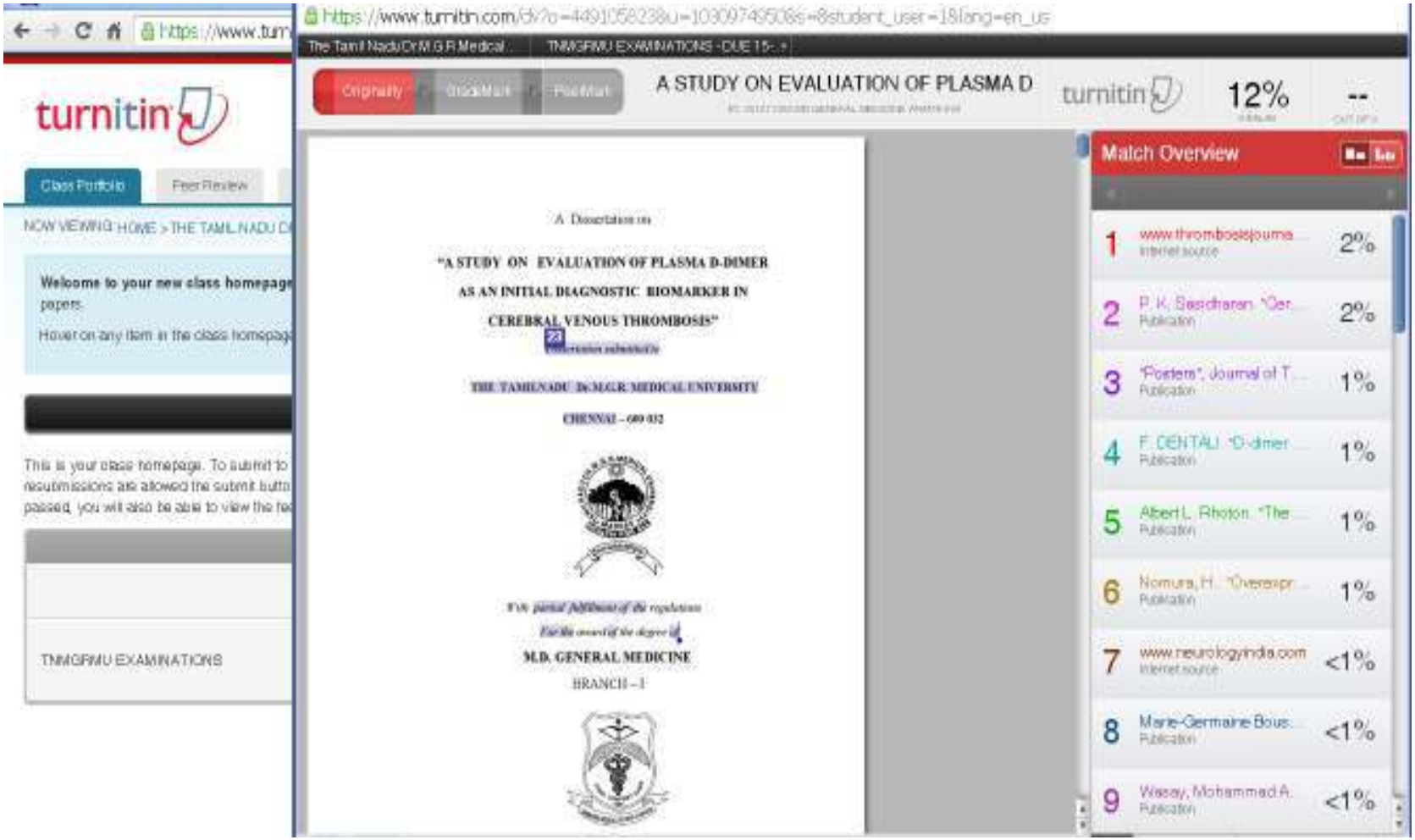
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ABBREVIATIONS

CVT	–	Cerebral Venous Thrombosis
TB	–	Tuberculosis
HIV	–	Human Immuno Deficiency Virus
DIC	–	Disseminated Intravascular Coagulation
PNH	–	Paroxysmal Nocturnal Hemoglobinuria
APLA	–	Anti Phospholipid Antibody Syndrome
OCP	–	Oral Contraceptive Pills
SLE	–	Systemic Lupus Erythematosis
IBD	–	Inflammatory Bowel Disease
SSS	–	Superior Sagittal Sinus
MRI	–	Magnetic Resonance Imaging
MRV	_	Magnetic Resonance Venography
CT	–	Computed tomography
UMN	–	Upper Motor Neuron
ICT	–	Intra Cranial Tension
ECG	–	Electrocardiography

TABLE OF CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

ABSTRACT

BACKGROUND :

Cerebral venous thrombosis (CVT) is a life threatening condition with varied clinical presentations. It is mainly a diagnosis by means of radiological tool. CT Brain is the initial investigation of choice. It may be normal in 30 – 40 % of the population .MRI with MRV is the gold standard for the diagnosis of CVT. D Dimer is a product of fibrinolysis which is usually used as an exclusion marker of venous thrombosis. Our study aims to analyse the usefulness of D Dimer as an initial diagnostic marker in CVT.

OBJECTIVES:

1. To estimate the level of plasma D-DIMER and its significance in diagnosing Cerebral Venous Thrombosis .
2. To correlate the relationship between plasma D-DIMER and MRI BRAIN in diagnosing Cerebral Venous Thrombosis.
3. To evaluate the diagnostic value of negative D-DIMER in ruling out Cerebral Venous Thrombosis.

METHODOLOGY :

The patients diagnosed to have CVT by MRI in Coimbatore Medical College above 18 yrs of age are included in the study. A total of 50 patients are included in the study. After confirming the diagnosis , blood samples were

drawn ,plasma separated and sent to laboratory. D Dimer tests were measured by ELISA test. A value of more than 500 ng/ml were considered positive. All the tests were entered in a data collection sheet in an Excel format and analysed using SPSS software.

RESULTS :

Out of the 50 patients, 28 were females, and 28 were above 35 yrs. The common presenting symptom is headache (96%), followed by seizures, altered sensorium, with papilledema (60%). The most common sinus involved is superior sagittal sinus (70%) followed by sigmoid and transverse sinus. CT Brain was normal in 50 % of the patients. Inherited thrombophilias contribute to 23 %.D Dimer was positive in 78 % of the study population. D Dimer and MRV has a highly significant correlation (0.034). D Dimer and onset of symptoms have a very high significant value of 0.000.

CONCLUSION :

D Dimer can be used as an initial diagnostic bio marker in CVT as there is a significant association with MRI .If patients present very early D Dimer is a highly reliable investigation. Further studies needed for the supportive evidence.

Key Words: Cerebral Venous Thrombosis, D Dimer ,Magnetic Resonance Imaging

INTRODUCTION

Cerebral venous thrombosis (CVT) is a common cerebrovascular accident due to a multitude of causes. The diagnosis is often missed because of its varied clinical presentation. The etiological factors are even more heterogenous making cerebral venous thrombosis a unique clinical entity .The disease can occur de nova as the first manifestation, or can overlap on another co existing clinical problem. The occurrence of thrombus depends upon the site, duration, extent and the rapidity with which the thrombus occurs. The presentation of CVT is variable in the form of convulsions, increased intra cranial tension, meningeal infection or hemorrhage.

Although CVT has its varied presentation, headache is the most common symptom.[1] The diagnosis requires a high index of suspicion. CT Scan may show direct and indirect signs. At times CT may be normal. MRI with MRV is the diagnostic investigation of choice. The early diagnosis of this condition will prevent the mortality and morbidity of the society as it is treatable condition.

Plasma D-Dimer (fibrin degradation product) may be a good investigation for the diagnosis of CVT. D Dimer has a very high negative predictive value of ruling out venous thrombo embolism in DVT and

pulmonary embolism. Several studies been done for analyzing the value of D- Dimer in excluding cerebral venous thrombosis. This study aims to evaluate the usefulness of plasma D-Dimer as an initial diagnostic biomarker for the diagnosis of cerebral venous thrombosis.

OBJECTIVES

1. To estimate the level of plasma D-DIMER and its significance in diagnosing Cerebral Venous Thrombosis .
2. To correlate the relationship between plasma D-DIMER and MRI BRAIN in diagnosing Cerebral Venous Thrombosis.
3. To evaluate the diagnostic value of negative D-DIMER in ruling out Cerebral Venous Thrombosis.

REVIEW OF LITERATURE

HISTORY :

The syndrome of cerebral venous thrombosis was recognized in the early part of 18th century. Ribes was the first to demonstrate the evidence of cerebral venous thrombosis in 1825.[2] John Abercombie of Scotland described this entity in a 24 yr female in 1828.[3] Autopsy showed features suggestive of ischemic and hemorrhagic infarct with thrombosed and sclerosed veins. With the advent of three dimensional flow imaging modalities, the prevalence of CVT is more common than reported previously and by early intervention morbidity and mortality has been reduced drastically.

EPIDEMIOLOGY :

Cerebral venous sinus thrombosis is rare. The incidence in adults is around 3- 4 cases per million. The major occurrence is in 3 rd decade, out of which females is around 75 %.[4] The use of oral contraceptive pills is the main reason for the disparity between the difference between males and females. It is more common in the middle east countries, because of the presence of Behcet's disease. The incidence of CVT in the west is 3-4 million, in developing countries it is 4.5 /10000 obstetric admission .[5]

ANATOMY OF CEREBRAL VENOUS SYSTEM :[6,7]

Cerebral venous circulation exhibits following anatomical characteristics

- Cerebral veins have specific feature that it lacks neither any valves nor tunica muscularis .The blood flow occurs in various directions because of the absence of valves. The dilatation of veins is mainly because of the tunica muscularis.
- There are several inter communications between the cerebral veins, and because of this only the recovery is either complete or with minimal residual disability
- Venous sinuses are enclosed between the two layers of duramater. This is the reason why cerebral veins are not compressed during raised intra cranial pressure
- There are several emissary veins draining into cerebral veins either directly or via venous lacunae. The emissary veins include from the scalp, face, paranasal sinuses, ears, diploic veins and meningeal veins. This is the reason behind the presence of CVT which occurs as a complication of infective pathology in catchment areas.
- The superior sagittal sinus receives blood from superficial cortical veins. The flow is in the opposite direction as that of the sinus thus causing a turbulent blood flow which is also increased by the

presence of fibrous septations at the inferior angle of the sinus. This is why superior sagittal sinus is the most common sinus involved in CVT .

- Arachnoid villi drain CSF into the superior sagittal sinus .The occurrence of thrombosis in this sinus causes obstruction of the CSF flow leading to intracranial hypertension and papilledema .
- Deep cortical veins forms a venous circle around midbrain, like the arterial circle of willis.
- The cerebral veins drain into the dural sinuses, which then drain into the two internal jugular veins .

DURAL VENOUS SINUSES:

Cerebral venous system can be classified into two major groups :

1. Superficial system – sagittal sinuses, cortical veins draining superficial surfaces of both cerebral hemispheres.
2. Deep system – lateral sinus, straight sinus, sigmoid sinus along with draining deep cortical veins.

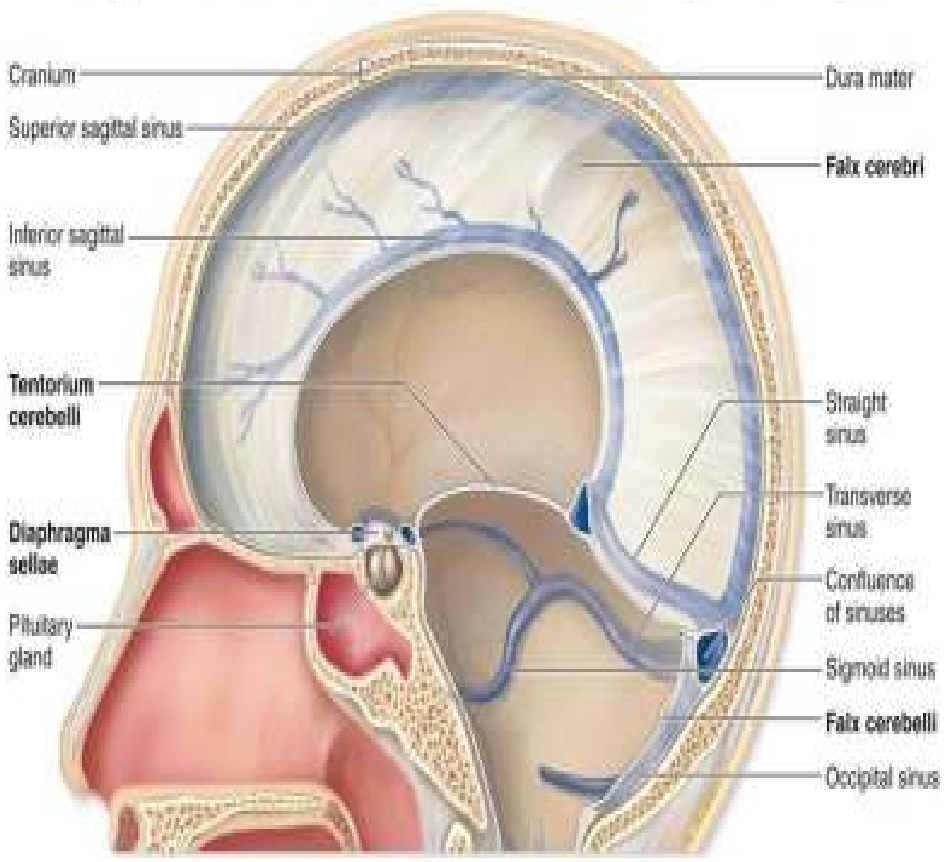


Figure 1: Anatomy of Cerebral Venous Sinuses

I. SUPERIOR SAGITTAL SINUS (SSS) :

- The superior sagittal sinus occupies the upper, attached margin of the falx cerebri. It is triangular in cross section.
- It begins anteriorly at the crista galli by the union of the tiny meningeal veins. It communicates with the veins of the frontal sinus and occasionally with the veins of the nose, through the foramen caecum.
- It ends near the internal occipital protruberance by turning to one side, usually the right, and continuous with the right transverse sinus.

- The junction of all these sinuses is called confluence of sinuses.

TRIBUTARIES:

- Superior cerebral veins
- Parietal emissary veins
- Venous lacunae

Thrombosis of the SSS may be caused by spread of infection from the nose, scalp and diploe. This gives rise to rise in intracranial tension, delirium, convulsions, paraplegia of UMN type.

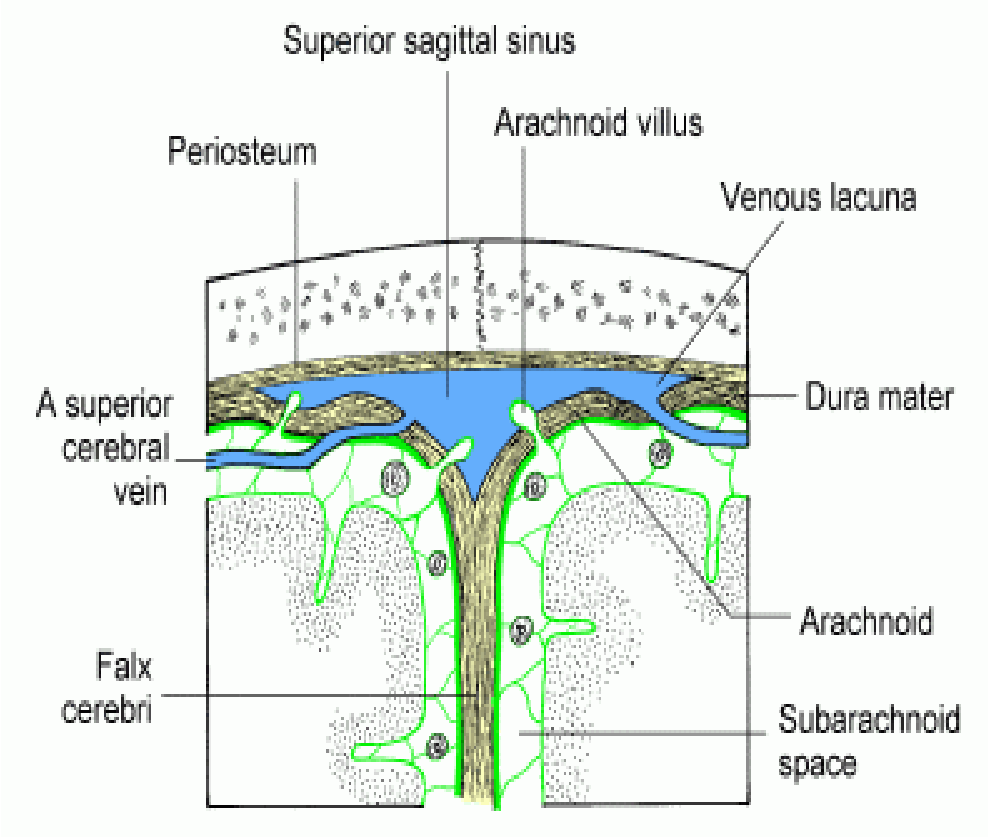


Figure 2 : Anatomy of Superior Sagittal Sinus

II. INFERIOR SAGITTAL SINUS :

- The inferior sagittal sinus , a channel lies in the posterior two thirds of the lower, concave margin of the falx cerebri.
- It forms the straight sinus by joining with the great cerebral veins.

III. STRAIGHT SINUS :

- The straight sinus lies in the median plane within the junction of falx cerebri and the tentorium cerebelli.
- The inferior sagittal sinus and the great cerebral vein joins to form the straight sinus. It ends at the internal occipital protruberance .It continues as the transverse sinus .
- At the termination of the great cerebral veins into the sinus, there exists a ball valve mechanism , formed by a sinusoidal plexus of blood vessels ,which regulates the secretion of CSF.

IV. TRANSVERSE SINUS :

- They are large sinuses..
- The right sinus usually bigger than the left situated in the posterior part of the attached margin of the tentorium cerebelli.

- The superior saggital sinus continues as the right transverse sinus.
- The straight sinus continues as the left transverse sinus.
- Each sinus extends from the internal occipital protruberance to the postero inferior angle of the parietal bone at the base of the mastoid process where it bends and becomes the sigmoid sinus.

V. SIGMOID SINUS :

- The transverse sinus continues as the sigmoid sinus.
- It is S shaped. It extends from the parietal bone to the posterior part of the jugular foramen .
- It grooves the mastoid part of the temporal bone .

VI. CAVERNOUS SINUS :

- Each cavernous sinus is a large venous space situated in the middle cranial fossa .
- It lies on either side of the sphenoid bone.
- Its interior is divided into a number of spaces or caverns by trabeculae.

STRUCTURES IN THE LATERAL WALL OF CAVERNOUS SINUS FROM ABOVE DOWNWARDS :

- Oculomotor nerve
- Trochlear nerve
- Ophthalmic nerve
- Maxillary nerve

STRUCTURES PASSING THROUGH THE CENTRE OF THE SINUS :

- Internal carotid artery
- Abducent nerve

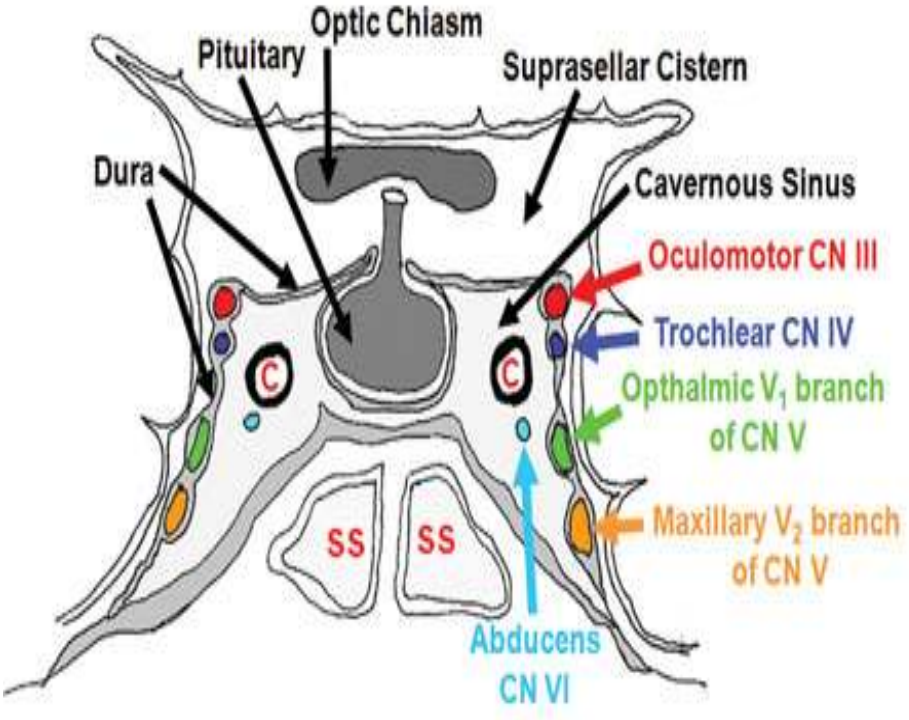


Figure 3 : Anatomy of Cavernous Sinus

VII. OTHER SINUSES :

- Occipital sinus
- Spheno parietal sinus
- Superior petrosal sinus
- Inferior petrosal sinus
- Basilar plexus of veins
- Petro squamous sinus
- Anterior and posterior intercavernous sinus

GROUPS OF VEINS :

- **EXTERNAL CEREBRAL VEINS :**

1. SUPERIOR CEREBRAL VEINS :
    - These are 6 – 1 2 in number.
    - The superolateral surface of the brain is drained by this vein.
    - They terminate in the superior sagittal sinus.
2. SUPERFICIAL MIDDLE CEREBRAL VEIN :
    - This drains the area around the posterior ramus of lateral sulcus.
    - It terminates in the cavernous sinus.
    - It communicates with the superior sagittal , transverse sinuses and the deep middle cerebral veins.

3. DEEP MIDDLE CEREBRAL VEIN :

- The area of insula is drained by this vein.
- It ends in the basal vein.

4. INFERIOR CEREBRAL VEINS :

- They are divided into 2 veins , orbital and tentorial veins.
- The orbital veins terminate in the superior cerebral veins or in the posterior sagittal sinus.
- The tentorial sinus terminate in the cavernous or any other surrounding sinus.

5. ANTERIOR CEREBRAL VEINS :

- The corpus callosum and the medial surface of cerebral hemisphere is drained by these veins and they ends in the basal vein .

- **INTERNAL CEREBRAL VEINS :**
  - There is one vein on each side .
  - It is formed by the union of the thalamostriate and chordal veins at the apex of the tela choroidea of the third ventricle .

- The right and left veins run posteriorly parallel to each other in the tela choroidea and unite together to form the great cerebral vein below the splenium of the corpus callosum .

- **TERMINAL VEINS :**

1. GREAT CEREBRAL VEIN :

- This is a single median vein. The two internal cerebral veins joined to form the great cerebral vein. It terminates in the straight sinus.

2. BASAL VEIN :

- There is one vein on each side . It is formed at the anterior perforated substance by the union of the deep middle cerebral veins, and the striate veins. It runs posteriorly and terminates by joining the great cerebral vein
- Ultimately all veins empty into the various cranial venous sinuses which in turn drain into the internal jugular vein.

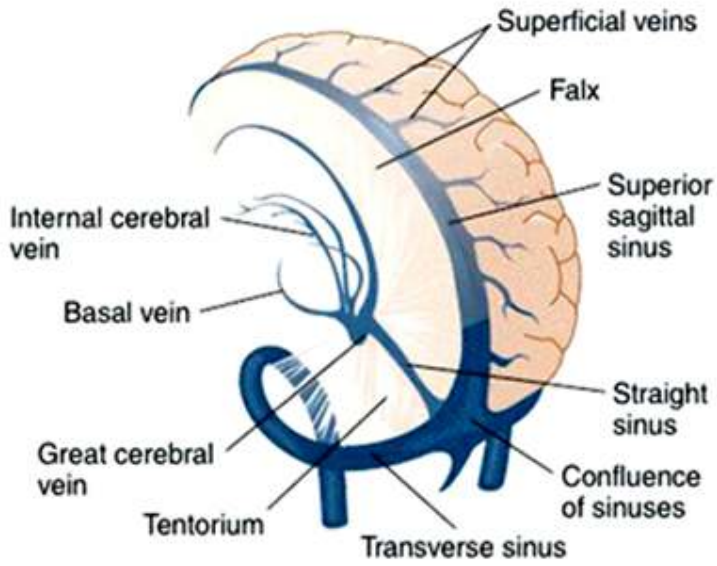


Figure 4 : Anatomy of cerebral veins

PATHOGENESIS:

The most commonly involved sinuses are the superior saggital sinus, lateral sinus (transverse sinus , sigmoid sinus) and cavernous sinus. The least frequently affected sinus are straight sinus and the vein of Gallen. The smaller cortical veins may be affected by thrombus even without involving the major sinuses .This is one reason for the misdiagnosis in computed tomography and magnetic resonance imaging .

The occlusion of the sinuses may be due to the formation of partial thrombus or by the complete occlusion produced by the extrinsic compression. The thrombus may extend to the cerebral cortical veins,

once the thrombus is blocked by the thrombus. The complete occlusion of the sinus by the thrombus results in cortical venous infarct .[8]

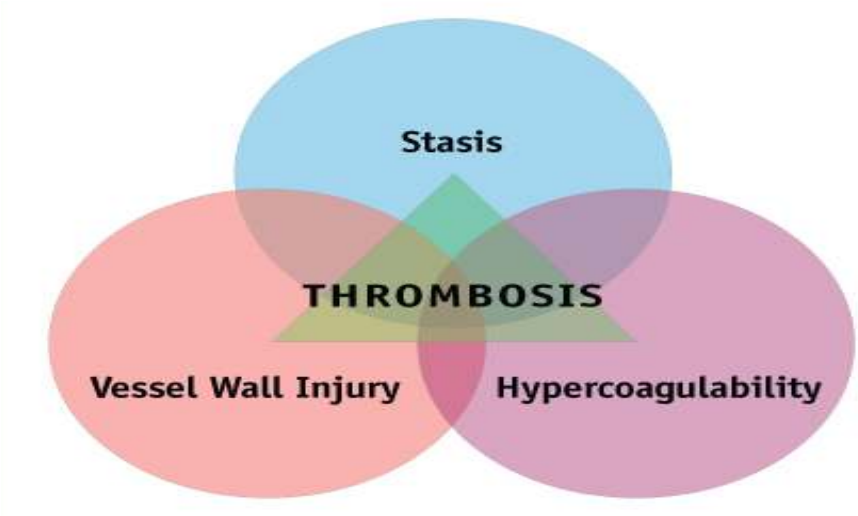


Figure 5 : Pathogenesis of Thrombosis – Virchow's Triad [8,]

The occurrence of intracranial hypertension is most common in venous thrombosis.[1] The main pathology is the development of intracellular swelling which occurs due to ischemia produced by the occlusion. This ischemia damages the cellular membrane pumps which are energy dependent. The disruption in the blood brain barrier and the leakage of plasma into the interstitial space causes vasogenic edema . If the underlying cause is treated promptly it is reversible. There will be defect in the absorption of CSF leading to increased intracranial tension because of the occluded sinus by the thrombus.[1] Thrombosis of the

venous sinuses leads to impaired absorption of CSF and consequently increased intracranial hypertension

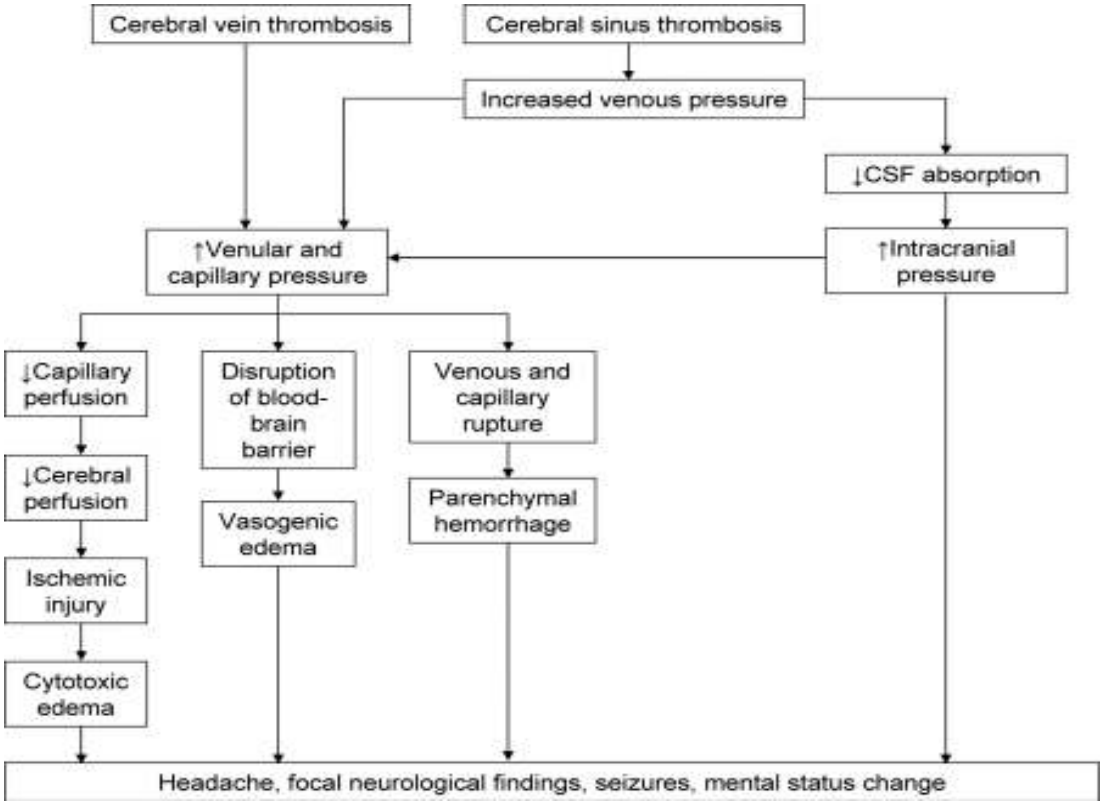


Figure 6: Pathogenesis of CVT

Various theories have been postulated for the pathogenesis of cerebral venous thrombosis. The main factors incriminated are

1. Infective theory
2. Embolism
3. Local endothelial damage
4. Hypercoagulability

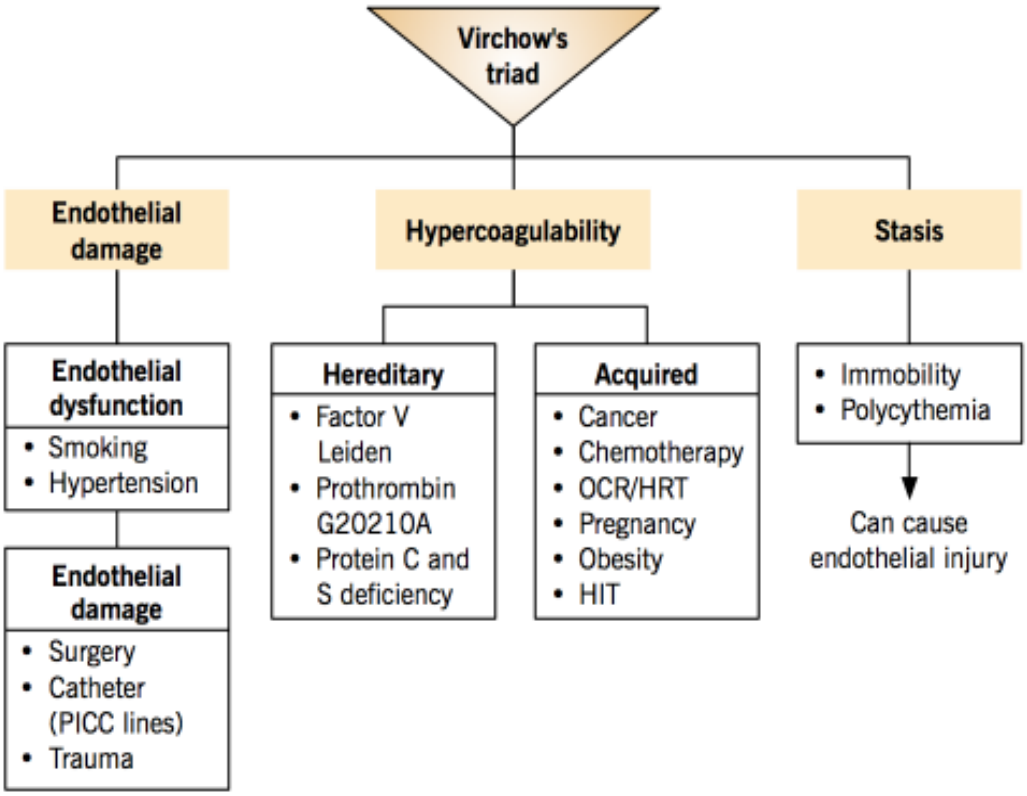


Figure 7: Pathology and Etiology

PATHOLOGY :

The pathological findings are determined by

- Underlying disease pathology
- Nature of sinus/cerebral vein involved
- Interval between the onset and pathological examination

Cortical vein thrombosis usually presents as a cord like swelling with minimal or absent hemorrhagic infarction of the brain. This has been explained based on the intercommunications between various cortical veins and sinuses. Cortical veins are also swollen and may rupture at some place giving rise to hemorrhagic infarction and even intracerebral hemorrhage .Microscopy shows typical changes of hemorrhage, but specific features appears to be profuse leukocytic invasion because of patent arteries allowing inflow of inflammatory cells. [9]

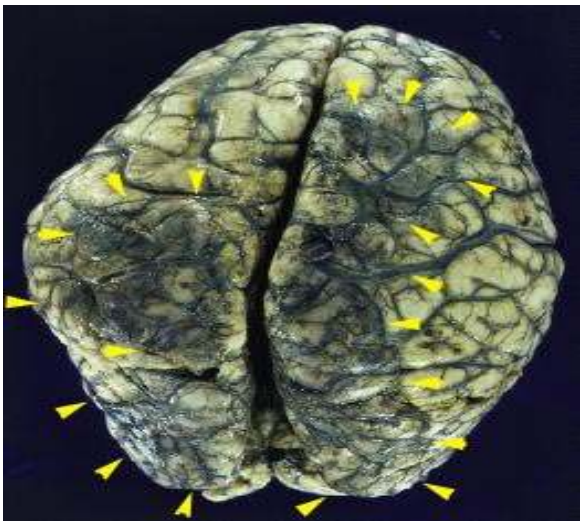


Figure 8: Pathology of Hemorrhagic Infarct

AETIOLOGY :

Venous thrombosis anywhere in the body results from increased activity of mechanism of hemostasis or decreased activity of one or more anti thrombotic mechanisms or a combination of both. The liquid state of blood is maintained by normal intact endothelium, prostacyclin,

anti thrombin III , heparin sulphate, thrombomodulin , protein C & S, fibrinolytic system, normal flow of blood and the absence of hypercoagulable state. Several causes has been documented as the cause of CVT. Even with elaborate investigations 20 – 25 % of causes no etiology has been found.[10]

CAUSES OF CVT :

TABLE 1 : SEPTIC DURAL SINUS THROMBOSIS

S.NO	LOCAL	SYSTEMIC
1.	Septic Trauma	BACTERIA- Typhoid, TB, Septicemia, Endocarditis
2.	Infection, Meningitis, Abscess	VIRUS – Measles, Hepatitis, Herpes , HIV
3.	Sinusitis	PARASITE – Malaria, Trichinosis
4.	Tonsillitis	FUNGUS – Aspergillosis

TABLE 2 : NON SEPTIC DURAL SINUS THROMBOSIS :

HEMODYNAMIC STATES • Dehydration • Fever • Cardiac failure	HEMATOLOGICAL DISORDERS • Polycythemia • DIC • Sickle cell anemia • Severe anemia • PNH • Thrombocytosis • APLA • Anti thrombin III deficiency • Protein C deficiency • Protein S deficiency • Homocysteinemia • Dysfibrinogenemia • Factor V Leiden mutation
HORMONAL DYSFUNCTION • OCP • Pregnancy • Androgen	TRAUMA • Head injury • Surgery • Cardiac pacemaker
METABOLIC DISORDERS • Homocystinuria • Diabetes mellitus • Osteopetrosis	NEOPLASM • Meningioma • Metastasis
INFLAMMATORY DISORDERS • Behcet's disease • Sarcoidosis • SLE , PAN ,Wegener's	VASCULAR DISORDERS • Arterio venous occlusions • Sturge weber syndrome

I. PROTHROMBOTIC CAUSES OF CVT :

Thrombophilia is a constellation of symptoms with predisposition to form clots inappropriately. Now ,it has been recognized that congenital thrombophilia and prothrombotic states are the most common non infective causes of CVT.[11]

The predisposition to form clots arise because of an association between genetic and acquired factors.[12] Inherited thrombophilias account for 22.4 %[12] of CVT cases .

In patients with age < 45 yrs ,with a family history of venous thrombosis and who has no apparent risk factors presented with recurrent CVT, inherited thrombophilia should be thought of .The risk of CVT is more in patients with inherited thrombophilia with the presence of other risk factors for CVT .[13] The mechanism underlying venous thrombosis include decreased neutralization of thrombi in patients with anti thrombin deficiency and reduction in the control of thrombin generation in patients with Factor V Leiden mutation, prothrombin gene mutation and protein C & S deficiency.[13]

II. TABLE 3 :GENETIC CAUSES OF CVT :[14]

Disorder	Gene	Inheritance	General population	With CVT (%)
Activated Protein C Resistance	Factor v Leiden mutation	AR	2- 15 %	5- 20
Prothrombin 20210	Prothrombin	AR	0.1	1- 5
Protein C deficiency	Protein C gene	AR	0.2 – 0.4	3- 6
Protein S deficiency	Protein S gene	AR	0.03 – 0.13	1-5
Factor VIII elevation	Von Willebrand factor deficiency	AR	10	25
Antithrombin III deficiency	Anti thrombin III	AR	RARE	3--8
Plasminogen deficiency	Plasminogen activator 1	AR		

The common hereditary thrombophilic states predisposing to CVT are described below:

(a) FACTOR V LEIDEN MUTATION :

There is a defect in the Factor V gene , with less susceptibility to inactivation by activated protein C .[15] Factor V a is sequentially cleaved at Arg 506 and Arg679 by activated protein c is demonstrated in 1995.[16] They demonstrated that the peptide bond cleavage at Arg506 facilitates the exposure of the subsequent cleavage sites at Arg306 and Arg679. The inactivation of factor VIII a by APC is mediated by the Factor V.[17] The transition results in the replacement of arginine by glutamine. This is called as Factor V leiden ,also known as factor v Q506 or Arg 506 Gln.Factor V is a variant of a normal gene.The activated protein C will not be helpful in cleaving the Factor V .This leads to the production of increased Factor V within the prothrombinase complex ,producing a hypercoagulable state and increased thrombin generation.[18]

(b) PROTHROMBIN GENE MUTATION :

This mutation was first described in 1996 by Poort . Thrombin is the end product of coagulation cascade which is formed by prothrombin. Prothrombin has 3 main activities related to coagulation which includes procoagulant,anticoagulant and anti fibrinolytic activities.Because of these varied properties, a disorder involving the prothrombin complex results in hemostasis disorder.[19]This gene mutation has a wide variable geographic distribution.

(c) PROTEIN C DEFICIENCY :

It is an autosomal dominant condition. It is most commonly associated with familial venous thrombosis.The chromosome 2 is the gene for protein C , which is related to the factor IX gene .[20]The heterozygous protein C deficiency is of two types.(Type I and Type II). [21]

- TYPE I Deficiency :
    - It is more common.
    - Most of them are heterozygous .
    - They have a reduced plasma protein C concentration
    - Majority of the mutations are missense and non sense mutations.
- TYPE II DEFICIENCY :
    - They have normal plasma Protein C antigen levels with decreased functional activity.[18]

The presence of protein C deficiency confers a high risk of venous thrombosis. More than 60 % of patients had recurrent venous thrombosis and about 40 % have features of pulmonary embolism.[22]

(d) PROTEIN S DEFICIENCY :

It was originally discovered and purified in Seattle, leading to the designation Protein S. There are two homologous genes for protein S :

PROS 1 and PROS 2. They have been mapped to the chromosome 3.[23] Based on total protein S antigen concentration, free protein S concentration and protein S functional activity, three phenotypes of protein S deficiency have been documented.

- TYPE I PROTEIN S DEFICIENCY :
  - This is the classical type .
  - This is associated with decreased level of total S antigen, marked decrease in free protein S antigen and protein S functional activity.[24]
- TYPE II PROTEIN S DEFICIENCY :
  - There is normal total and free protein S levels, but protein S functional activity is reduced .[25]
- TYPE III PROTEIN S DEFICIENCY :
  - This is characterized by normal protein S antigen,decreased free protein S and its functional activity .[26]

The clinical manifestations are similar to those seen with protein C and antithrombin deficiency. The probability of acquiring thrombosis is increased 9 times higher compared to controls.

(e) <u>DYSFIBRINOGENEMIA :</u>

The dysfibrinogenemia occurs because of the defect in the production of fibrinogen. The binding between TPA and fibrin

remains normal.[27] The activation of plasminogen with fibrin is mediated by fibrin, and this is reduced with the abnormal type known as fibrinogen Dusard. It has an autosomal dominant pattern of inheritance. Most of the patients are asymptomatic. Some of the patients present with features of bleeding diathesis, thrombophilia or a combination of both.[18]The occurrence of venous thrombosis in congenital dysfibrinogenemia is estimated to be 0.8%.

(f) <u>ELEVATED FACTOR VIII:</u>

The risk of venous thrombosis is increased in patients with increased levels of factor VIII.[28,29,30] This accounts for about 20 % of patients with venous thrombosis. In addition, normally 10 % of patients had increased factor VIII level. The mechanism of thrombosis in condition is not clear. It has been postulated as an independent risk factor for recurrent venous thrombosis. False positive results can occur in pregnancy, inflammation, trauma and renal diseases. However in patients with thrombosis the elevated levels will persist for a longer duration of time. This test should be taken as a part of routine examination in patients with suspected thrombophilia , as this has an increased risk of venous thrombosis.[31]

(g) HYPERHOMOCYSTEINEMIA:

Hyperhomocysteinemia can occur both as a congenital or as an acquired abnormality. Homocysteine is an amino acid which is a by product of methionine. Homocysteine is metabolized in the body by transsulfuration and remethylation. The cysteine is produced by the trans sulfuration of homocysteine and the reaction is catalysed by cystathinonie beta synthase. The cofactor needed in this reaction is pyridoxal phosphate. Methionine is produced by the remethylation of homocysteine and is catalysed by methionine synthase. Vitamin B12 is a cofactor for methionine synthase. Elevated levels of plasma homocysteine can thus occur because of enzymatic defect or due to nutritional deficiencies .The most common mutation associated with genetic hyperhomocysteinemia results from the production of thermolabile variant of methylene tetrahydrofolate reductase with reduced enzymatic activity. This is the most specific and strong risk factor for CVT.[32,33,34]

(h) ANTI PHOSPHOLIPID ANTIBODY SYNROME (APLA):

Antiphospholipid antibodies are acquired serum immunoglobulins. The anticardiolipin antibodies and lupus anticoagulant are the most frequently studied antibodies. It is an important cause of systemic arterial and venous thrombosis. The presence of anticardiolipin antibodies poses

an increased risk of CVT at an early age group and they have an more extensive involvement of sinuses[35] and they carry a more frequent risk of thrombosis. This entity has been identified as an important cause of acquired thrombophilic defect.[36]

PREGNANCY AND CVT :

- Pregnancy and postpartum period are the important period in occurrence of CVT .
- Pregnancy itself is a hypercoagulable state because of the changes in the blood composition
- Obesity , caesarean section , immobilization is also a contributing factor for CVT in pregnancy.
- Hyperhomocysteinemia is an associated co factor in pregnancy because of malnutrition and folic acid deficiency.
- Frequency of peri/postpartum CVT is 12/100000 deliveries

CONTRIBUTORS OF THROMBOSIS IN PREGNANCY

- Release of thromboplastin from placenta into circulation
- Ischemia during delivery of fetus
- Reactive thrombocytosis due to hemorrhage
- Iron deficiency

CLINICAL FEATURES:

- The clinical presentation of CVT is varied, depending upon the site, extent and the rate of thrombosis.
- There is a slight female preponderance .[37]
- Usual onset is in 3 rd or 4 th decade[38]
- The superior sagittal sinus[39] and lateral sinus are more commonly involved than the deep venous system.
- If the symptoms are restricted to dural sinuses it will manifest with features suggestive of raised intracranial hypertension
- If the cortical veins are involved , focal deficits and seizures may be the presenting features .[40]

FACTORS DETERMINING THE CLINICAL PROFILE OF CVT :

- Underlying sinus/venous system involved
- Mode of onset – acute,subacute or chronic
- Time interval between onset and presentation
- Nature of primary disease giving rise to CVT[41]

SYMPTOMS AND SIGNS : There are varied mechanisms for the development for signs and symptoms of CVT .

1. Venous obstruction, ischemia ,infarction or hemorrhage and the neuronal dysfunction .

2. The compressive effect of a mass
3. Venous obstruction leading to sudden increased intra cranial tension
4. Hyperexcitability with neuronal dysfunction due to the underlying etiology responsible for a thrombophilic state.

i. HEADACHE :

Headache is the most common presenting symptom .It is the manifestation in 70 – 80 %[42] of the patients. It may present as a very acute, severe presentation[43] like thunderclap headache or it may present as subacute or chronic. Usually it is not decreased by taking rest .It increase gradually over a few days. It may be associated with nausea, vomiting and other features of raised intra cranial hypertension .It mainly occurs because of leakage of blood to the surface which stimulates pain sensitive fibres in the dura or due to rise of intracranial pressure.

ii. FEVER :

It occurs in 15 – 60 % of cases. This is often present with septic CVT or those secondary to systemic infection [44].Superior saggital sinus thrombosis in infants and children may present only with fever and convulsions which may mimic febrile seizures .

iii. SEIZURES :

Seizures are more common in patients presenting with focal neurological deficits. 40 % of patients present with seizures of which it is focal in 50 % of the cases [45]. Seizures may be focal, multifocal or generalized .It occurs commonly due to irritation of the cortex because of the hemorrhagic venous infarct. Seizures are the most common manifestation in venous infarct than in arterial stroke .

iv. FOCAL DEFICITS AND ALTERED SENSORIUM :

Focal signs vary with extent and site of thrombosis. They may be motor or sensory, unilateral or bilateral .It occurs in approximately 60 % of patients. Thrombosis of the deep venous system produces features of delirium, amnesia, mutism. If the infarct is big enough to cause compressive symptoms patient will be in coma because of herniation.

Altered sensorium is usually due to raised intracranial pressure and is often preceded by headache and severe focal deficits.

v. CRANIAL NERVE SYNDROMES :

They are most commonly seen with lateral venous sinus thrombosis. These include features suggestive of 6,7,8 cranial nerve involvement . If the thrombus in the lateral sinus extends to the jugular veins ,[46,47] the

patient have features suggestive of lower cranial nerve involvement involving IX , X, XI ,XII .

vi. PAPILLOEDEMA :

The incidence of papilloedema is variable and depends on the etiology, rate and site of venous thrombosis. It is less common in puerperal CVT. Severe papilloedema can cause transient as well as permanent visual loss. The underlying mechanism is due to an increase in venous pressure secondary to thrombosis of the of the dural venous sinuses, which alters the pressure gradient resulting in poor CSF absorption through the granulations [47]

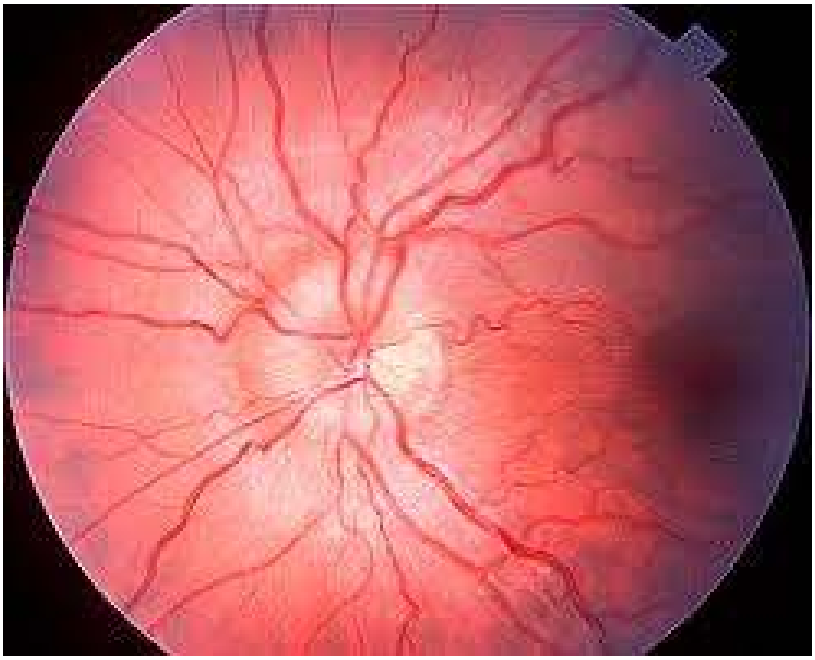
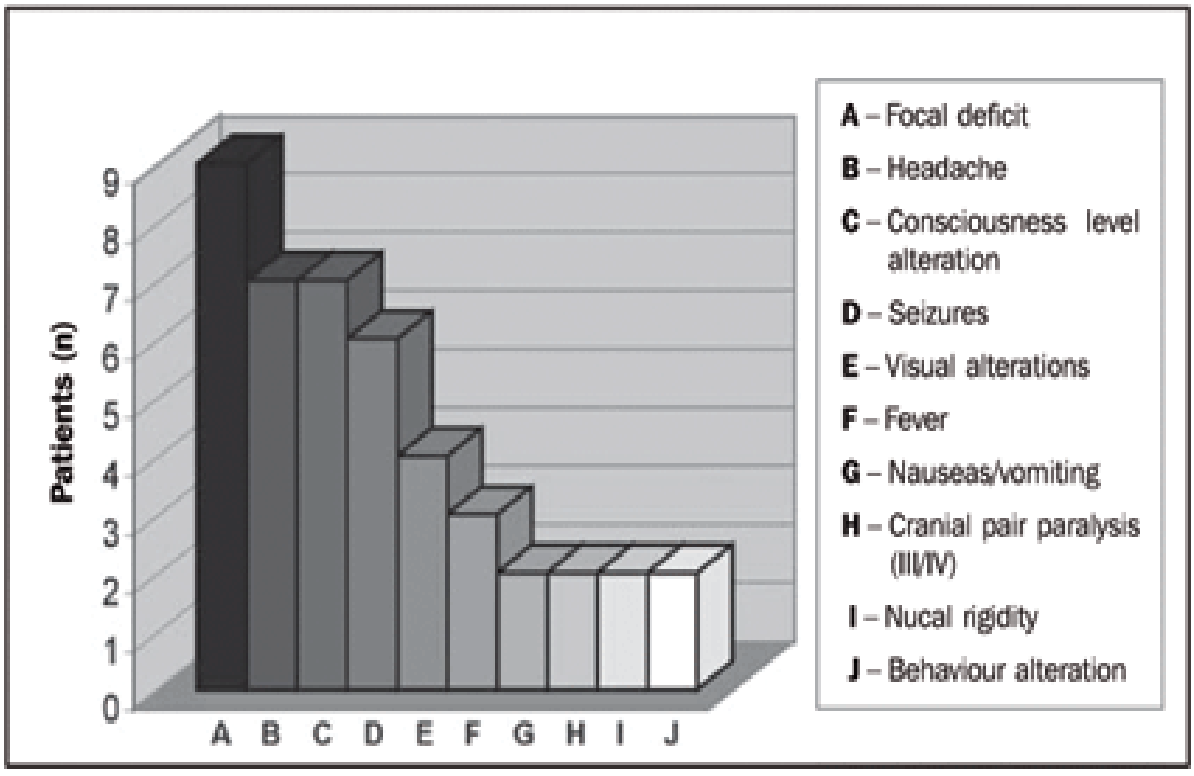


Figure 9: Fundus picture of papilloedema

vii. OTHER PRESENTATIONS :

These are uncommon and include signs of meningeal irritation , cortical blindness, akinetic mutism , dystonia, attacks of migraine with aura ,psychiatric disturbances , etc..[44,47]

GRAPH 1 : FREQUENCY OF CLINICAL MANIFESTATIONS



PATTERNS OF PRESENTATION :

There are 4 main clinical presentations of CVT

1. FOCAL DEFICITS / PARTIAL SEIZURES :

It is characterized by seizures, headache, altered sensorium, focal deficits. It may also manifest as isolated seizures.

2. ISOLATED INTRACRANIAL HYPERTENSION :

This comprises headache , nausea,vomiting , papilledema, nerve palsy.

3. SUBACUTE DIFFUSE ENCEPHALOPATHY :

This is characterized by a decreased level of consciousness without ICT features.

4. PAINFUL OPHTHALMOPLEGIA : This is caused by lesions of the 3 ,4 ,6 cranial nerves, chemosis and proptosis in patients with cavernous sinus thrombosis .[48]

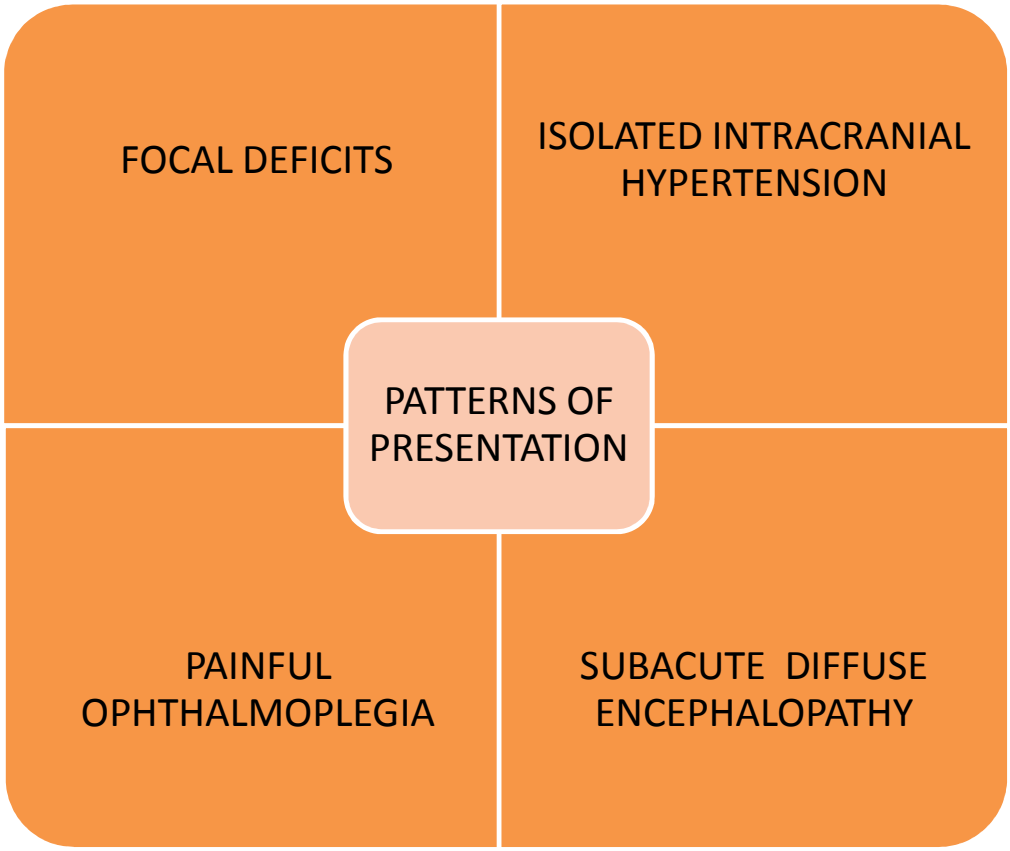


Figure 10: Patterns of presentation of CVT

RELATIONSHIP BETWEEN CLINICAL MANIFESTATIONS AND THE SITE OF OCCLUSION :

- Occlusion of cortical veins – motor/ sensory deficits, seizures or both
- Occlusion of sagittal sinus - motor deficits, seizures
- Occlusion of lateral sinus – isolated intracranial hypertension syndrome

- Occlusion of deep cerebral veins – severe coma, delirium , bilateral motor deficits
- Occlusion of cavernous sinus – orbital pain , chemosis, proptosis , occulomotor palsies [49]

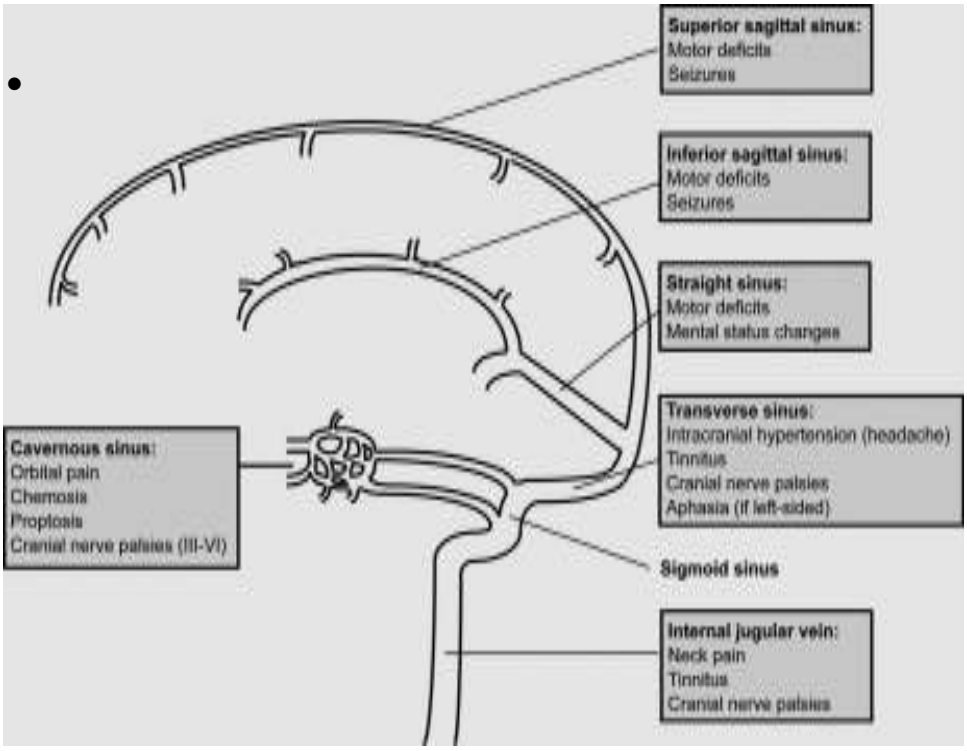


Figure 11: sinuses and their clinical features

INVESTIGATIONS :

NEURO IMAGING OF THE THROMBOSED VESSEL :

The diagnosis of CVT is mainly based on imaging modalities. It usually shows non specific lesions . Moreover , neuroimaging may be normal in 25 – 30 % of the patients with CVT . CVT is identified by the imaging of the venous circulation which identifies the thrombus in the

occluded vessel. The current gold standard test for the diagnosis of CVT is MRI with MRV[50]. The neuroimaging methods commonly used to describe CVT are described below

(A) COMPUTED TOMOGRAPHY (CT BRAIN) :

Conventional CT is the best non invasive investigation of choice for identifying CVT. CT may be normal in 25 – 30 % of the patients with isolated intracranial hypertension[50] .However CT BRAIN is the initial investigation in the emergency room not only to find out CVT but also to rule out other causes which may mimic CVT .The diagnostic value of CT may be increased, when it is combined with helical CT venography .[51]

The infarction in the non arterial distribution with hemorrhage implies the possibility of CVT.

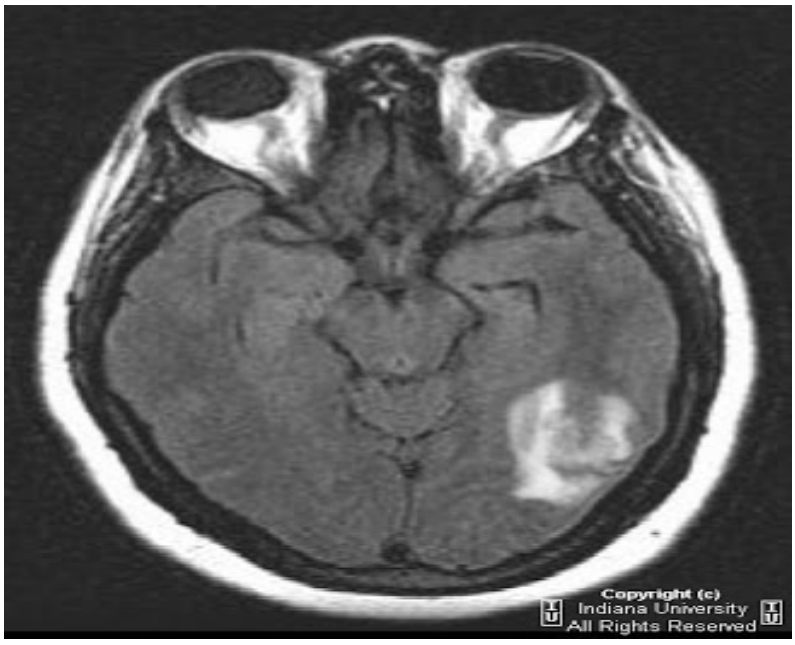


Figure 12: CT Brain showing hemorrhagic infarct

The CT findings of CVT may be as follows

- **CORD SIGN :** This is seen in plain CT scans. It represents the visualization of a thrombosed cortical veins spontaneously without any contrast. It is not very reliable as it can be also seen in internal cerebral vein thrombosis.
- **DENSE TRIANGLE SIGN :** It represents spontaneous superior sagittal sinus obscuration by freshly coagulated blood. It is present in only less than 2 % of cases.

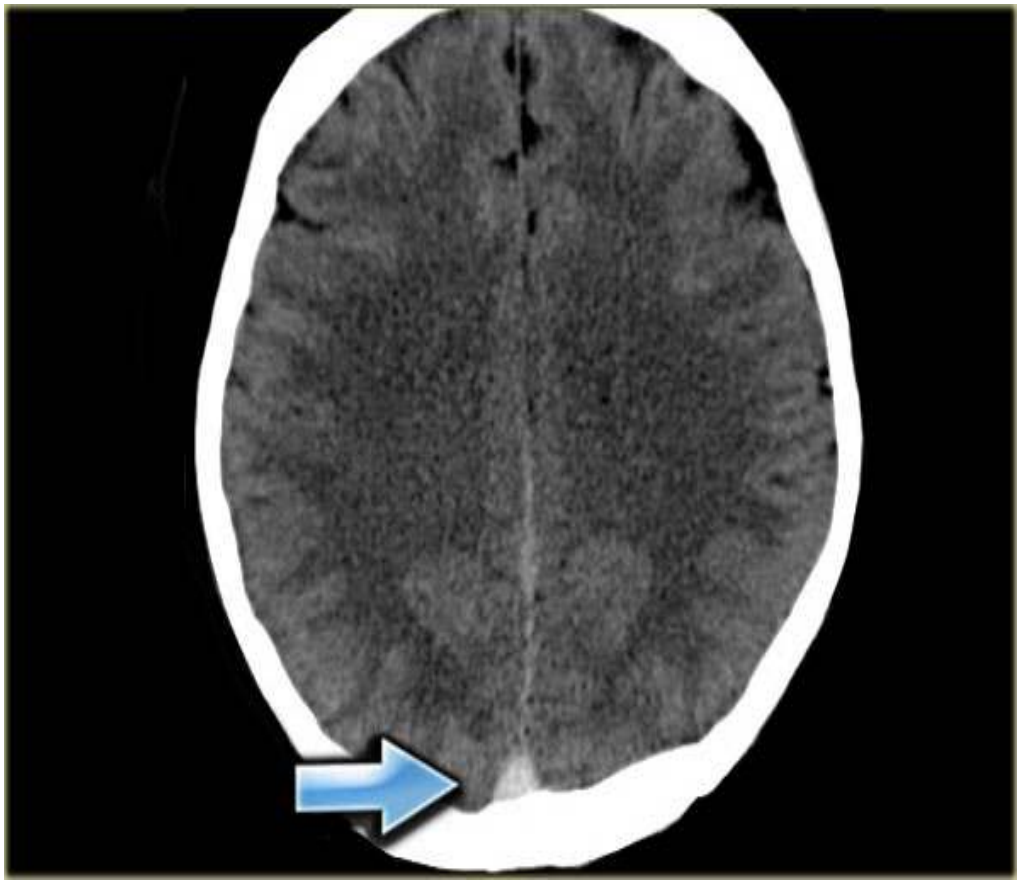


Figure 13 : CT Brain showing dense triangle sign

- **EMPTY DELTA SIGN :** It is seen in contrast enhanced CT and it was first described by Buonanno and colleagues. It reflects the contrast between the opacified and the non opacification of the clot inside the sinus. The most common direct sign in CVT is empty delta sign and it is demonstrated in approximately 28- 72 % % of the cases.

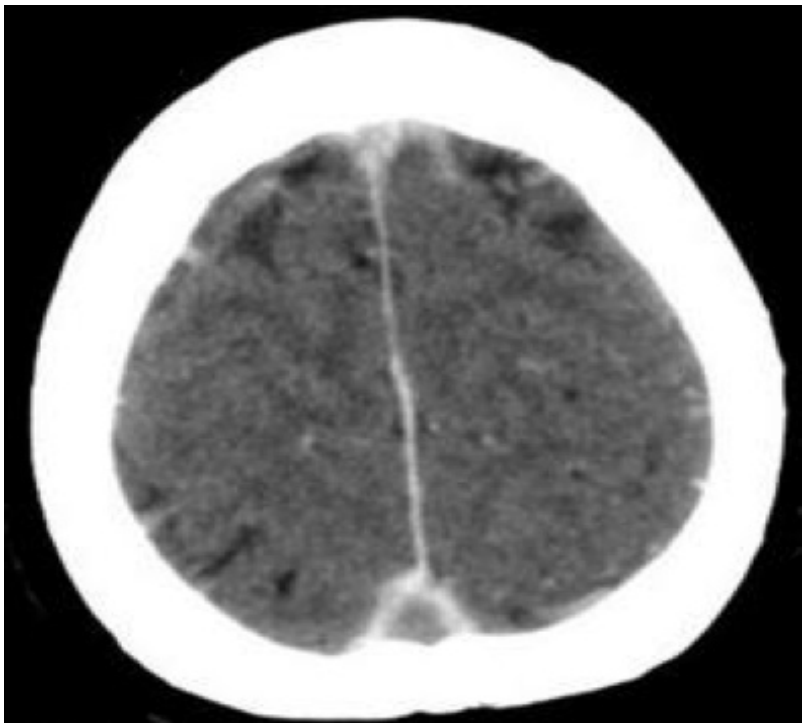


Figure 14: CT Brain demonstrating Empty delta sign

ABSENCE OF EMPTY DELTA SIGN :

- When posterior third of superior saggital sinus is not involved in thrombosis.
- CT scan is done either early or very late after the onset of symptoms.

INDIRECT SIGNS OF CEREBRAL VENOUS THROMBOSIS :

- Approximately 20 % of cases will demonstrate intense contrast enhancement of the falx and tentorium. Superior saggital sinus thrombosis is usually demonstrated by tentorial enhancement. There may be dilated transcerebral medullary veins, implying a major venous stasis, indicating a large SSS thrombosis.
- cerebral edema is characterized by white matter hypodensity without any enhancement..It is seen in upto 75 % of patients.
- Hemorrhagic venous infarct – in 10 – 50 % of the patients .There is an associated sub arachnoid hemorrhage or a subdural hematoma in rare instances. It can only present as the only sign of CVT.
- Non hemorrhagic venous infarct – the incidence is almost equal to that of hemorrhagic venous infarct. They may be seen in the hemispheres or in the basal ganglia..[52]

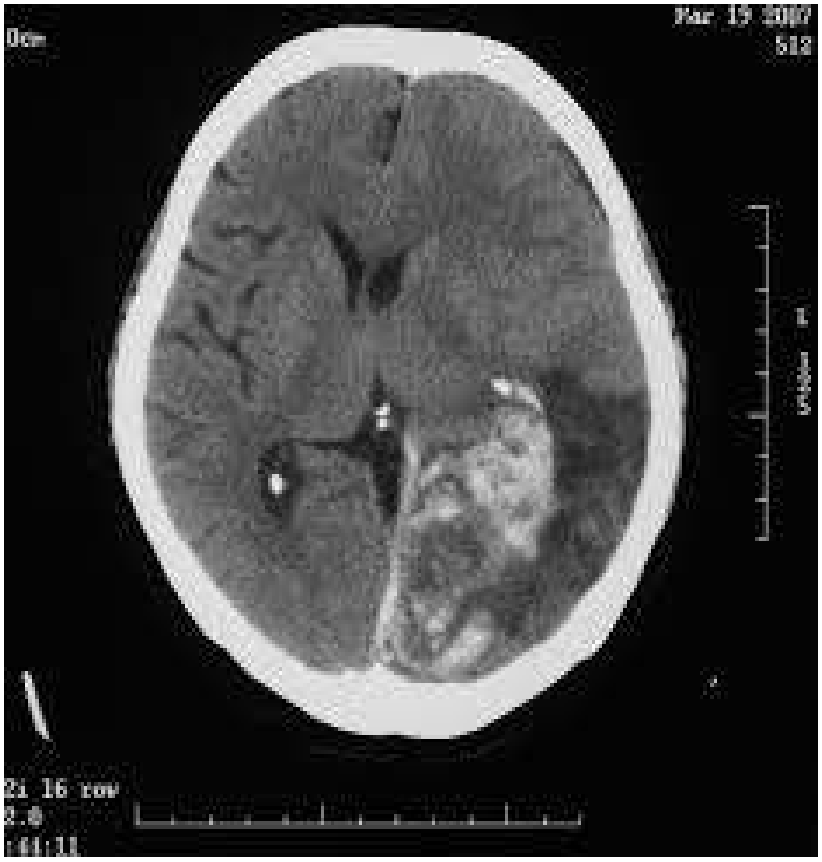


Figure 15: CT Brain showing massive hemorrhagic infarct

NORMAL CT SCAN - CVT :

In 20 – 30 % of patients with CVT ,CT may be normal. In patients with isolated intracranial hypertension it may be normal in 50 % of cases [53]. The main aim of CT is rule out the other conditions mimicking CVT. Very few CT shows the classical domain of CVT . MRI /MRV is the diagnostic modality preferred nowadays.

(B) MAGNETIC RESONANCE IMAGING :

MRI with MRV is the sole diagnostic investigation of choice for CVT[39] .The clot can be directly visualized in the sinus with the help of MRI .The clot has a varied picture depending upon the duration of thrombosis. The thrombosed vessel appears isointense on T1 MRI and hypointense on T2 image in the very early stages of formation of thrombus. This phenomenon may not be visualized in MRI. This difficulty can be overcome by MRV. The flow void becomes absent and the thrombus becomes hyperintense, first on T1 and later on T2 MRI , which is mainly due to the conversion of oxyhemoglobin to methemoglobin within the thrombus .It starts about 5 days after and lasts nearly for 35 days. The occlusion will be removed or there may be recanalisation of the vessels after a certain period, during that period even MRI is not diagnostic .The abnormalities may persist for more than 6 months in about 2/3 rd of patients .[54]

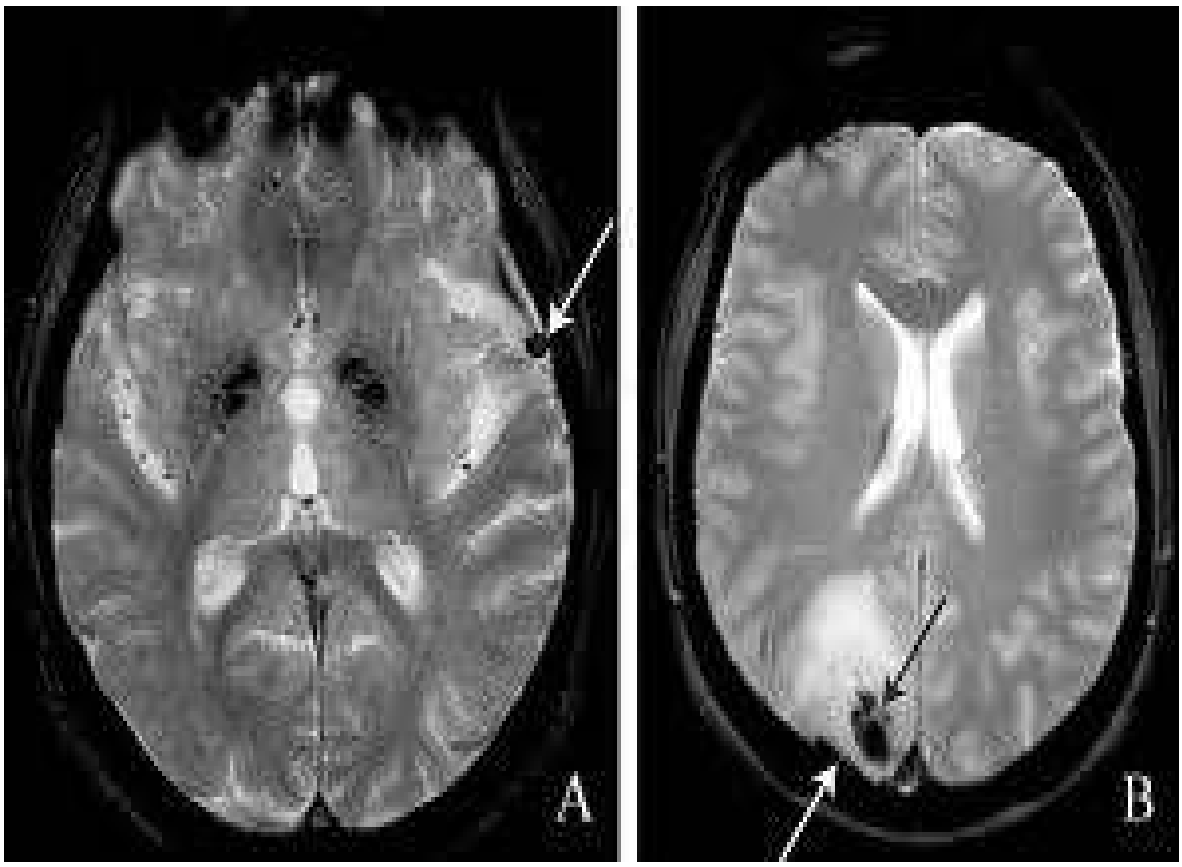


Figure 16: MRI Brain showing transverse sinus thrombosis

MRI is also useful in assessing other associated features apart from CVT , which includes cerebral edema or infarct . However false negative and false positivity can also occur.

DWI - LIMITATIONS

False positive	False negative
• Slow flow of blood without thrombus	• Acute thrombus – early stage • Isolated cortial vein thrombosis • Partial recanalisation

Diffusion weighted imaging – Advantages :

- Direct visualization of clots
- Heterogenous signal intensity
- No diffusion abnormality

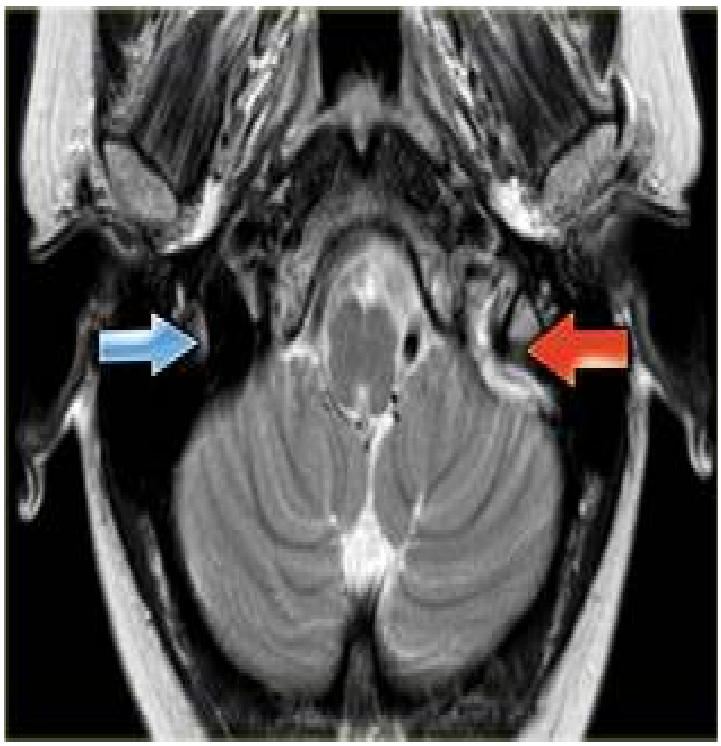


Figure 17 : MRI - SIGMOID SINUS THROMBOSIS

(C) MAGNETIC RESONANCE VENOGRAPHY :

MRV is now the best diagnostic modality of choice at present .There are three methods , which are as follows

- Two dimensional time of flight (TOF)
- Three dimensional time of flight
- Phase contrast

The most commonly used method is two dimensional flight..The slices will be 1.5 and 3mm.The absence of flow in the veins is the typical appearance in CVT in MRV indicating complete occlusion of the veins.

LIMITATIONS :

- Difficult to diagnose partial thrombosis
- Difficult to diagnose hypoplasia and thrombosis[54]
- Difficulty in detecting cortical vein and cavernous sinus thrombosis

ADVANTAGE :

- Easily repeatable
- Non invasive

TABLE 4 :DIFFERENCE BETWEEN CT AND MRI/ MRV

S.no	Characteristics	CT brain	MRI/ MRV
1.	Visualisation	Major venous sinuses	Superficial & deep venous system
2.	Time	Not time consuming	Time consuming
3.	Radiation hazard	Present	Absent
4.	With mechanical devices	Can be used	Contraindicated
5.	Contrast reactions	Present	Absent
6.	Availability	Easy	Difficult
7.	Accuracy	Good	Excellent

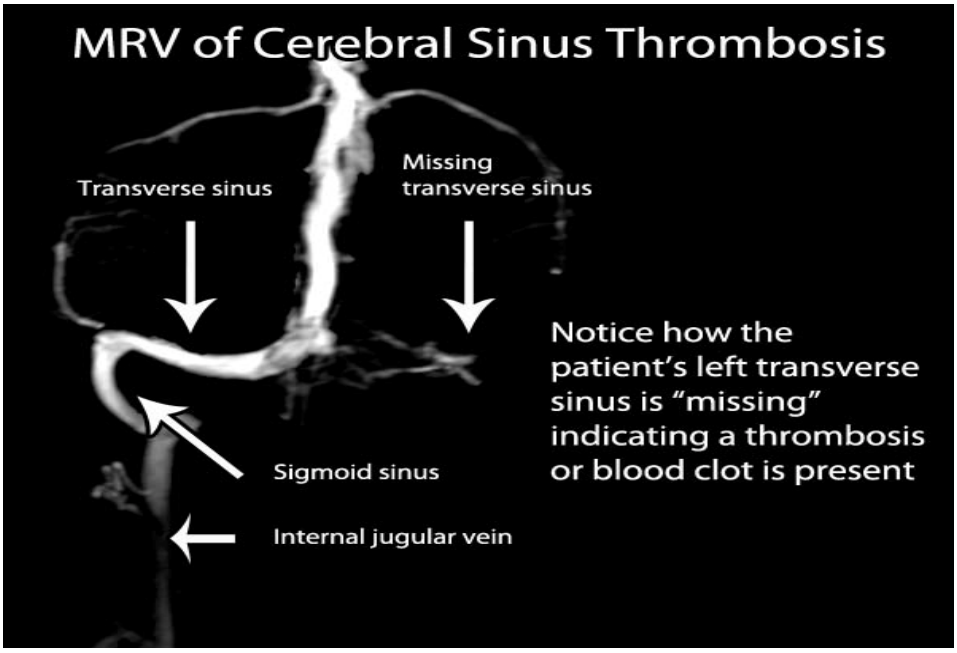


Figure 18 : MRV of Left Transverse Sinus Thrombosis

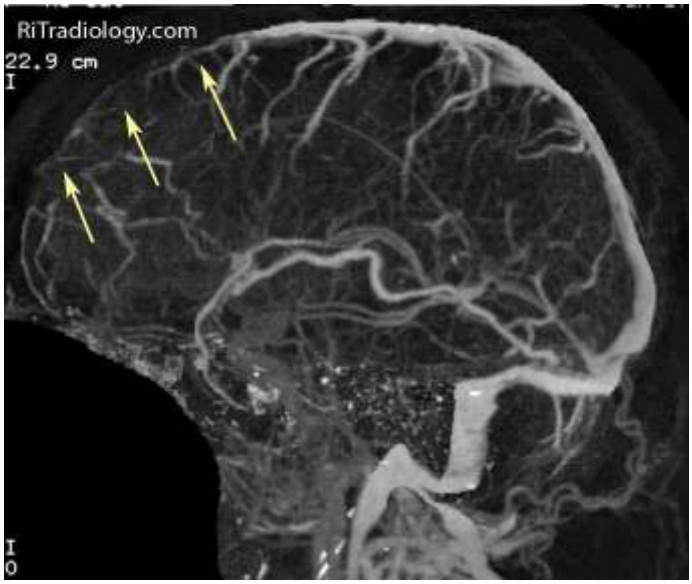


Figure 19: MRV Showing superior sagittal sinus thrombosis

(D) CT HELICAL VENOGRAPHY :

CT venography can be used as an alternative tool for MRI.[39] CT venography more or less resembles CT angiography. There will be a little delay after giving contrast in order to visualize the venous system clearly .The non ionic contrast is injected intravenously at a rate of 3 ml/sec. From the images obtained bone images are deleted. After that images are reconstructed by maximum intensity projection. The images of this is closely related to MRI images. Compared to MRV they have less artifacts.

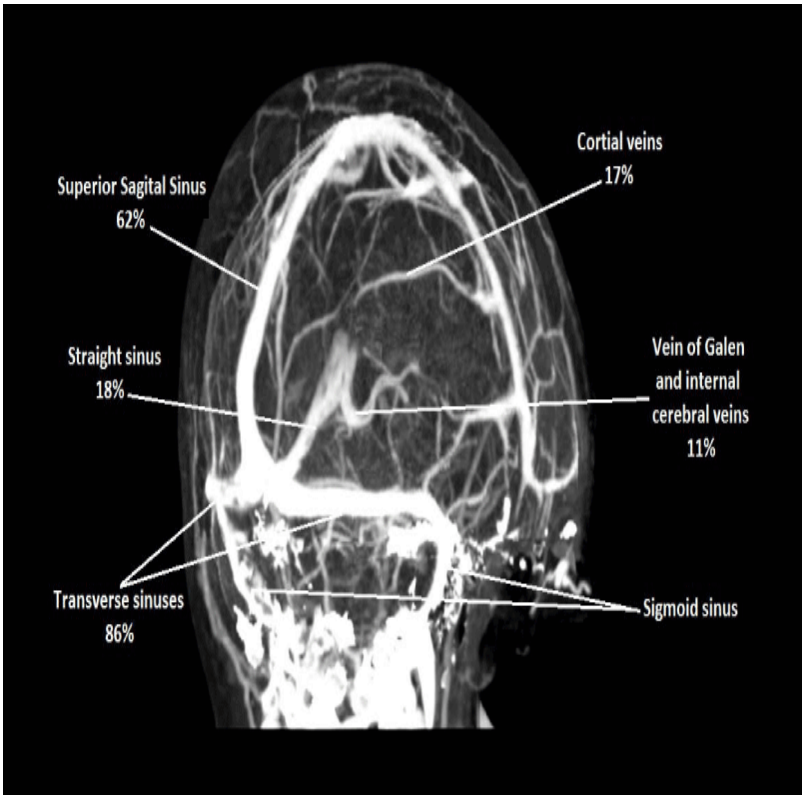


Figure 20:CT Venography demonstrating the sinuses involved in CVT

ADVANTAGES :

- 3D CT – reduces the mis interpretation of normal anatomic findings which alike CVT

DISADVANTAGES :

- Insufficient time for enhancement

(E) D- DIMER :

D- Dimer is a fibrin degradation product .It is a product of fibrinolysis. It contains two cross linked D fragments of the fibrin proteins and so it is called . The value of the measurement helps to predict the presence of thrombosis. The negative D Dimer test always rules out the possibility of thromboembolism .[55,56] The positive test implies the presence of thrombus ,but it does not rules out other possible causes of elevation..

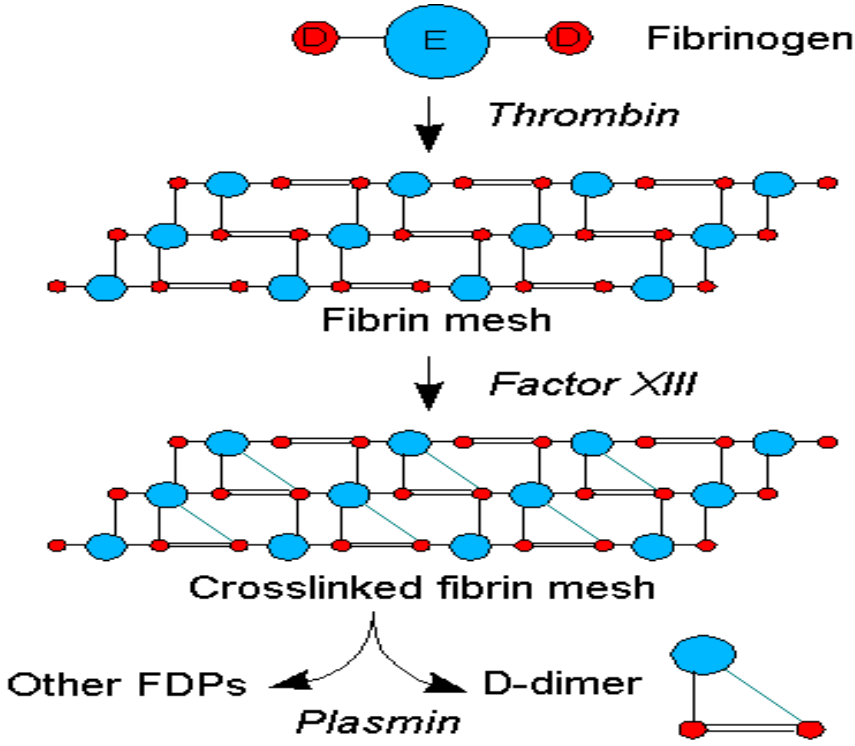


Figure 21 : D Dimer Formation

In the normal human circulation, D Dimers are usually not present. It is elevated only when the coagulation cascade is activated .The D Dimer assay depends on the interaction between the monoclonal antibody and the D Dimer fragment.

D-dimer levels are not always uniform. They have a peak value during the acute phase of thrombosis. As time goes on the levels of D Dimer starts decreasing[57] .So in patients presenting with subacute or chronic symptoms , there will be not much elevation in the level of D Dimer. The level of D Dimer correlate with the clot burden. If there is a lesser clot burden then the levels wont be much high. At present a variety of techniques are employed for determining D D imer tests.

A study conducted in 2004, proves that D Dimer levels was abnormal in 34 of 35 patients., giving it a sensitivity of 97.1%, a negative predictive value of 99.6%, a specificity of 91.2%, and a positive predictive value of 55.7%[58,59]. This study is followed by another study, which proves that even with clear cut thrombosis , 10 % of patients had normal values of D Dimer. The patients who had only features of isolated headache without any other symptoms had normal values of D Dimer. The D DIMER levels above 500 ng/ml is[60] considered to be positive for CVT. The method used for estimation is latex slide agglutination method.

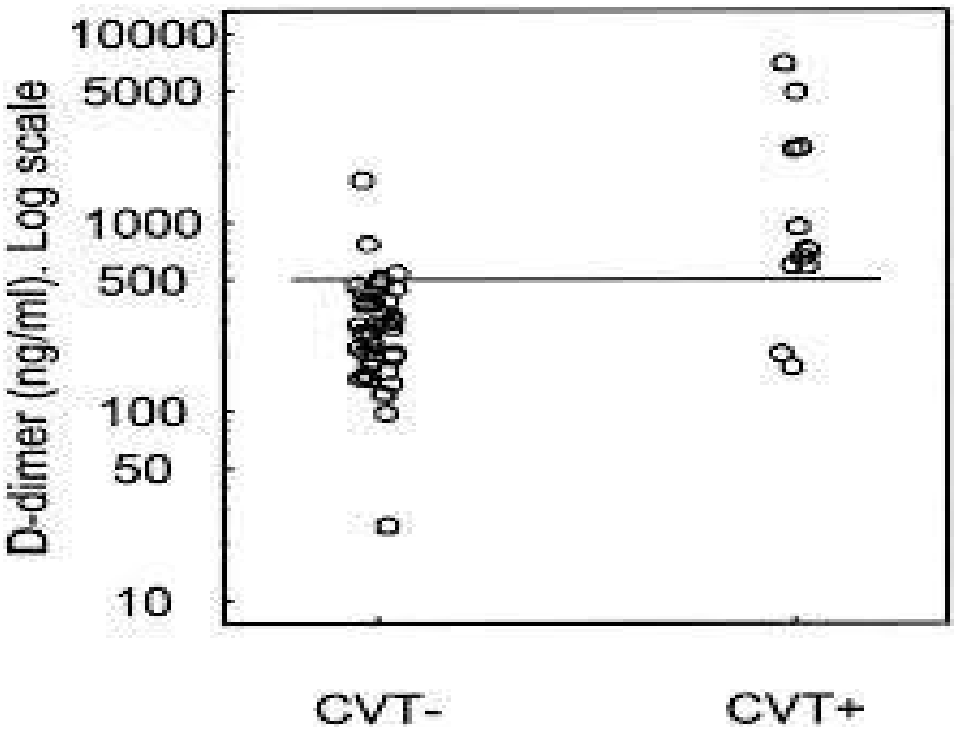


Figure 22: D Dimer and CVT Correlation

TREATMENT :

The treatment of CVT is based on assessment of individual cases as the spectrum of presentation of CVT is varied .Anticoagulants with low molecular weight heparin or dose adjusted intravenous heparin are used as first line therapy. It is still a question whether to use anticoagulants in the acute phase of CVT .[61] On one hand it can decrease the extension of thrombus ,but on the other hand it may worsen the hemorrhage.According

to Martinelli et al ,it is better to delay the initiation of anticoagulation till the hemorrhage is stabilized.

SYMPTOMATIC TREATMENT :

- The most common cause for CVT is dehydration .In order to treat the cause of dehydration use of IV fluids is mandatory.
- Anticonvulsants for the patients with seizures. There is no clear data for the use of prophylactic use of anti convulsants in seizures. It is continued for a minimum period of 1- 2 yrs and then withdrawn gradually[62]. The withdrawl of anticonvulsants should be based on that the patient had no recurrent seizures , has a normal EEG and no neurological sequelae.
- Measures to reduce increased intracranial hypertension .The measures includes steroids, mannitol, glycerol, dextran, acetazolamide, lumbar puncture, shunting or even surgical decompression .[60]
- Heparin therapy
- There is no role of steroids in CVT[63]
- Decompressive hemi craniectomy may be life saving in patients with features suggestive of herniation because of mass effect.[64]

ETIOLOGIC TREATMENT :

The main line of management in CVT is the treatment of the underlying etiology behind CVT . The use of wide spectrum of antibiotics for treatment of septic CVT and surgical debridement for primary site of infection. Malignancies, collagen vascular disorder and hematologic disorders need specific treatment.

ANTITHROMBOTIC TREATMENT :

AIMS :

- Recanalisation of occluded sinus
- Prevent progression of thrombus
- Treatment of prothrombotic state
- Prevention of recurrence

The optimal duration of heparin therapy is uncertain. Once symptomatic improvement occurs, heparin is replaced with oral anticoagulation. The INR should be maintained within 2-3.The treatment should be continued for 6 months if there is no specific prothrombotic cause identified . When there is increased risk of further thrombosis like that of inherited thrombophilias , treatment should be continued for a long time.

THROMBOLYTIC THERAPY :

If patients deteriorate inspite of adequate anticoagulation, thrombolysis may be considered if facilities are available. [65] Intravenous Urokinase was used in the early 1970's for thrombolysis . Now r TPA is the most commonly used agent .Both these agents carry the risk of hemorrhage. There is no clear cut clinical evidence to show that these agents have a better clinical outcome .Angio – jet rheolytic thrombectomy is a novel technique. In this method a vacuum is created by means of bernoullie effect .This vacuum is used for aspirating the thrombus. It can be used for even hemorrhagic CVT, as it has an added advantage of lack of hemorrhagic complications.[62]

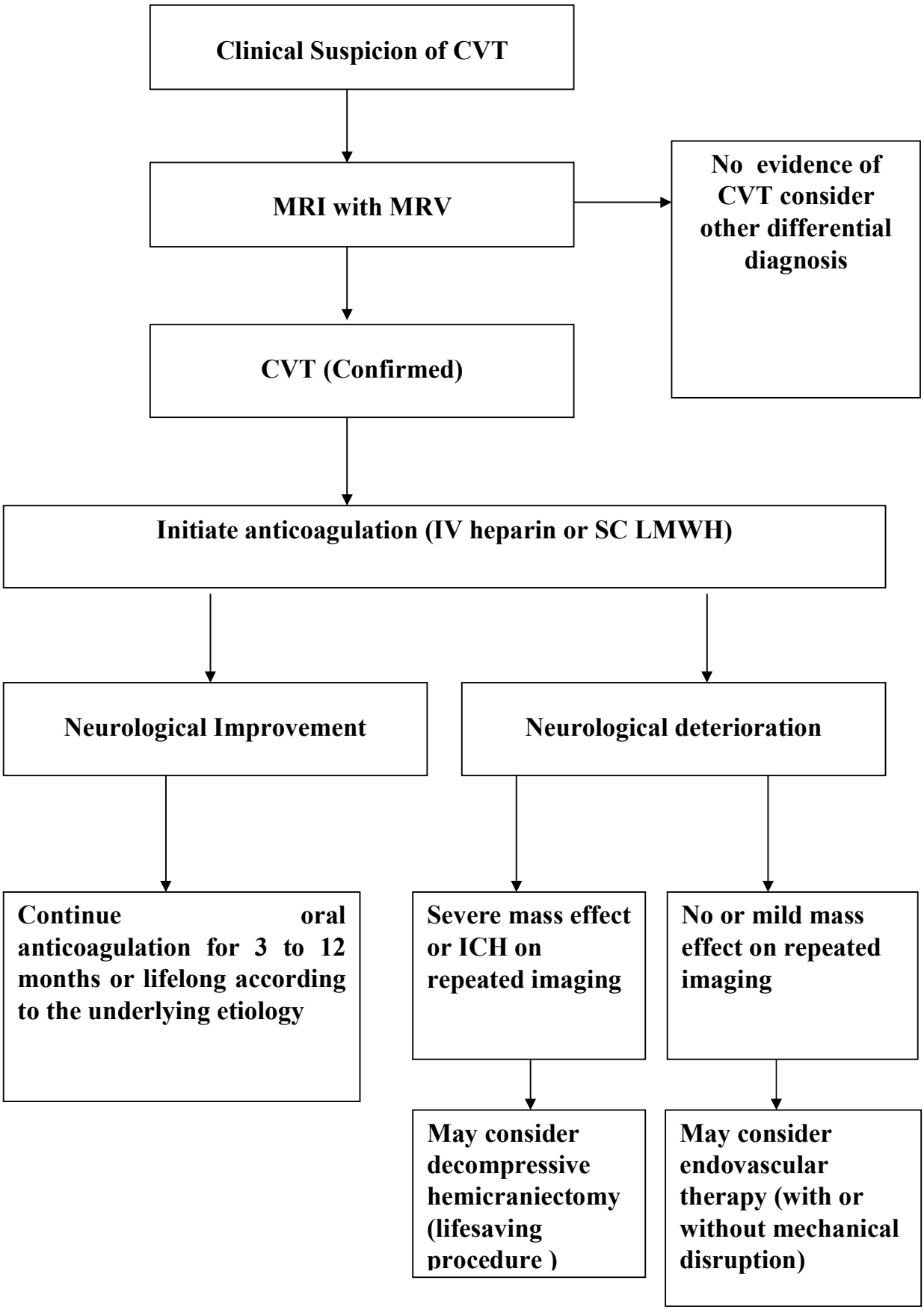


Figure 23 : Algorithm for management of CVT

PROGNOSIS :

SHORT TERM OUTCOME :

The cause of death in CVT are

1. Large hemorrhagic infarct
2. Complications like sepsis, uncontrolled seizures, pulmonary embolism
3. Carcinoma, septicemia, leukemia and PNH

FACTORS SUGGESTING BAD PROGNOSIS :

- Rapid progression of thrombus
- Patient's age
- Infection
- Focal symptoms and coma
- Hemorrhagic infarct
- Empty delta sign on CT scan
- Type of veins involved

FUNCTIONAL RECOVERY :

The prognosis is better for venous infarct than the arterial infarct.

LONG TERM OUTCOME :

During the initial episode of CVT ,if patient had seizures ,the possibility of having residual epilepsy is around 10 – 30 %.

If the cause of CVT is a hypercoagulable state, there is a possibility of recurrence of venous thrombosis. But because of long term anticoagulation it is generally uncommon.

METHODOLOGY

SOURCE OF STUDY : Patients diagnosed to have Cerebral venous thrombosis at Coimbatore Medical college.

DESIGN OF STUDY : Cross sectional Study

PERIOD OF STUDY : AUGUST 2013 – JULY 2014

SAMPLE SIZE : 50

INCLUSION CRITERIA:

- Patients who are diagnosed to have cerebral venous thrombosis by means of MRI and MRV in Coimbatore medical college within 30 days of symptoms onset, not started on anticoagulation.
- Age above 18 yrs.

EXCLUSION CRITERIA:

- Pregnancy
- Puerperium upto 4 weeks
- Arterial stroke within past 3 months
- Pulmonary embolism or Deep vein thrombosis
- Head injury within past 3 months
- Rheumatoid Arthritis

- Intra cerebral mass lesion

METHODOLOGY:

The patients diagnosed to have cerebral venous thrombosis confirmed with MRI BRAIN during the study period were included. After getting informed written consent,careful medical history was obtained including clinical features, precipitating risk factors, family history .All patients were subjected to meticulous general and neurological examination .Patients were subjected to MRI BRAIN with Venography on a 1.5 Tesla machine.

After confirming the diagnosis of CVT by MRI and MRV ,blood samples were drawn ,plasma was separated, frozen at -80 C and sent to the laboratory. A basic hematological work up including complete blood counts, peripheral blood smear, ESR, PT/APTT were done. D-Dimer tests were measured by using a conventional ELISA Test. A value of more than 5oo ng/ml were considered positive tests. In order to find out the etiology of CVT , dsDNA, APLA, serum homocysteine was done .

STATISTICAL ANALYSIS :

All the dates were entered in a data collection sheet in an Excel format and analysed using SPSS Software. Numerical values were reported using mean and standard deviation or median. categorical values

are reported using number and percentages. probability value (p) value less than 0.05 was considered a statistically significant.

OBSERVATION AND RESULTS

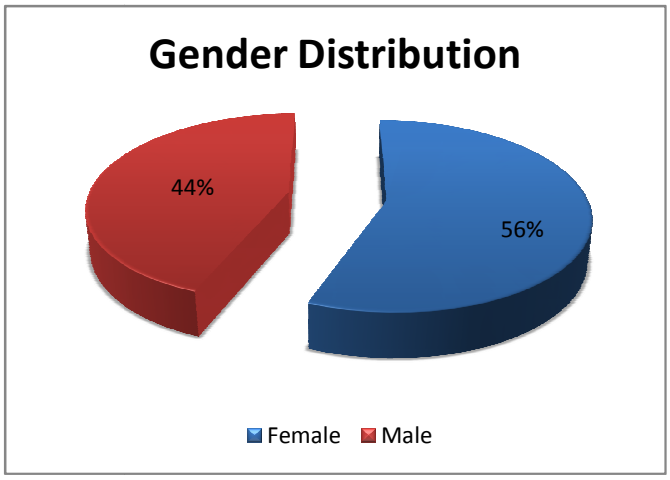
During the 12 month study period , a total of 50 patients were studied for finding out the usefulness of D DIMER as an initial diagnostic bio marker in CVT.

SEX DISTRIBUTION :

Table 5: Sex distribution among the study population

SEX	Frequency	Percent (%)
Female	28	56.0
Male	22	44.0
Total	50	100.0

GRAPH 2– Sex Distribution among the population



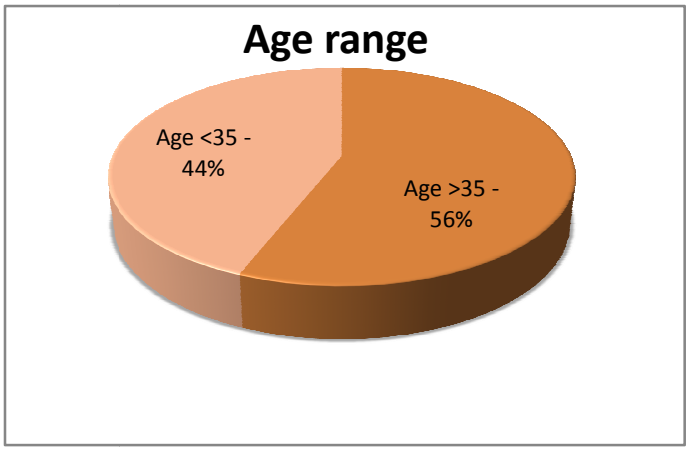
Among the 50 patients , 28 were females (56%) and 22 were males (44%). The ratio of female: male was 1.3:1.

AGE DISTRIBUTION:

Table 6: Age distribution among the study population

AGE GROUP	Frequency	Percentage (%)
Above 35 yrs	28	56.0
Upto 35 yrs	22	44.0
Total	50	100.0

Graph 3 :Age wise distribution of cases



The age of the patients comes under 2 categories . The majority of them are above 35 yrs (56 %) .The patients below 35 yrs are around 44 % .

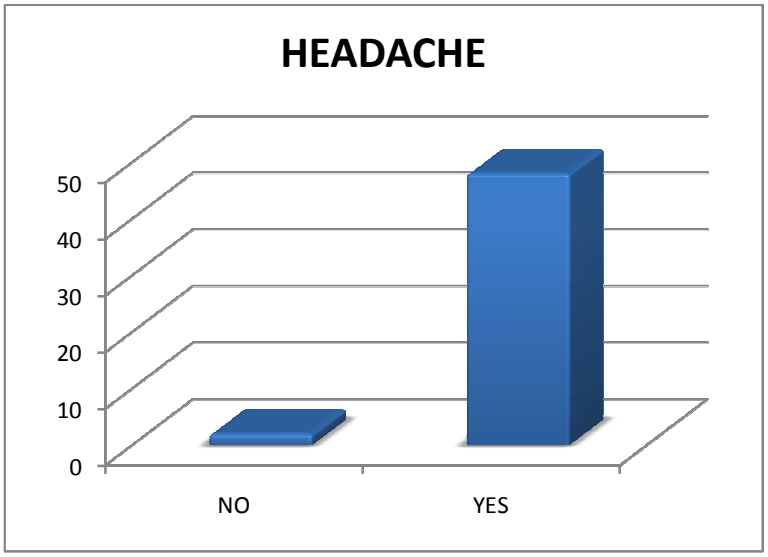
SOCIOECONOMIC STATUS : Majority of the cases were within the low socioeconomic status (64.4%) , the rest belonged to the middle socioeconomic status.

SYMPTOMATOLOGY AND SIGNS:

Table 7: Clinical Profile of Headache

HEADACHE	FREQUENCY	%
NO	2	4.0
YES	48	96.0
TOTAL	50	100.0

Graph 4 : Distribution of Headache

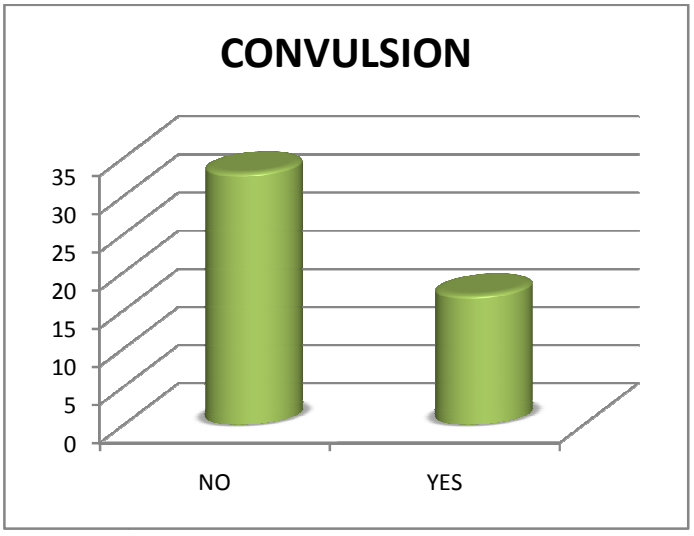


Among the 50 patients , 48 patients (96 %) were having headache . Remaining 2 patients (4 %) didn't have headache.

Table 8: Clinical Profile of Convulsions

CONVULSIONS	FREQUENCY	%
NO	33	66.0
YES	17	34.0
TOTAL	50	100.0

Graph 5: Distribution of Convulsions

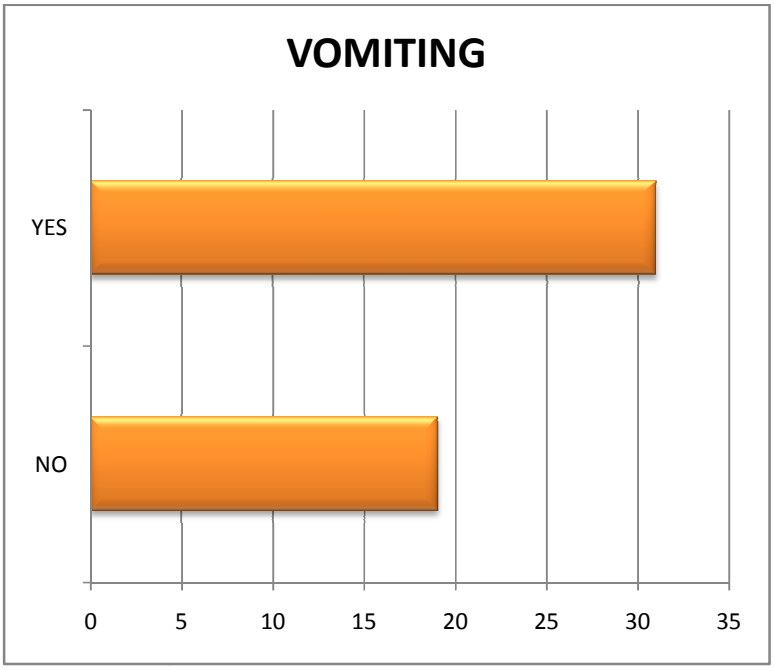


Among the 50 patients , 33 patients (66 %) didn't have convulsions ,and the remaining 17 patients (34 %) had convulsions

Table 9: Clinical Profile of Vomiting

VOMITING	FREQUENCY	%
NO	19	38.0
YES	31	62.00
TOTAL	50	100.0

Graph 6: Clinical Profile of Vomiting

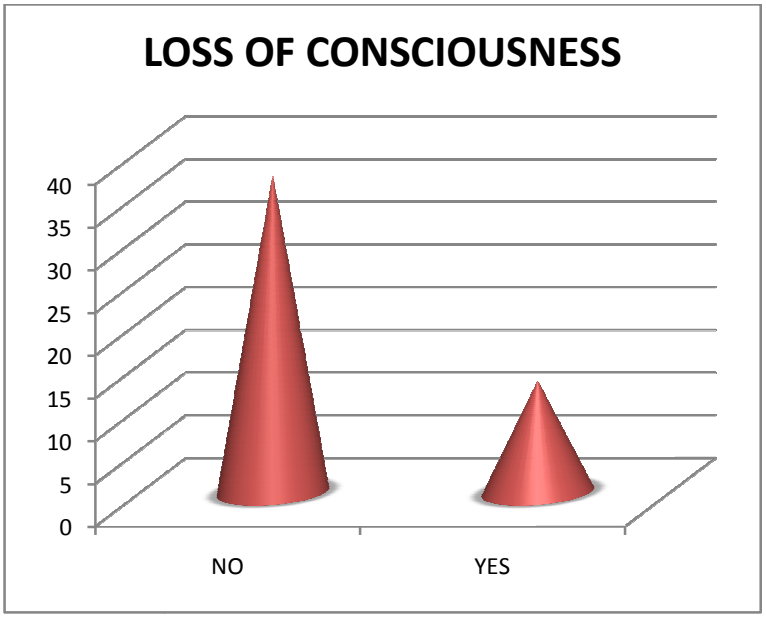


In our study, 31 patients (62 %) of CVT had vomiting and 19 patients(38%) did not have vomiting.

Table 10: Clinical Profile of Loss of Consciousness

LOC	FREQUENCY	%
NO	37	74.0
YES	13	26.0
TOTAL	50	100.0

Graph 7: Clinical Profile of Loss of Consciousness

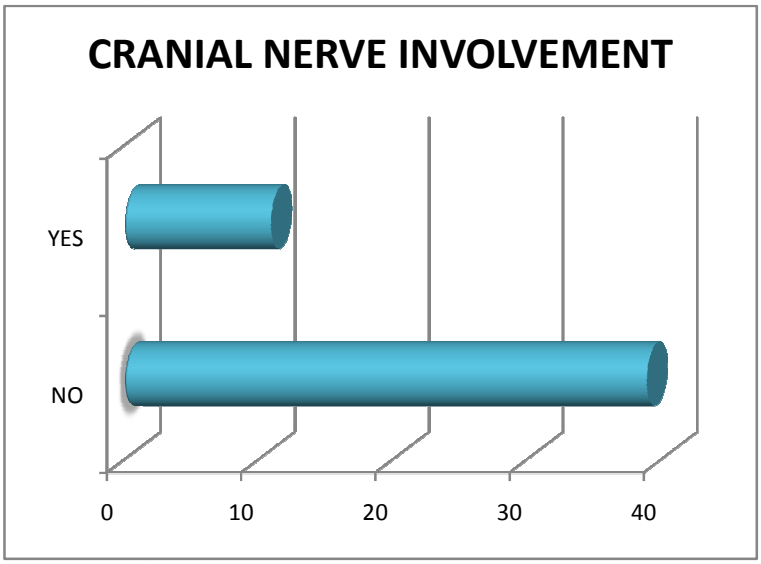


The patients that presented with loss of consciousness in our study are 13 (26 %) , and the remaining 37 patients (74) did not have loss of consciousness .

Table 11: Clinical Profile of Cranial Nerve involvement

CRANIAL NERVE	FREQUENCY	%
NO	39	78.0
YES	11	22.0
TOTAL	50	100.0

Graph 8: Graph Showing Cranial Nerve involvement

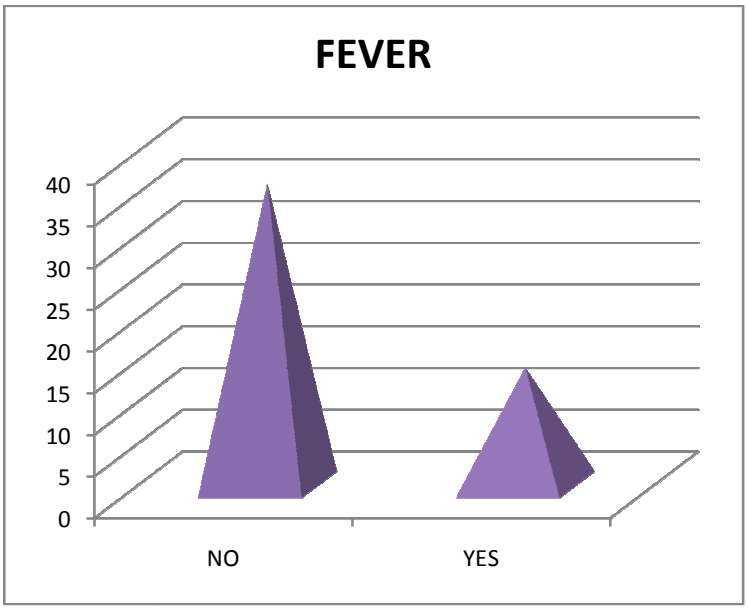


Among the 50 patients , 11 patients (22%) had cranial nerve involvement , and the remaining 39 (78%) had no cranial nerve involvement .

Table 12: Profile of Fever

FEVER	FREQUENCY	%
NO	36	72.00
YES	14	28.00
TOTAL	50	100.0

Graph 9: Profile of Fever

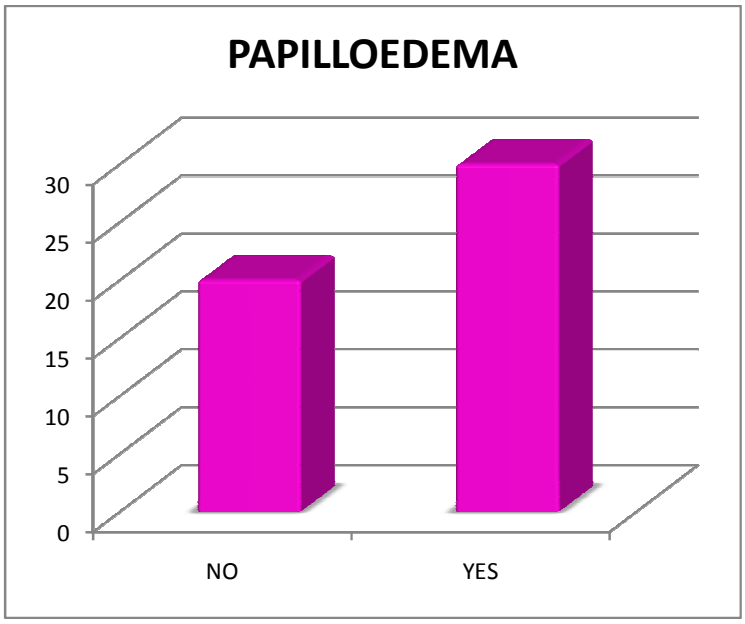


In our study population , 36 patients (72 %) had no fever and the remaining 14 (28 %) patients had fever.

Table 13 : Spectrum of Papilloedema

PAPILLEDEMA	FREQUENCY	%
NO	20	40.0
YES	30	60.00
TOTAL	50	100.0

Graph 10: Spectrum of Papill0edema

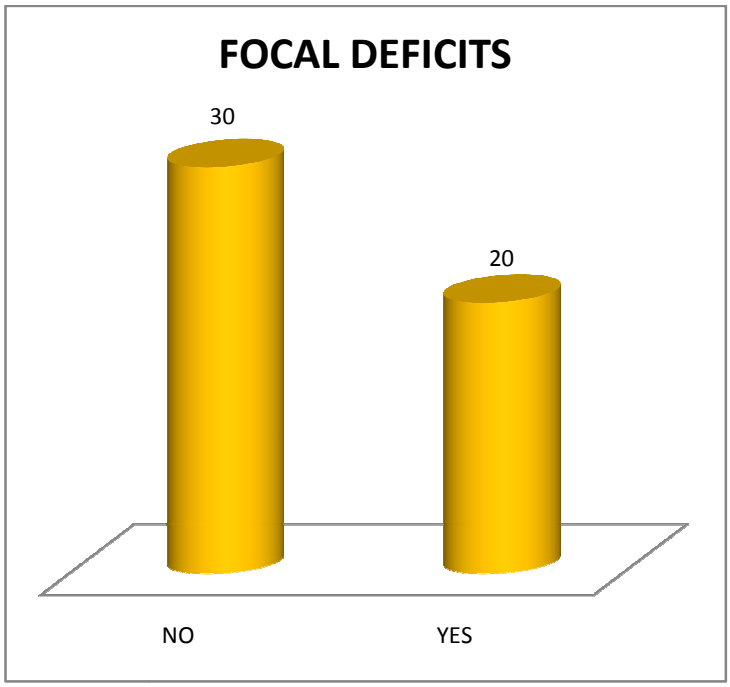


Among the 50 patients , 30 patients (60 %) had papilledema and 20 patients (40%) had no features of papilledema

Table 14: Profile of Focal Deficits

FOCAL DEFICITS	FREQUENCY	%
NO	30	60.0
YES	20	40.0
TOTAL	50	100.0

Graph 11: Spectrum of Focal Deficits

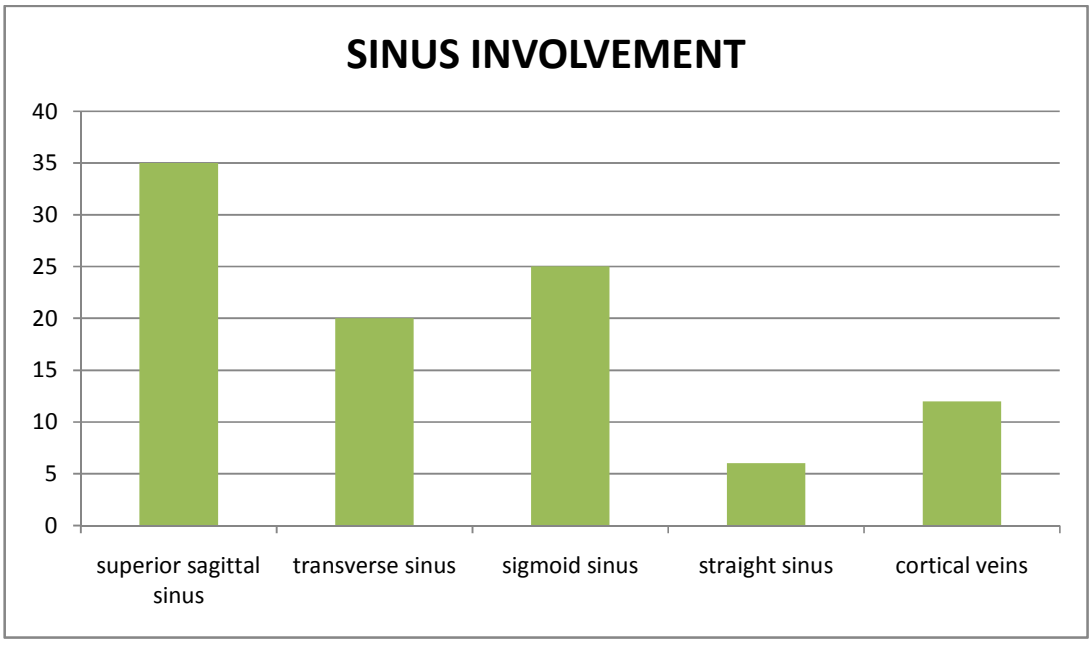


In our study population of 50 patients, 30 (60 %) had no evidence of focal deficits and 20 (40 %) had focal neurological deficits .

Table 15: Sinuses Involved

SINUS INVOLVED	NUMBER	PERCENTAGE
Superior Sagittal Sinus	35	70%
Transverse sinus	20	40%
Sigmoid Sinus	25	50%
Straight Sinus	6	12%
Cortical veins	12	24%

Graph12: Sinuses Involved



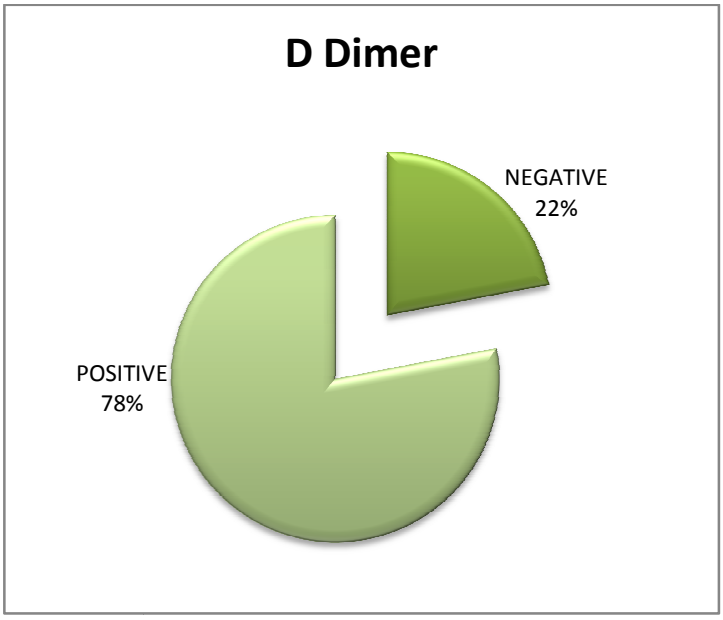
In our study ,most common sinus involved is superior sagittal sinus (70%),followed by sigmoid sinus (50%),transverse sinus (40%),cortical veins (24%) and straight sinus (12%).

INVESTIGATIONS:

Table 16: D Dimer Distribution

D DIMER	FREQUENCY	%
NEGATIVE	11	22.0
POSITIVE	39	78.0
TOTAL	50	100.0

Graph 13: D Dimer Distribution

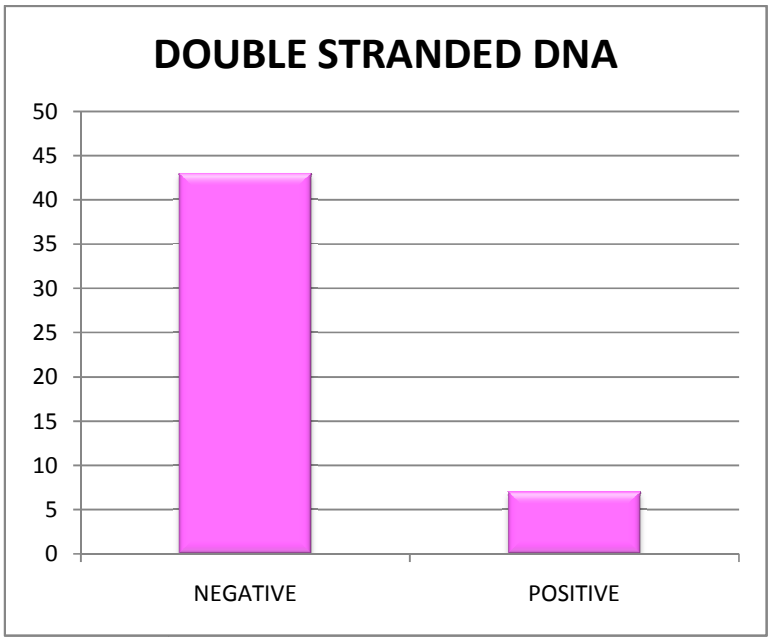


Among the study population of 50 patients with CVT , 39 (78%) had positive D DIMER value which is above 500 ng / ml .The remaining 11 (22%) patients had negative D DIMER values .

Table 17: Spectrum Of Double Stranded DNA

ds DNA	FREQUENCY	%
NEGATIVE	43	86.0
POSITIVE	7	14.0
TOTAL	50	100.0

Graph 14: Distribution of ds DNA

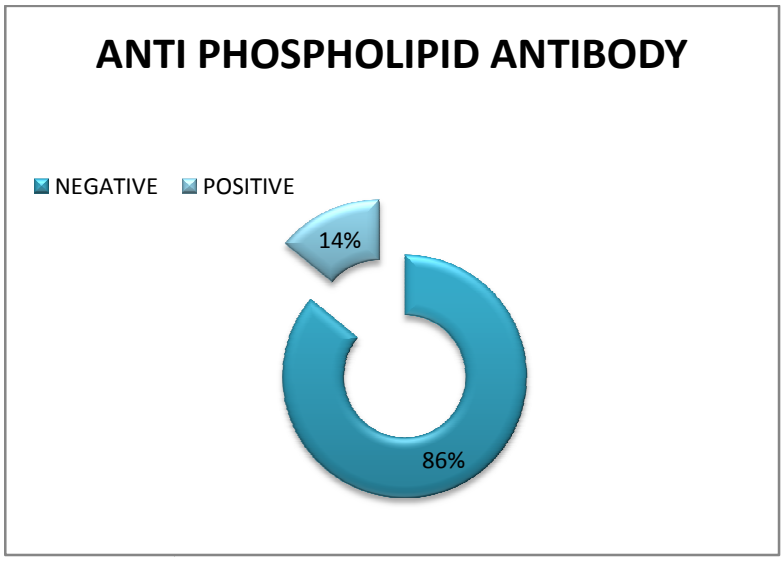


43 patients (86 %) in the study population ,had negative ds DNA , and 7 patients (14 %) had positive ds DNA .

TABLE 18: Spectrum of APLA

APLA	FREQUENCY	%
NEGATIVE	43	86.0
POSITIVE	7	14.0
TOTAL	50	100.0

Graph 15: Spectrum of APLA

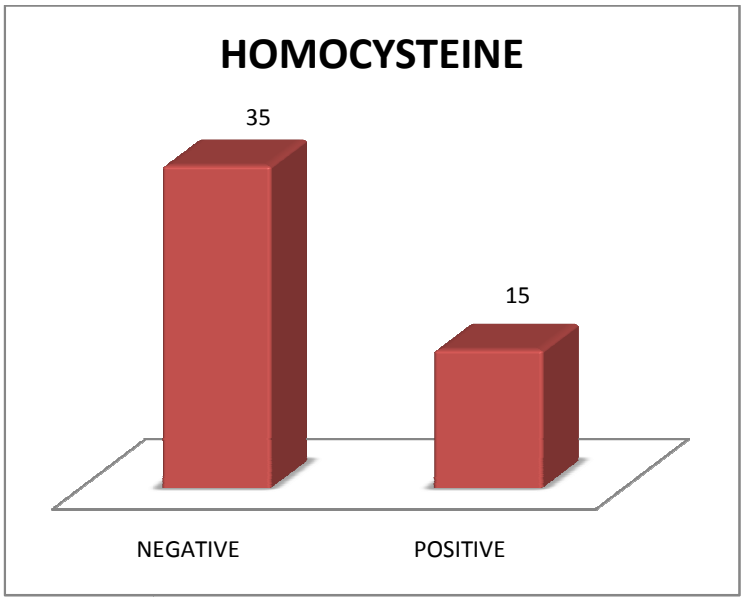


APLA syndrome was positive in 7 (14 %) out of 50 patient. Out of these patients had associated SLE .

TABLE 19: Hyperhomocysteinemia in CVT

HOMOCYSTEINE	FREQUENCY	%
NEGATIVE	35	70.0
POSITIVE	15	30.0
TOTAL	50	100.0

Graph 16: Hyperhomocysteinemia in CVT

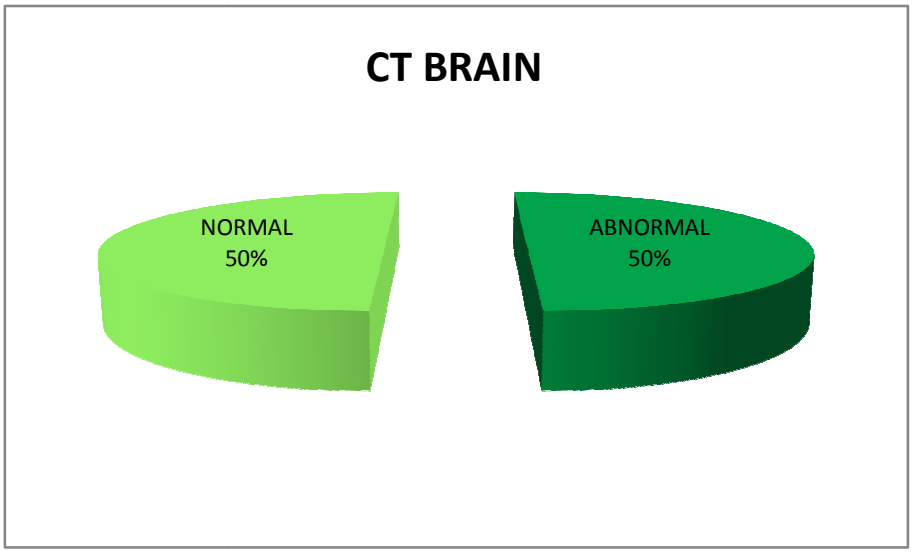


Out of 50 patients , in whom homocysteine were tested, 15 patients (30 %) were found to have elevated homocysteine levels .

Table 20: Neuro Imaging Studies – CT Brain

CT BRAIN	FREQUENCY	%
ABNORMAL	25	50.0
NORMAL	25	50.0
TOTAL	50	100.0

Graph 17: CT Brain Abnormality

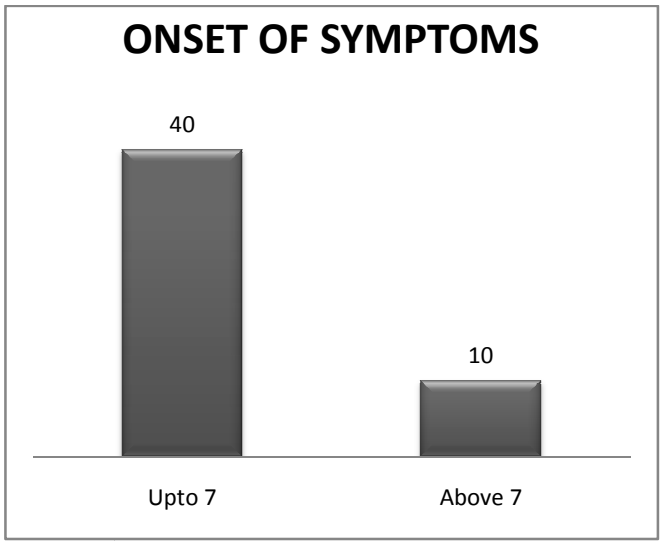


Among the 50 population studied, 25 patients had normal CT Brain and 25 patients had abnormal CT Brain findings such as cord sign, empty delta sign and features of hemorrhagic infarct.

Table 21 : Onset Range

ONSET	FREQUENCY	%
UPTO 7 DAYS	40	80.0
ABOVE 7 DAYS	10	20.0
TOTAL	50	100.0

Graph 18: Onset of Symptoms

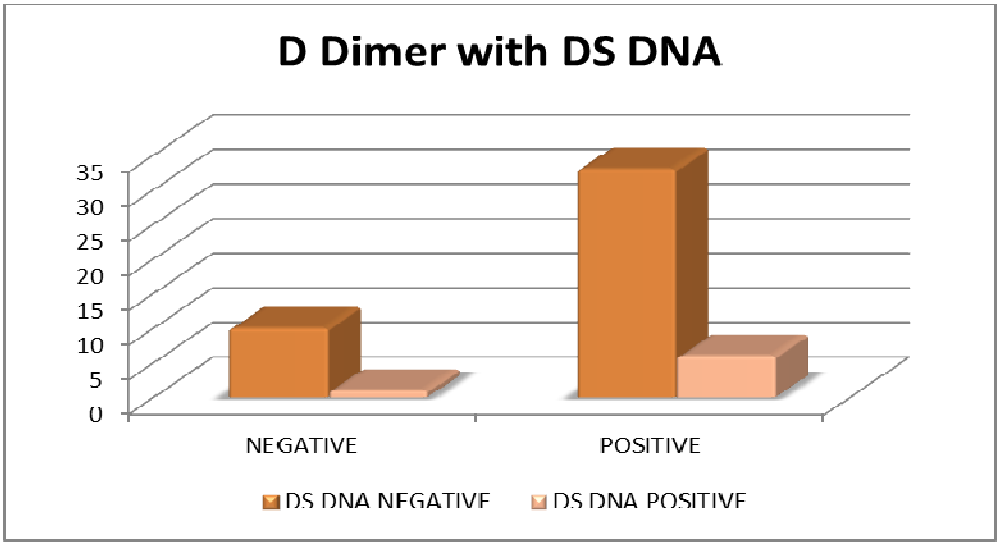


Out of 50 patients , 40 patients (80 %) of the study population , had an early onset of symptoms within a period of 7 day.

Table 22: Correlation of D Dimer and ds DNA

			D DIMER		Total	
			NEGATIVE	POSITIVE		
ds DNA	NEGATIVE	Count	10	33	43	P Value
		% within D DIMER	90.9%	84.6%	86.0%	
	POSITIVE	Count	1	6	7	0.595
		% within D DIMER	9.1%	15.4%	14.0%	
Total		Count	11	39	50	
		% within D DIMER	100.0%	100.0%	100.0%	

Graph 19: Correlation of D Dimer and ds DNA

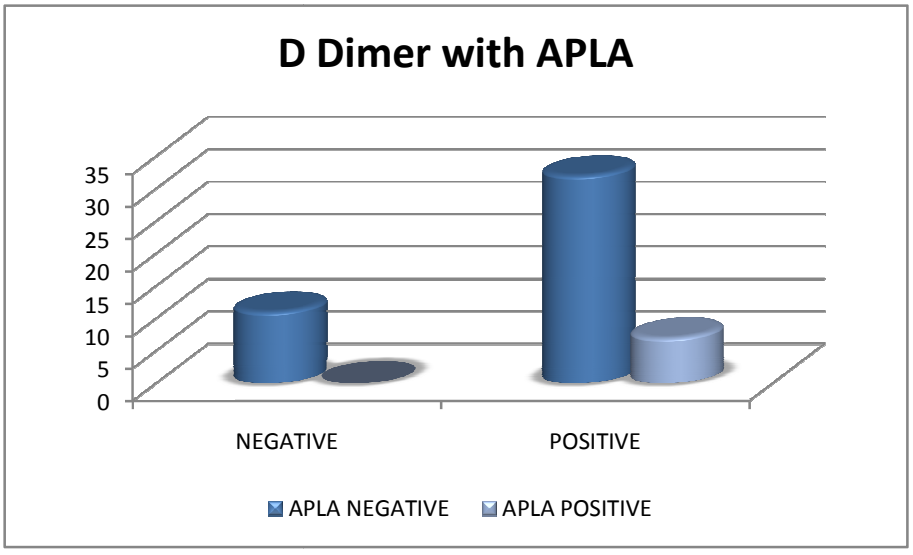


Out of the 7 dS DNA positive cases, 6 cases are found to have D DIMER positive . Out of the 43 negative ds DNA Patients 33 have D Dimer positivity and 10 D Dimer negativity. There is no significant positive correlation with ds DNA and D Dimer in this study.

Table 23: Correlation of APLA and D Dimer

			D DIMER		Total	
			NEGATIVE	POSITIVE		
APLA	NEGATIVE	Count	11	32	43	P Value 0.130
		% within D DIMER	100.0%	82.1%	86.0%	
	POSITIVE	Count	0	7	7	
		% within D DIMER	0.0%	17.9%	14.0%	
Total		Count	11	39	50	
		% within D DIMER	100.0%	100.0%	100.0%	

Graph 20: Correlation of APLA and D Dimer

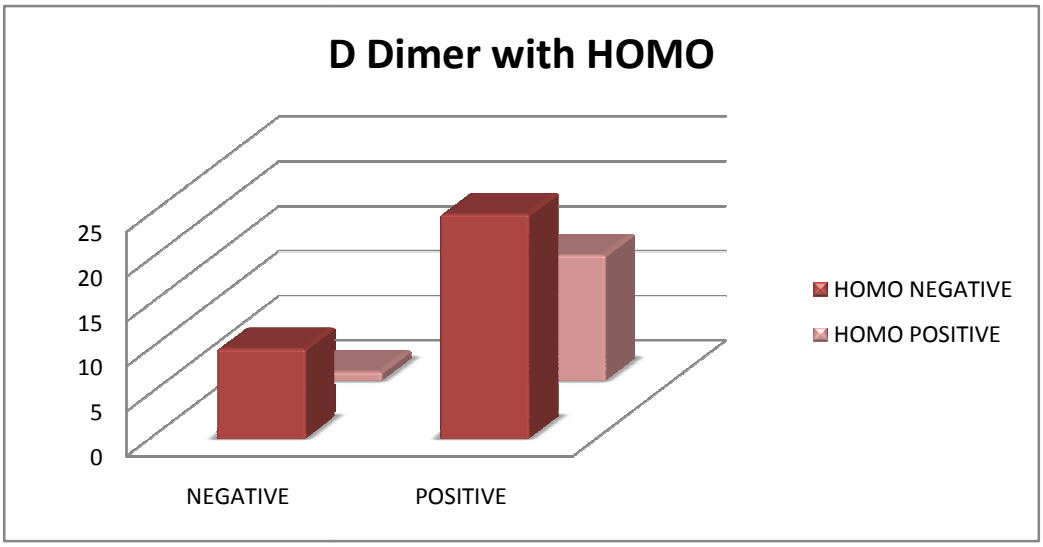


Out of the 7 positive case of APLA , all the 7 positive cases had D Dimer positivity and out of the 43 negative APLA , 32 had D Dimer positive and 11 had D Dimer negative. There is no significant positive correlation with D Dimer and APLA in this study.

Table 24: Correlation of D Dimer and Homocysteine

			D DIMER		Total	
			NEGATIVE	POSITIVE		
HOMO	NEGATIVE	Count	10	25	35	P Value 0.087
		% within D DIMER	90.9%	64.1%	70.0%	
	POSITIVE	Count	1	14	15	
		% within D DIMER	9.1%	35.9%	30.0%	
Total		Count	11	39	50	
		% within D DIMER	100.0%	100.0%	100.0%	

Graph 21: Correlation of D Dimer and Homocysteine

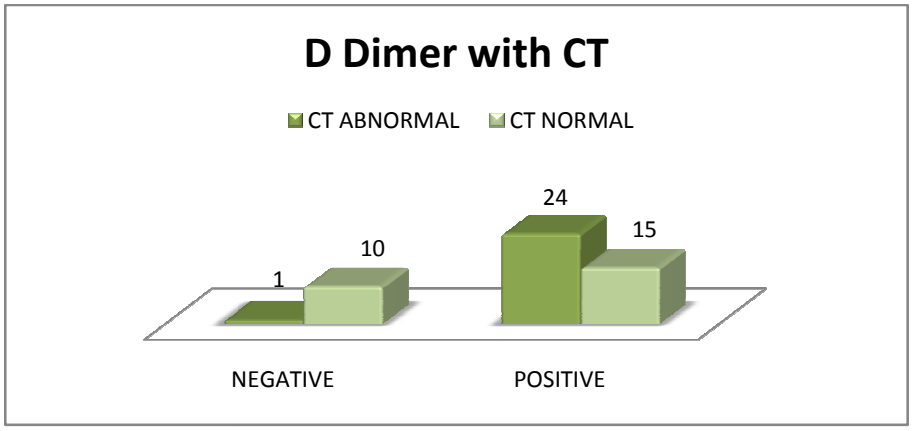


In this study , 15 patients have elevated homocysteine levels. Out of these 14 had D Dimer positive. Out of the 35 negative cases 25 patients had D Dimer positive. There is no significant positive correlation between D Dimer and homocysteine in this study.

Table 25: Correlation of D Dimer With CT Brain

			D DIMER		Total	
			NEGATIVE	POSITIVE		
CT	ABNORMAL	Count	1	24	25	P Value 0.002 HIGHLY SIGNIFICANT
		% within D DIMER	9.1%	61.5%	50.0%	
	NORMAL	Count	10	15	25	
		% within D DIMER	90.9%	38.5%	50.0%	
Total		Count	11	39	50	
		% within D DIMER	100.0%	100.0%	100.0%	

Graph 22: Correlation of D Dimer With CT Brain

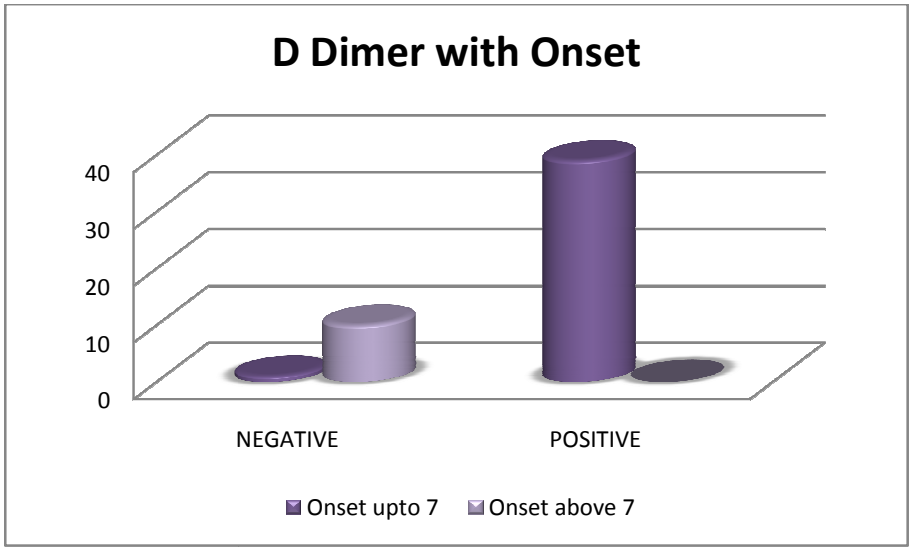


The D Dimer and CT brain has a strong positive correlation in our study. in our study , there is positive findings in 50 % of the study group. In the 25 patients , out of the 25 negative CT patients ,24 patients had positive D Dimer .This implies that eventhough CT may be normal , D Dimer is elevated in majority of population .So D Dimer can be used as an initial diagnostic bio marker in diagnosing CVT.

Table 26: Correlation of D Dimer and Onset of Symptoms

			D DIMER		Total	
			NEGATIVE	POSITIVE		
ONSET RANGE	Upto 7 days	Count	1	39	40	P Value 0.000 HIGHLY SIGNIFICANT
		% within D DIMER	9.1%	100.0%	80.0%	
	Above 7 days	Count	10	0	10	
		% within D DIMER	90.9%	0.0%	20.0%	
Total		Count	11	39	50	
		% within D DIMER	100.0%	100.0%	100.0%	

Graph 23: Correlation of D Dimer and Onset of Symptoms

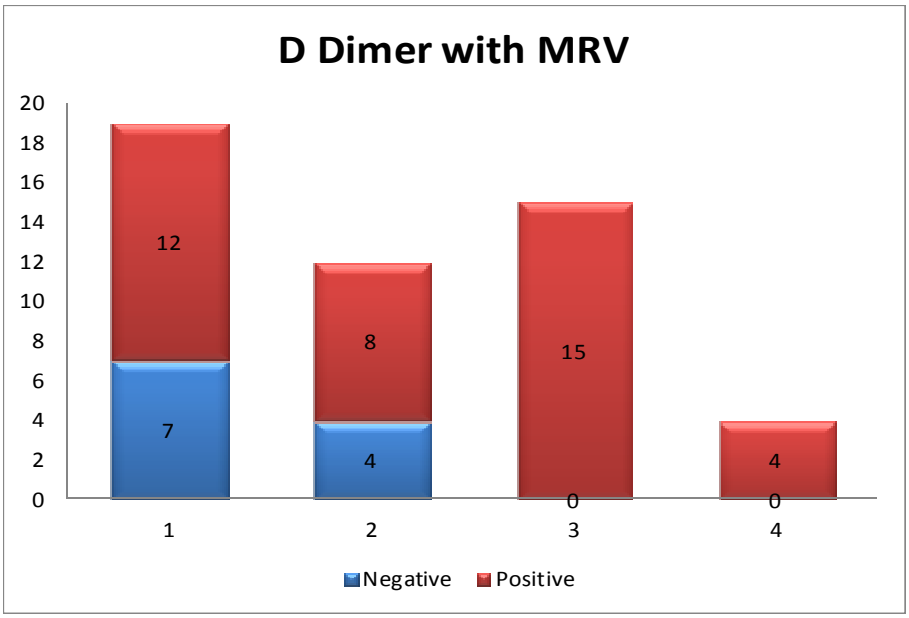


The D Dimer was positive in patients who presented early .Out of the 40 D Dimer positive patients , 39 patients presented to us within 7 days . There is a significant positive correlation between between D Dimer and onset of symptoms in our study. So D Dimer can be used as an diagnostic marker in CVT.

Table 27 :CORRELATION OF D DIMER WITH MRI/MRV :

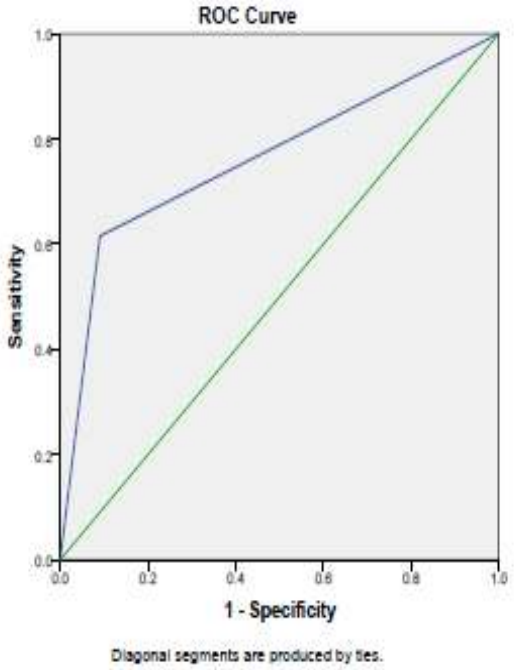
			D DIMER		TOTAL	
			NEGATIVE	POSITIVE		
MRV	No of Sinuses involved	1	7	12	19	P VALUE - 0.034 HIGHLY SIGNIFICANT
		2	4	8	12	
		3	0	15	15	
		4	0	4	4	
TOTAL			11	39	50	

Graph 24: Correlation Between MRV and D Dimer



In this the correlation between MRV and D DIMER is highly significant .if there is a single sinus involvement the positivity of d dimer is less. When the number of sinus involvement is more , the positivity of d dimer is high.since d dimer is positive in most of the sinus involvement, it can be used as an initial diagnostic bio marker in CVT .

AREA UNDER THE CURVE – ROC CURVE



Coordinates of the Curve

Test Result Variable(s): CT

Positive if Greater Than or Equal To[a]	Sensitivity	1 - Specificity
-1.00	1.000	1.000
.50	.615	.091
2.00	.000	.000

The values in the ROC curve indicates that there is a positive correlation between the variables mentioned as shown in the table and curve above.

DISCUSSION

This section contains the comparison of the results of this study with various studies conducted earlier.

TABLE 28: Sex distribution compared to other studies

STUDIES	MALE : FEMALE
Present study	1:1.3
Srinivasan et al	1: 1.04
Daif et al	1:1.3
Agarwal DS et al	1:1.38
Mehta SR	1:1.4

The ratio of the male and female population in this study was 1:1.3 and this closely correlated with the ratio obtained in the study carried out by Daif , where the ratio was 1:1.3.Similar observations are observed in the studies conducted by Agarwal et al and Mehta et al .

TABLE 29: Age distribution compared to other studies

Study	Age
Present study	34.82
Tarek gounda et al	36.2
M.ghaffarpour et al	31.2
Isabelle et al	36.2
Khealani et al	35.4
Tharaknath et al	22
Nagaraja et al	32.3

The mean age in this study is 34.8 .Previous studies conducted by Tarek, Ghaffarpour, Isabelle, Khealani, Nagaraja et al are 36.2, 31.2, 36.2, 35.4 and 32.3 respectively . The study conducted by Tharaknath et al showed a mean age distribution of 22. By this we can conclude that CVT mainly occurs in younger population and mostly in their early 30 ‘s.

CLINICAL PROFILE

Table 30: Comparing Headache With Other Studies

HEADACHE	PERCENTAGE (%)
Present study	96
Biousse et al	82
Katrak et al	73
Neki S et al	85.5
STROLZ et al	73.4
Mehta SR et al	77.8

The fact that CVT has a varied presentation is depicted in our study also. In this study the most common presenting symptom was headache which was observed in 96 % of the study group. This was compared with the study conducted by Biousse et al with the presence of headache in 82 % and by katrak et al with 73 %. NEKI S , strolz E , and Mehta et al demonstrated the incidence of headache around 85.8,73.4 and 77.8 % respectively. This explains that headache is the most common manifestation in CVT. The D Dimer was positive in most of the patients with headache. The patients with negative D Dimer values had only features of isolated headache and presented with a late presentation.

Table 31: Comparing Seizures With Other Studies

STUDIES	PERCENTAGE
Present study	34%
Nagaraja et al	56%
Biousse et al	39%
Katrak et al	58%
Strolz E et al	39.2%

Seizures was observed in 34 % of our study population. The study conducted by Nagaraja et al and katrak et al showed the incidence of seizures as 56 % and 58% respectively. Biousse et al showed an incidence of around 39 % which closely correlates with our study. A study conducted by strolz et al demonstrated the occurrence of seizures in 39.2 % .

Table 32: Comparing Sensorium With Other Studies

STUDIES	PERCENTAGE
Present study	26%
Nagaraja et al	50%
Katrak et al	42%
Biousse et al	52%

Altered sensorium was found in 26 % of the patients in our study of 50 patients. Nagaraja et al reported an incidence of altered sensorium of 50% ,katrak et al of 42 % and Biouse et al of around 52 %.Compared to other studies , the incidence of seizures is low in our study.

Table 33: Comparing Papilloedema with Other Studies

STUDIES	PERCENTAGE
Present study	60%
Biousse et al	51%
Katrak et al	55%
Tharakanth et al	47%
Kumar s et al	32%
Neki et al	80%
Strolz et al	30%

In our study, a significant proportion of patients had evidence of papilloedema at the initial presentation of around 60 %.Our observations are related to the studies conducted by katrak et al of 55%.The other studies conducted by Biousse, Tharakanth showed an incidence of 51 and

47 %.similar observations were noted in the studies conducted by kumar s et al ,Neki et al and strolz et l with 32 % , 80 5 and 30 % respectively .

Table 34: Comparing Focal Deficits With Other Studies

Studies	Percentage (%)
Present study	40%
Daif et al	27%
Strolz et al	56.9%
Kumar s et al	66%

The focal neurological deficits were noted in 40 % of our study population. Daif et al reported an incidence of 27 % ,whereas strolz et al and kumar s et al showed an incidence of around 56.9 % and 66 % respectively

Table 35: Comparing Cranial Nerve Palsy With Other Studies

Present study	Daif et al
22	14%

The cranial nerve involvement is around 22 % in our study and in a study conducted by daif et al is aroud 14 %.

Table 36: Comparing Sinus Involvement In CVT

	Present study	Christo et al	Wysokinska et al	Breteau et al	Strolz et al
T S	40	73	68	69%	38 %
Sigmoid sinus	50	-	-	-	-
SSS	70	53	55	67%	72.2

In our study the commonest sinus involved was the superior saggital sinus (70%) followed by the sigmoid sinus (50%) , then by the transverse sinus (40%).Most of the patients in our study group had involvement of more than 1 cortical venous sinuses. The studies conducted by Christo et al demonstrated the presence of transverse sinus(73%) and superior sagittal sinus (53%).Similar findings were reported in the studies conducted by Wysokinska et al .The study by breteau et al demonstrated the prevalence of transverse sinus involvement (69%) and superior sagittal sinus (67%) .the study conducted by strolz et al has the same rate of involvement of sinuses compared to our study. The involvement of more than 1 dural sinus has more D Dimer positive value compared to a single sinus involvement. This explains that D Dimer values depends upon the extent of thrombus involvement.

CT BRAIN ;

The commonest and the initial modality of radiological tool used in our study is the CT Brain. Out of the 50 patients included in our study, CT was normal in 50 % of the patients.The remaining 50 % of the patients showed features of hemorrhagic infarct , delta sign , cord sign.

Table 37: Comparing CT Findings With Other Studies

	Present study	**Nagaraja et al**	**Dixit et al**
Hemorrhagic infarct	39	40.9	48.4
Non hemorrhagic infarct	42	51.6	32.3
Empty delta sign	17	32	32

The most common finding in the present study is non hemorrhagic infarct (42%). Similar observations are noted in the studies conducted by nagaraja et al and dixit et al .

Table 38: Comparing APLA With CVT

Studies	Percentage (%)
Present study	14
Katrak et al	38.5
Christopher et al	22.6
Chandrashekhara et al	14.2
Carhuapoma et al	8

In our study , 14 % of patients had a positive profile of APLA , which is in close relation to the study conducted by chandrashekara. Other studies conducted by katrak ,Christopher and carhuapoma showed positivity of around 38.5 ,22.6 and 8 % respectively .

Table 39: Comparing D Dimer and CVT

Studies	Percentage (%)
Present study	78
Misra et al	77
Wildberger et al	100
Lalive et al	83
Tarek et al	85.7
Isabellee et al	90

In our study , D Dimer was positive in 78 % of the patients. Out of 50patientss 39 had positive D Dimer values. The study conducted by wildberger showed a positivity of 100 %.Misra et al conducted a study on D Dimer ,the results of which are similar to our study. Isabelle et al , lalive te al tarek et al and m ghaffarpour et al showed the positivity of 90 ,83 , 85.7 and 95.3 % respectively. In our study there is a significant correlation between D Dimer and the findings in MRV .

Table 40: Comparing Hyperhomocystinemia In Cvt

Studies	Percentage (%)
Present study	30
Cantu et al	37.8
Martinelli et al	27.27

In our study hyperhomocysteinemia was present in 30 % of the study population. This in correlation with the studies conducted by cantu et al and martinelli et al Hyper homocystenemia is an important cause of hpercoagulability and it increase the risk of CVT 4 fold. Therefore it is important to assay Homocysteine levels in the initial prothrombotic workup for venous thrombosis.

ETIOLOGY IN CVT ;

In our study the etiology of CVT is varied. Out of the 50 patients the etiology of 14 patients could not be found out. OCP is the cause in 4 patients . Homocysteine was positive in 15 patients . Out of the rare cause protein C & S deficiency has been documented .Dehydration causes CVT in 2 patients. HIV, Orbital cellulitis, varicella, meningitis each contributes to 1 case. Mastoiditis cause CVT in 3 patients. Connective tissue disorders like SLE contribute to 5 cases. Tharakannth et al studied 15 out of 49 cases having a predisposing prothrombotic states in CVT. Majority of cases document a hypercoagulable state, a full prothrombotic work up is essential in diagnosing the cause of CVT.

EARLY ONSET OF CVT AND D DIMER :

In our study there is a strong relationship between the D Dimer values and the duration of presentation of the patient .The D Dimer is positive in 39 patients out of the 50 patients included in our study population. All the D Dimer positive patients are presented to us within 7 days of symptoms onset .Negative D Dimer in CVT patients is attributed to a decrease D Dimer value after a certain period of time.This implies that D Dimer can be used as a diagnostic biomarker if the patients present early. In our study there is a positive correlation between the early onset of CVT and the D Dimer levels.

D DIMER AND MRV :

D Dimer has a strong relationship with the MRV findings . in our study, all the D Dimer positive patients had features of CVT in MRI. The association between D Dimer and MRI is statistically significant in our study. This study implies that though MRI / MRV is the diagnostic modality for CVT, the presence of D Dimer positivity can be taken as positive sign of CVT .Negative D Dimer assay excludes the presence of thrombosis with a high certainity and MRI / MRV should be preferably used only in patients with positive D Dimer test and highly suspected cases.

SUMMARY

This study was undertaken to study the usefulness of D Dimer as an initial diagnostic bio marker in cerebral venous thrombosis. A total of 50 patients were studied over a period of one year .The salient features in our study are highlighted below:

1. The mean age of presentation in our study is 34.82 .
2. There is a slight female preponderance in our study .The sex ratio was 1.3 :1.
3. The most common presenting feature is headache (96%) though non specific, followed by seizures (34%),altered sensorium (26%).The most common sign is papilledema (60%) followed by focal deficits (40%)
4. Isolated headache has a negative D Dimer value
5. The commonest sinus involved is superior sagittal sinus (70%),followed by sigmoid and transverse sinus.Most of the patients had more than one sinus involvement.
6. CT Brain was normal in 50 % of the patients.
7. Inherited Thrombophilias contribute to around 23 % of patients with CVT. The most common in our study is Hyperhomocystenemia.
8. No cause is identified in 14 patients.

9. D Dimer was positive in 78 % of the patients with CVT.D Dimer has a high sensitivity when presented early
10. D Dimer and MRV has a significant correlation. So in early diagnosis of CVT , D Dimer can be used as a diagnostic tool.MRI / MRV being a superior modality than CT, should be used in patients suspected of having CVT.

CONCLUSION

- Positive D Dimer test with high sensitivity and negative predictive value may be a useful diagnostic modality in suspected CVT patients
- Normal value of D Dimer makes the diagnosis of CVT unlikely
- MRI should preferably be done only in patients with positive D Dimer test and highly suspected cases.
- Further studies are needed to highlight the importance of D Dimer in CVT.

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PROFORMA

Name : IP NO :

Age : DOA:

Sex : DOD /E :

Occupation : Education :

Address :

Socioeconomic status :

Clinical diagnosis :

Present complaints :

1. Headache

2. Seizures

3. Vomiting

4. Altered sensorium

5. Weaknes of limbs

6. Visual disturbances

7. Fever

8. Sensory symptoms

9. Speech difficulties

SIGNS :

1. Consciousness
2. Raised ICT
3. Cranial nerve palsies
4. Focal deficits
5. Sensory deficits

PAST HISTORY : DM/ HT/ TB/ CAHD / SEIZURES/ OCP

Intake , venous thrombosis

FAMILY HISTORY : Similar illness

GENERAL EXAMINATION

1. Anemia
2. Jaundice
3. Clubbing
4. Pedal edema
5. Lymphadenopathy
6. Signs of dehydration
7. Purpura / rash

VITAL SIGNS :

1. Pulse
2. Blood pressure
3. Respiratory rate
4. Temperature

NEUROLOGICAL EXAMINATION :

1. Glassgow coma scale
2. Mini mental status examination
3. Higher mental functions
4. Cranial nerves with fundus examination
5. Motor power
6. Tone
7. Reflexes – superficial , deep
8. Plantar response
9. Sensory system
10. Cerebellum
11. Speech
12. Gait
13. Autonomic system
14. Meningeal signs
15. Spine and cranium

16. Other system examination

CVS , RS,GIT,ENT,OPHTHALMOLOGY

INVESTIGATIONS :

1. Complete blood count
2. Blood sugar
3. Renal function test
4. Liver function test
5. Peripheral smear
6. Urine routine
7. Coagulation profile
8. ECG
9. X-Ray chest
10. CT Brain
11. MRI / MRV Brain
12. ANA
13. APLA
14. Serum Homocysteine
15. D DIMER

CONSENT FORM

Mr/Mrs/Ms…….

S/W/D of……(legal guardian) is being asked to be a participant in the research study titled "" A Study on Evaluation of plasma D-DIMER as an initial Diagnostic Biomarker in Cerebral Venous Thrombosis "" in CMC Hospital, Coimbatore, He /she satisfies eligibility as per the inclusion criteria. You (legal guardian) can ask any question you may have before agreeing to participate.

Research Being Done

A STUDY ON Evaluation of plasma D-DIMER as an initial Diagnostic Biomarker in Cerebral Venous Thrombosis.

Purpose of Research

Aim of the study is to evaluate the role of plasma D-DIMER as an initial Diagnostic Biomarker in Cerebral Venous Thrombosis.

Procedures involved

It includes details like age, sex and about history of the problem and associated risk factors as well as clinical examination.

Investigations includes complete hemogram, renal function tests(blood urea, serum creatinine), blood sugar, lipid profile ,coagulation profile, MRI- BRAIN .

Decline from Participation

You have the option to decline from participation in the study existing protocol for your condition.

Privacy and Confidentiality

Privacy of individuals will be respected and any information about you or provided by you during the study will be kept strictly confidential.

Authorization to publish Results

Results of the study may be published for scientific purposes and/or presented to scientific groups, however you will not be identified.

Statement of Consent

I volunteer and consent to participate in this study. I have read the consent or it has been read to me. The study has been fully explained to me, and I may ask questions at any time.

---------- ----------

Signature /Left thumb impression (volunteer) Date

---------- ----------

Signature of witness Date

ஒப்புதல் படிவம்

பெயர் :

பாலினம் : வயது :

முகவரி :

அரசு கோவை மருத்துவக் கல்லூரியில் பொது மருத்துவத் துறையில் பட்ட பயிலும் மாணவி அவர்கள் மேற்கொள்ளும் **"மூளையின் இரத்தக்குழாய் உறையும் தன்மையை (CVT) அளவிட டி-டைமரை முதல் நிலை கருவியாக பயன்படுத்தலாமா?"** குறித்த ஆய்வில் செய்முறை மற்றும் அனைத்து விவரங்களையும் கேட்டுக் கொண்டு எனது சந்தேகங்களை தெளிவுப்படுத்திக் கொண்டேன் என்பதை தெரிவித்துக் கொள்கிறேன்.

நான் இந்த ஆய்வில் முழு சம்மதத்துடனும், சுய சிந்தனையுடனும் கலந்து கொள்ள சம்மதிக்கிறேன்.

இந்த ஆய்வில் என்னுடைய அனைத்து விபரங்கள் பாதுகாக்கப்படுவதுடன் இதன் முடிவுகள் ஆய்விதழில் வெளியிடப்படுவதில் ஆட்சேபனை இல்லை என்பதை தெரிவித்துக் கொள்கிறேன். எந்த நேரத்திலும் இந்த ஆய்விலிருந்து நான் விலகிக் கொள்ள எனக்கு உரிமை உண்டு என்பதையும் அறிவேன்.

இடம் : கையொப்பம் / ரேகை

நாள் :

KEY TO MASTER CHART

OCCU	–	OCCUPATION
HA	–	HEADACHE
CON	–	CONVULSION
VOM	-	VOMITING
LOC	–	LOSS OF CONSCIOUSNESS
CN	–	CRANIAL NERVE INVOLVEMENT
PAP	–	PAPILLEDEMA
FD	-	FOCAL DEFICITS
DS DNA	–	DOUBLE STRANDED DNA
APLA	-	ANTI PHOSPHOLIPID ANTIBODY
HOMO	–	HOMOCYSTEINE
CT	–	COMPUTED TOMOGRAPHY
MRV	-	MAGNETIC RESONANCE VENOGRAPHY
HW	–	HOUSEWIFE
C	-	COOLY

STU	–	STUDENT
ENG	–	ENGINEER
LOR DRI	–	LORRY DRIVER
SSS	-	SUPERIOR SAGITTAL SINUS
SS	-	SIGMOID SINUS
TS	–	TRANSVERSE SINUS
STS	–	STRAIGHT SINUS
F	-	FEMALE
M	-	MALE
CTD	–	CONNECTIVE TISSUE DISORDER
OCP	–	ORAL CONTRACEPTIVE
CV	–	CORTICAL VEIN

MASTER CHART

S.NO	NAME	AGE	SEX	IP NO	OCCU	HA	CON	VOM	LOC	CN	FEVER	PAP	FD	ONSET	D DIMER	DS DNA	APLA	HOMO	CT	MRV	ETIOLOGY
1	BHUVANA	26	F	21654	HW	YES	NO	YES	NO	NO	NO	YES	NO	2	POSITIVE	NEGATIVE	NEGATIVE	POSITIVE	NORMAL	SSS,SS	HOMO
2	VEERARAGAVAN	46	M	12685	C	YES	YES	YES	YES	NO	NO	YES	YES	1	POSITIVE	NEGATIVE	NEGATIVE	POSITIVE	ABNORMAL	SSS,SS,TS	HOMO
3	FRANCIS	30	M	23421	BUS	YES	NO	YES	NO	YES	NO	NO	YES	2	POSITIVE	NEGATIVE	POSITIVE	POSITIVE	ABNORMAL	SSS,TS,CV	APLA
4	RANGAN	45	M	32431	C	YES	YES	YES	NO	YES	YES	YES	YES	2	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	ABNORMAL	SSS	VARICELLA
5	AJITH	19	M	26542	STU	YES	NO	NO	NO	NO	NO	YES	NO	2	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	ABNORMAL	TS,SS,CV	TRAUMA
6	SARASWATHI	28	F	23487	HW	YES	NO	YES	NO	NO	NO	NO	NO	8	NEGATIVE	POSITIVE	NEGATIVE	NEGATIVE	NORMAL	SS	SLE
7	RAMU	28	M	29654	C	YES	NO	NO	NO	NO	YES	YES	NO	3	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	NORMAL	TS,SS,CV	MASTOID
8	MANJULA	26	F	12876	HW	YES	NO	NO	NO	NO	NO	NO	NO	3	POSITIVE	NEGATIVE	NEGATIVE	POSITIVE	ABNORMAL	SSS,TS,CV	HOMO
9	JANSI	36	F	32143	HW	YES	YES	YES	YES	NO	NO	YES	YES	2	POSITIVE	POSITIVE	NEGATIVE	NEGATIVE	NORMAL	SSS,SS	CTD
10	DINESH	31	M	23135	Bank	YES	NO	NO	NO	NO	NO	NO	NO	8	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NORMAL	TS,SS	MASTOID
11	PRIYA	26	F	27432	CLERK	YES	NO	YES	NO	NO	NO	YES	NO	2	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	NORMAL	SSS	OCP
12	MATHI	62	M	31242	ENG	NO	NO	NO	NO	YES	NO	YES	YES	8	NEGATIVE	NEGATIVE	NEGATIVE	POSITIVE	NORMAL	SSS	HOMO
13	SANGEETHA	38	F	27432	HW	YES	NO	YES	NO	NO	NO	NO	NO	2	POSITIVE	NEGATIVE	NEGATIVE	POSITIVE	ABNORMAL	TS,SS,CV	HOMO
14	GOWRI	25	F	31743	MANAGE	YES	NO	YES	NO	NO	YES	YES	YES	1	POSITIVE	POSITIVE	POSITIVE	POSITIVE	ABNORMAL	SSS,SS,STS	APLA
15	ARUMUGAM	46	M	21097	C	YES	NO	NO	NO	NO	NO	NO	NO	7	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NORMAL	SSS	-
16	GIRIJA	28	F	21075	HW	YES	YES	YES	YES	NO	NO	YES	YES	1	POSITIVE	POSITIVE	NEGATIVE	NEGATIVE	NORMAL	SSS ,TS,SS	SLE
17	SURYA	14	M	31276	VENDOR	YES	NO	YES	NO	YES	YES	NO	NO	1	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	NORMAL	SSS,TS,CV	ORBITAL CELLULITIS
18	UMA	38	F	39567	HW	YES	NO	NO	NO	NO	NO	NO	NO	2	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	ABNORMAL	SSS	OCP
19	GOPALSAMY	68	M	32178	C	YES	NO	YES	NO	NO	NO	NO	NO	3	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	ABNORMAL	SS	DEHYDRATION
20	RAMYA	31	F	19306	HW	YES	NO	NO	NO	NO	NO	YES	NO	2	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	NORMAL	SSS	OCP
21	BRINDHA	39	F	16209	HW	YES	NO	NO	NO	NO	NO	NO	NO	9	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NORMAL	SSS,CV	-
22	RAJAMMAL	62	F	20419	HW	YES	YES	YES	NO	NO	YES	NO	NO	2	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	NORMAL	SSS,SS	DEHYDRATION
23	PRABHU	29	M	31035	BANK	YES	NO	NO	NO	NO	NO	NO	NO	8	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	ABNORMAL	SSS,TS	-
24	SINGARAM	43	M	21745	LOR DRI	YES	YES	YES	YES	YES	YES	YES	YES	2	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	ABNORMAL	SSS,ST S,SS,TS	HIV
25	SAROJA	36	F	21836	HW	YES	YES	YES	YES	YES	YES	YES	YES	2	POSITIVE	POSITIVE	POSITIVE	POSITIVE	ABNORMAL	SSS,ST S,SS,TS	SLE

26	CHITRA	29	F	21644	TYPIST	YES	NO	YES	NO	NO	NO	NO	NO	2	POSITIVE	NEGATIVE	NEGATIVE	POSITIVE	ABNORMAL	SSS,STS,CV	HOMO
27	GOPAL	37	M	30912	C	YES	YES	YES	NO	NO	NO	YES	NO	2	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	NORMAL	SS,CV	-
28	AKILA	31	F	20198	TEACHE	YES	YES	YES	NO	YES	YES	YES	YES	2	POSITIVE	POSITIVE	POSITIVE	POSITIVE	ABNORMAL	SSS,SS,TS,STS	PROTEIN S
29	MUTHAIYAN	54	M	10286	C	YES	NO	NO	NO	YES	YES	YES	YES	8	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NORMAL	SSS	-
30	GAYATHRI	25	F	10357	HW	YES	NO	YES	NO	NO	NO	YES	YES	2	POSITIVE	POSITIVE	NEGATIVE	NEGATIVE	ABNORMAL	SS,TS,STS,CV	CTD
31	RAVI	32	M	20194	C	YES	YES	YES	YES	NO	YES	YES	YES	2	POSITIVE	NEGATIVE	NEGATIVE	POSITIVE	NORMAL	SS	HOMO
32	ANNAMMA	43	F	38413	HW	YES	NO	NO	NO	NO	YES	NO	NO	8	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NORMAL	TS,STS	-
33	KUMAR	62	M	21964	C	YES	YES	YES	YES	NO	NO	YES	YES	1	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	ABNORMAL	SSS,SS,TS	METASTASIS
34	GEETHA	28	F	19632	STU	YES	NO	NO	NO	NO	NO	YES	NO	1	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE	ABNORMAL	SSS,STS	APLA
35	SOWMIA	26	F	23167	TYPIST	YES	NO	NO	NO	NO	NO	NO	NO	1	POSITIVE	NEGATIVE	NEGATIVE	POSITIVE	ABNORMAL	SS,STS	HOMO
36	BALAJI	34	M	15276	VENDOR	NO	YES	YES	YES	NO	NO	YES	YES	4	POSITIVE	NEGATIVE	NEGATIVE	POSITIVE	ABNORMAL	SSS,TS,CV	HOMO
37	SASI	39	F	31356	HW	YES	NO	NO	NO	NO	NO	NO	NO	10	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NORMAL	SSS	-
38	DEVI	40	F	19524	C	YES	YES	NO	YES	NO	NO	YES	YES	4	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	ABNORMAL	STS,SS	-
39	ELAKIYA	23	F	13334	LAWYER	YES	NO	YES	NO	NO	NO	NO	NO	2	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE	ABNORMAL	SSS	APLA
40	GIRIDAR	46	M	20000	C	YES	YES	YES	YES	YES	YES	YES	YES	3	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	NORMAL	SS	-
41	AMBIKA	43	F	23433	HW	YES	NO	YES	NO	NO	NO	YES	NO	2	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	ABNORMAL	SS,TS,CV	MASTOID
42	MEERA	34	F	10293	HW	YES	NO	NO	NO	NO	NO	YES	YES	2	POSITIVE	NEGATIVE	NEGATIVE	POSITIVE	NORMAL	SSS	HOMO
43	CHINNADURAI	28	M	31232	LOR DRI	YES	YES	YES	YES	YES	YES	YES	NO	1	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	NORMAL	SSS	-
44	KANIMOZHI	26	F	18346	TYPIST	YES	NO	YES	NO	NO	NO	NO	NO	4	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	ABNORMAL	SSS,SS,TS	MENINGITIS
45	SUDHA	34	F	32133	HW	YES	NO	NO	NO	NO	NO	NO	NO	8	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NORMAL	SSS	-
46	JAMES	26	M	12322	C	YES	NO	YES	NO	YES	NO	YES	YES	3	POSITIVE	NEGATIVE	POSITIVE	POSITIVE	ABNORMAL	SSS	PROEIN C ,S
47	LAKSHMI	39	F	23109	HW	YES	YES	YES	YES	NO	NO	YES	NO	2	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	ABNORMAL	SSS,SS,CV	-
48	NARASIMMAN	45	M	10098	COBBLE	YES	NO	NO	NO	NO	NO	NO	NO	8	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NORMAL	SSS	-
49	REKHA	31	F	31795	HW	YES	NO	YES	NO	NO	NO	YES	NO	3	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	NORMAL	SSS	OCP
50	BALU	31	M	18264	C	YES	YES	YES	YES	NO	YES	YES	YES	3	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	NORMAL	SS,TS	-