



**SAINT PAUL'S HOSPITAL MILLENIUM MEDICAL
COLLEGE**

DEPARTMENT OF INTERNAL MEDICINE

**INPATIENT CLINICAL OUTCOME OF ADULT CEREBRAL
VENOUS THROMBOSIS PATIENTS IN SAINT PAUL'S HOSPITAL
MILLENIUM MEDICAL COLLEGE AND ZEWDITU MEMORIAL
HOSPITAL, ADDIS ABABA, ETHIOPIA: 5 YEARS REVIEW**

By: Fana Hagos (MD, internal medicine resident)

A thesis submitted to the department of internal medicine and public health, St. Paul's hospital millennium medical college in partial fulfillment of the requirement for specialty certificate in internal medicine

October 2022, Addis Ababa, Ethiopia



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By: Fana Hagos (MD, internal medicine resident)

Advisors

Dr. Tesfaye (MD, Internist, Neurologist)

Mr. Getachew T. (MSc., MPH)

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ACRONYMS AND ABBREVIATIONS

APS: Anti phospholipid syndrome

CRP: C-Reactive protein

CT scan: Computed tomography scan

CSF: Cerebrospinal fluid

CVT: Cerebral venous thrombosis

GCS: Glasgow coma scale

HMIS

LMWH: Low molecular weight heparin

MRI: Magnetic resonance imaging

MRV: Magnetic resonance venography

mRS: Modified Rankin score

OCP: Oral contraceptive pills

SPHMMC: Saint Paul's hospital millennium medical college

ZMH: Zewditu memorial hospital

ABSTRACT

Background

Cerebral venous thrombosis is a relatively uncommon neurological disorder predominantly affecting women. It has a good outcome in most patients. Few patients may end up with permanent neurological deficits or even die if not managed early. CVT is under reported and not properly studied in our country.

The main objective of this study is to assess the clinical presentation and inpatient outcome of adult patients diagnosed to have cerebral venous thrombosis in SPHMMC and ZMH over the past 5 years.

Method

A cross sectional retrospective chart review was conducted over 3 months from June 2022 up to august 2020 G.C at SPHMMC and ZMH on all patients who were admitted between September 2017 up to September 2021. Outcome was assessed in response to clinical presentation and inpatient outcome. Data was collected through chart review using a structured questionnaire. Collected data was analyzed using SPSS version 20. Frequency was used to summarize descriptive statistics of the data. Tables and figures were used for data presentation.

Result

The median age of patients was 28 years. Majority of the patients (76.3%) were female. The commonest presenting symptom was headache (97.4%) followed by motor weakness (47.4%) and visual impairment (42.1%). Majority of the patients (57.9%) had symptoms lasting less than 2 weeks. About 52.6% of patients were found to be either pregnant or in the peurperium period. All of the studied patients received an anticoagulation medication. The inpatient outcome of the patients was good in general with majority of the patients (71%) having a complete recovery at discharge.

Conclusion

Pregnancy / peurperium was found in more than half of the patients in this study. Attention should be given to the diagnosis of CVT in pregnant/ post partum females who present with signs and symptoms of this illness. Multidisciplinary approach should be practiced in the diagnosis of these patients by actively including the obstetricians.

1. INTRODUCTION

BACKGROUND

Cerebral venous sinus thrombosis (CVST) is the presence of a blood clot in the cerebral veins or in the dural venous sinuses or both. CVT is less common than other types of strokes but can be more challenging to diagnose. It is more commonly found in women than men, with female to male ratio of 3:1. This imbalance may be due to the increased risk of CVT in pregnancy and puerperium and with oral contraceptives (ferro JM, 2004).

The pathogenesis of CVT is incompletely understood because of the high variability in the anatomy of the venous system. There are two different mechanisms contributing to the clinical features of CVT. These are thrombosis of cerebral veins or dural sinus leading to cerebral parenchymal lesions and occlusion of dural sinus resulting in decreased CSF absorption and elevated intra cranial pressure. (M, 1993)

The major risk factors of CVT in adults can be grouped as transient or permanent. The most frequent are prothrombotic conditions (either genetic or acquired), oral contraceptives, pregnancy and puerperium, malignancy, infection, head injury and mechanical problems. In more than 85 % of adult patients, at least one risk factor for CVT can be identified, most often a prothrombotic condition. The risk of CVT is influenced by the individual's genetic background. (G, 2011)

Cerebral vein and dural sinus thrombosis (CVT) has a highly variable clinical presentation. The onset can be acute, subacute or chronic. Symptoms and signs of CVT can be grouped in three major syndromes. The first is isolated intracranial hypertension syndrome which may present as headache with or without vomiting, papilledema and visual problems. The second is focal syndrome and it may present as focal deficits, seizures or both. The last one is encephalopathy and it may present with multifocal signs, mental status changes, stupor or coma. (MG, 1985)

Several factors may affect the presentation and course of CVT. These factors include the site and number of occluded sinus and veins, presence of parenchymal brain lesions, patient's age, gender and interval from CVT onset to presentation. (MG, 1985)

The neuroimaging features of CVT include findings suggesting the primary underlying pathology of venous thrombosis and associated brain parenchymal lesions. These may include focal areas of edema or venous infarction, hemorrhagic venous infarction, diffuse brain edema or (rarely) isolated subarachnoid hemorrhage. In patients with CVT, the proportion of patients who present with intracerebral hemorrhage is 30 to 40 percent. (Sztajzel R, 2001)

MRI using gradient echo T2* susceptibility weighted sequences in combination with MR venography is the most sensitive imaging method for demonstrating the thrombus and the occluded dural sinus or vein. On gradient echo T2* weighted MRI sequences, the clot can be directly seen as an area of hypo intensity in the affected cortical vein and / or sinus. (Sztajzel R, 2001)

Head CT is normal in up to 30 percent of patients with CVT and most of the findings are nonspecific. Brain CT scan is useful to rule out other acute or subacute cerebral disorders. In about one – third of cases, CT demonstrates direct signs of CVT. In patients with clinically suspected CVT, the clear demonstration of absence of flow and intraluminal venous thrombus by CT or MRI is the most important finding for confirming the diagnosis. Aside from neuroimaging, there is no simple confirmatory laboratory test that can rule out CVT. Routine blood tests should be done to look for preexisting conditions that may contribute to CVT. The utility of D- dimer and lumbar puncture is less certain. . (Sztajzel R, 2001)

CVT is associated with good outcome (complete recovery or minor residual symptoms) in close to 80 percent of patients. Approximately 5 percent patients die during the acute phase and longer-term mortality is nearly 10 percent. The commonest cause of acute death with CVT is neurologic, most often from brain herniation. (Stam, 2002)

For adults with symptomatic CVT, with or without hemorrhagic venous infarction, initial management with subcutaneous LMWH or intravenous heparin is recommended. After the acute phase, anticoagulation with warfarin is given for 3 to 12 months aiming at an INR of 2.5. Seizure prophylaxis is given for those with seizures and focal supratentorial lesions such as edema or infarction on brain CT or MRI. (Einhaupt k, 2010)

Statement of the problem

Cerebral venous thrombosis is a relatively uncommon neurological disorder. It mostly affects women especially those who are pregnant or in the puerperium period. Most of the studies done worldwide show that CVT has a favorable outcome if diagnosed and managed before complications occur. Studies done in Africa showed that there are low number of reported CVT cases suggesting that CVT is not diagnosed or not reported. (baduro, 2021)

Because of lack of proper definitive diagnostic modalities, patients with CVT are under diagnosed or are misdiagnosed as having other types of strokes. They are also unnecessarily exposed to use of medications for a longer duration.

There is no available local data regarding the clinical presentation, outcome or risk factor of patients that were diagnosed with CVT. This study is intended to contribute to the lack of data.

Significance of the study

Cerebral venous thrombosis is an under diagnosed / undiagnosed disease. It is associated with readily manageable complications which need early detection. Knowledge on the presentation and outcome of CVT in our country will help medical personals to understand the disease better and focus on the identifying the predisposing factors. This will help sensitize health professionals to intervene early and achieve a good outcome. This study will also identify any difference in the disease pattern in our country as compared to the available worldwide data.

As there are no previously done researches about CVT in Ethiopia, this study will contribute some new information and it may also stimulate researchers to do a more detailed study in the future.

2. LITERATURE REVIEW

In a study done in Saudi Arabia on adult CVT patients, 47 % had a clinical picture of pseudo tumor cerebri. Bechet's disease was found in 25 % of the patients. Other conditions found were anti phospholipid antibodies, protein C deficiency, intracranial tumors, oral contraceptives and postpartum. Infection was no longer an important cause and new coagulation disorders were common. (Abdulkader Daif, p. July 1995)

In another prospective study done in Asia, anemia was found in 51 % of the patients. Use of OCP was seen in 12 % of women and hypercoagulable state in > 40 % of tested patients. Around 18 % of the CVT cases were seen in women who were either pregnant or in the puerperium state. Infection in any part of the body was found in 10.5% of the patients. Majority of the patients (87.3%) had good functional outcome at discharge. The study concluded that important difference was found as compared to the western data like younger age, higher frequency of anemia, low use of OCP and higher frequency of hypercoagulable states. (Wasat, Oct. 2019)

A Multicenter study was done in Turkey on Caucasian patients with CVT (the VENOST study). The most frequent symptoms seen in men were headache (89.4%) and visual field defects (28.9%). In women, headache was the commonest symptom (86.1%) followed by epileptic seizures (18.3%). Gynecological factors, particularly puerperium (18.3%) comprised the largest group in women. Prothrombotic conditions (26.4%) were found in 26.4 % of patients. 8.1% of the patients had infection associated and 5.2 % had malignancy related etiology. This study concluded that clinical and radiologic findings were consistent with previous larger studies but predisposing factors were different with a higher incidence of puerperium. (Duman, 2017)

In an African study done in Tunisia, the mean age of the patients was 37.3 years with female predominance (83.1%). The mode of onset of CVT was subacute in most cases (56.2%). Headache was the most common symptom (71.3%) and focal neurological symptoms were the main clinical presentations (41.8 %). Commonest sites of thrombosis were superior sagittal sinus (65%) and lateral sinus (60.6%). Obstetric causes were seen in 38.6 % women aged <50 years. Anemia and congenital acquired thrombophilia were seen in 28.1 % and 16.2% of patients respectively. Mortality rate was 6.6 %. Good outcome at 6 months (mRS ≤2) was observed in 87.5% of patients available for follow up. In conclusion, it was stated that clinical and radiologic presentation of CVT in Tunisia were quite similar to other parts of the world except the high frequency of obstetric causes seen. This study also recommended for plasma CRP level to be considered as a prognostic factor in CVT. (Sassi, 2017)

A systematic review of studies on CVT in sub-Saharan Africa stated 20 observational studies describing 287 CVT patients. It stated that all of the studies had a high risk of bias. In the case series reviewed, 58.6 % of the patients were female. Most common condition found was infection (63%) followed by OCP (7.3%), pregnancy/ puerperium (6.2%) and prothrombotic conditions (2.2%). CT scan was the commonest method used to diagnose CVT (85%). 99 % of the patients reported in the case series were anticoagulated. This review concluded that the low number of CVT cases reported from sub-Saharan Africa suggested CVT is either infrequent, not diagnosed or not reported. Death rate was higher than high income countries. (Baduro, 2021)

Another African study was done in Kenyatta national hospital. The median age of patients was 30 years. Females were more affected (74.5%) than male. Commonest presenting clinical features were headache, seizure and neurological deficits. Infection was seen in 39.2% of the patients. Pregnancy/ puerperium and oral contraceptives were found in 13.7 % and 3.9% of patients respectively. Commonest CT scan finding was hyper dense sinus and parenchymal changes. (Onyambu, sep. 2013)

A case report of a young female patient with anomia and CVT was published in February 2022 in Ethiopia. She presented on her second month post partum with headache, blurred vision and word finding difficulty(anomia). She was started on warfarin for 6 months and significant resolution of symptoms was seen. This case report described reversible anomia as a complication of CVT . The report highlighted the importance of timely diagnosis and treatment. (Biniyam, Feb.2022)

There are no studies published other than a case report on cerebral venous thrombosis in Ethiopia to date.

3. OBJECTIVES

3.1 General objective

The major aim of this study is to identify the inpatient clinical outcome of adult patients with cerebral venous thrombosis admitted to SPHMMC or ZMH from September 2017 to September 2021.

3.2 Specific objectives

1. To assess the clinical presentations of adult patients with CVT admitted to SPHMMC/ZMH from September 2017 to September 2021
2. To assess the inpatient clinical outcome of adult CVT patients admitted to SPHMMC/ZMH from September 2017 to September 2021

4. METHODOLOGY

4.1 STUDY AREA

The study was conducted in two government hospitals located in Addis Ababa, Saint Paul's hospital millennium medical college and Zewditu memorial hospital. SPHMMC is the second largest governmental tertiary care hospital located in Gulele sub city. It is a medical center with a catchment area of more than 5 million people. On average, daily, the hospital gives medical service to 1200 patients with diversified complaints, in several specialty and subspecialty fields. Patients with CVT are primarily seen by neurologist at SPHMMC and followed by hematologists and neurologists in respective specialty clinics. Zewditu memorial hospital is located in central Addis Ababa and operated by the ministry of health. CVT patients at ZMH are evaluated by neurologists. They are followed at neurology referral clinic which is functional for 3 days out of a week.

4.2 STUDY DESIGN

A cross sectional retrospective chart review was used in this study.

4.3 STUDY POPULATION

SOURCE POPULATION- The source population was all patients diagnosed to have cerebral venous thrombosis and admitted to either SPHMMC or ZMH.

STUDY POPULATION

This study included all of the patients admitted to SPHMMC or ZMH with a diagnosis of cerebral venous thrombosis over duration of 5 years (September 2017 to September 2021)

4.4 INCLUSION AND EXCLUSION CRITERIA

4.4.1 INCLUSION CRITERIA

All adult patients who were admitted for CVT with brain imaging evidence

4.4.2 EXCLUSION CRITERIA

- *Children with CVT
- *Adults with other types of strokes
- *Adults with CVT who were not admitted

4.5 SAMPLE SIZE

All patients who were admitted with diagnosis of CVT from year 2017 to 2021 were included. The total number of patients was 55 (40 patients from SPHMMC and 15 patients from ZMH). From these, the data of 16 patients (10 from SPHMMC and 6 from ZMH) couldn't be reviewed (chart was lost). One of the remaining patients in ZMH was not treated with anticoagulation medication and was excluded from the study. A total of 38 patients were assessed in this study.

4.6 Study variables

4.6.1 Dependent variables

- Treatment outcome (death, persistent motor weakness, complete recovery)

4.6.2 Independent variables

- I. Age
- II. Sex
- III. Use of oral contraceptives
- IV. Trauma history
- V. Clinical symptoms (seizures, weakness, headache etc.)
- VI. Pregnancy or puerperium
- VII. Infections

5. Data collection tools, procedures and quality assurance

Data was collected from June 2022 up to August 2022 from medical records of patients using a questionnaire. The questionnaire had components assessing the clinical presentations and inpatient outcome of patients. Data was checked for completeness after collection.

5.1 Data analysis

Data was analyzed using the statistical package for the social sciences (SPSS) version 20 for Microsoft Windows. Frequencies were used to summarize the descriptive statistics of the data. The results were presented by using charts and tables.

5.2 ETHICAL CONSIDERATION

Ethical clearance was obtained from the institutional review board of St. Paul's Hospital Millennium Medical College and then permission was sought from the school administration through the academic provost of the school to carry out the study. Each patient's information was collected using a structured checklist. The collected information was only used for this particular study and was kept confidential.

6. RESULTS

6.1 Socio demographic characteristics

A total of 38 adult patients with cerebral venous thrombosis admitted to either SPHMMC or ZMH from September 2017 up to September 2021 were assessed in this retrospective study. Of these patients, 23 of them (60.5 %) were in the age range of 18 to 30 yrs. The median age was 28 years.

Out of the total 38 adult CVT patients assessed in this study, the number of female and male patients was **29** (76.3 %) and **9** (23.7%) respectively.

Table 1. Age sex distribution of adult CVT patients admitted to SPHMMC/ZMH from September 2017 up to September 2021

Age of the patients	Sex of the patients			
		Male	Female	Total
	18-30	3	20	23
	30-45	5	8	13
	>=45	1	1	2

6.2 CLINICAL PRESENTATION OF THE STUDIED POPULATION

Majority of the studied patients (89.5%) presented with multiple symptoms. Headache was the commonest presenting symptom and was seen in 97.4% of patients. All of the motor weakness found was hemiparesis.

Table 2. Clinical presentation of adult CVT patients admitted to SPHMMC or ZMH from September 2017 up to September 2021

Clinical presentation of the patients	YES (number/ percentage)	NO	NOT MENTIONED
Headache	38 (97.4%)	1(2.6%)	0
Seizure	15(39.5%)	22(57.9%)	1(2.6%)
Motor weakness	18(47.4%)	18(47.4%)	2(5.3%)
Change in mentation	17(44.7%)	19(50%)	2(5.3%)
Visual impairment	16(42.1%)	8(21.1%)	14(36.8%)

6.3 Duration of symptoms in the studied population

Majority of patients (57.9 %) had symptoms lasting less than two weeks.

6.4 Medical/ surgical conditions found in the studied population

One or more risk factors were found in 34 patients (89.5 %), with pregnancy/ puerperium being the commonest (52.6 %) followed by CNS infections (23.7%). Meningitis was the CNS infection identified .

TABLE 3. MEDICAL/ SURGICAL CONDITIONS FOUND IN ADULT CVT PATIENTS ADMITTED TO SPHMMC/ZMH FROM SEPTEMBER 2017UPTO SEPTEMBER 2021

Risk factor	Frequency	Percent
Pregnancy/ puerperium	20	52.6
OCP use	4	10.5
Malignancy	0	0
CNS infection	9	23.7
Prothrombotic conditions (coagulopathy,thrombophilia etc.)	5	13.2
Head injury/ mechanical precipitants	2	5.3
No conditions identified	4	10.5

6.5 Other investigations done in the study population

Sero status(PICT) was found to be negative and positive in 76.3 %(29) and 5.3 %(2) of the patients respectively . It was not determined for seven of the patients which accounts for 18.4 % of the total patients.

CBC profile was determined for all of the patients. It was normal in 28 patients (73.7 %). The remaining ten patients (26.3%) has an abnormal CBC profile of which 7 had mild anemia and 3 of them has leukocytosis.

Coagulation profile was determined for all of the patients and it was normal.

Stool occult test was not done for any of the patients

Brain imaging (MRI /MRV/ CT) was done in all of the patients and was diagnostic of CVT.

6.6 Treatment with anti-coagulation in the study population

Treatment with an anticoagulant medication was given for all of patients. Unfractionated heparin followed by warfarin was the anti coagulation medications used in all patients. Unfractionated heparin was started immediately after diagnosis in all of the patients that received anticoagulation. The mean duration of to the initiation of warfarin was 10 days.

6.7 IN PATIENT OUTCOME OF THE STUDY POPULATION

Out of the 39 adult CVT patients assessed in this study, 27 of them (71.1%) completely improved up on discharge from the hospital. Eight patients (21.1%) were discharged with some neurologic sequelae which were all motor weakness.

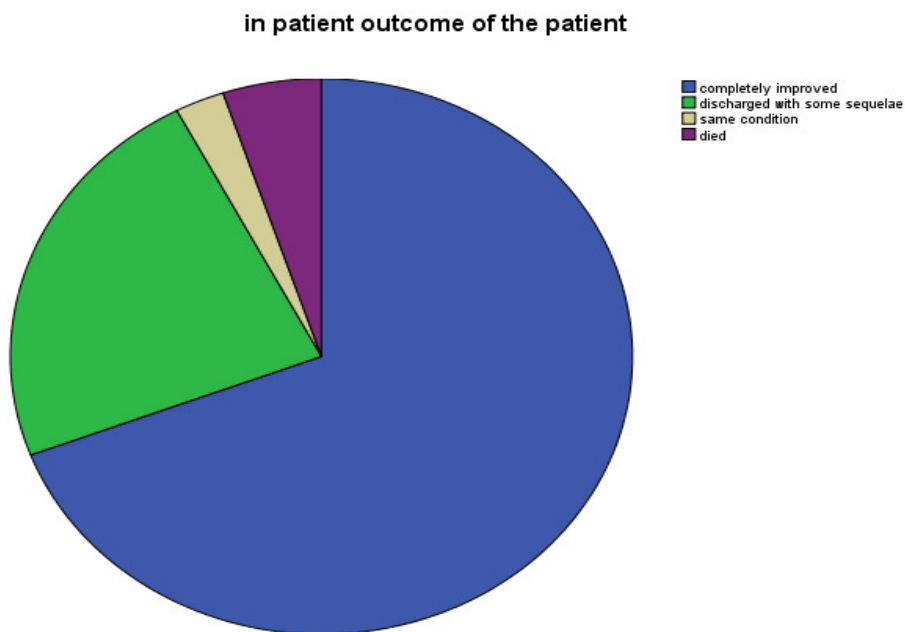


Figure 1. Inpatient outcome of adult CVT patients admitted to SPHMMC/ZMH from September 2017 up to September 2021

7. DISCUSSION

This five year study was conducted at the inpatient wards in SPHMMC and ZMH with the aim of assessing the clinical presentation, risk factors and outcome of adult CVT patients.

In this study, the median age of the patients was 28 years. Majority of the patients (60.5%) are in the age range of 18 to 30 years. Majority of the patients assessed were female (76.3%). This finding is similar to a study done in Kenyatta hospital, Kenya in 2013 in which female accounted for 74.5% of the total study population. Females are more affected by CVT as seen in previous studies because two of the most common risk factors (pregnancy/ puerperium and OCP use) occur specifically in them.

The commonest presenting symptom was headache (97.4%) followed by motor weakness (47.4%) and visual impairment (42.1%). Headache occurs in CVT patients because of blockage of blood vessels by the thrombus. This was similar to a study done in Tunisia in 2017 in which headache and motor weakness were seen in 71.3% and 41.8 % of the studied patients respectively. Majority of the patients (57.9%) had symptoms lasting less than two weeks.

One or more conditions were seen in 89.5 percent of patients. Pregnancy/puerperium was found in 52.6% of the patients. CNS infection and pro thrombotic conditions were seen in 23.7 % and 13.2% of patients respectively. Malignancy was not incriminated in any of the patients. No conditions were found in 10.5 % of patients. This was slightly different from a systematic review done in sub-Saharan Africa in 2021 in which infection was identified as the commonest risk factor (63%) followed by OCP use (7.3%) and then pregnancy/ puerperium (6.2%). Pregnancy/ puerperium is a common risk factor identified in CVT patients in general because it is a hyper coagulable state.

All of the studied patients were started on treatment with anticoagulant medication.

The inpatient outcome of the studied population was good in general. Majority of patients (71.1%) had a complete recovery at discharge and around 21.1 percent of patients has motor sequele which was hemiparesis. There was slight improvement in terms of motor power at discharge in all of these patients as compared to the admission. One patient had no improvement in terms of presenting symptom. There were two deaths documented which accounts for 5.26% of the total patients. The cause of death was documented as hospital acquired infections. This rate is slightly lower than the number of deaths seen in a systematic review done in sub Saharan Africa in which 10 percent of the patients died.

8. STRENGTH AND LIMITATION

8.1 strengths of the study

There is no study other than a case report published on CVT in Ethiopia. This makes it the first study to be done in our country.

The study included a longer period of review which was five years making it more inclusive.

8.2 limitations of the study

There were lost patient charts which have decreased the total number of study population.

The number of study population found to have CVT was low. This made it difficult to do associations among factors.

9. CONCLUSION AND RECOMMENDATION

9.1 CONCLUSION

In this study, majority of the patients with CVT were female and aged 18 to 30 years. Headache was the commonest clinical presentation. Pregnancy/ puerperium was the commonly identified condition. Almost all of the patients received treatment with anticoagulation. Most of the patients had a good inpatient outcome with majority having a complete recovery at discharge. The low number of CVT patients may suggest that CVT is either infrequent, not diagnosed or not properly reported due to poor documentation on the HMIS.

9.2 RECOMMENDATION

Based on the findings of the study, the following recommendations are forwarded

To health care professionals

- Attention should be given for diagnosing CVT in female patients who are pregnant or in the puerperium period
- Multidisciplinary approach including obstetricians should be practiced in evaluating postpartum/ pregnant patients who present with headache and associated neurologic manifestations so as to not miss CVT patients.

To local health policy makers

- Short course lectures and sensitization should be given on CVT

To researchers

- Further prospective studies that include more hospitals should be done

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ANNEXES

ANNEX 1: Information sheet

Research title: Clinical presentation and treatment outcome of cerebral venous thrombosis among adult patients admitted to SPHMMC or ZMH :5 years review

Principal investigator (PI): Fana Hagos (MD, Internal medicine resident)

Phone number (mobile): +251-921625789

Advisors: Dr. Tesfaye (MD, Internist, consultant neurologist)

Mr. Getachew T (MPH)

Sponsor: Saint Paul's Hospital Millennium Medical College

ANNEX 2 :QUESTIONNAIRE

1. Age (In years)
 - A. 18 -30 B. 30-45 C.>=45
2. Sex
 - A. Male B. Female
3. Presenting symptom (More than one answer is possible)
 - A. Headache A. YES B. NO C. NOT MENTIONED
 - B. Seizure A. YES B. NO C. NOT MENTIONED
 - C. Motor weakness A. YES B. NO C. NOT MENTIONED
 - If answer is YES , type of motor weakness.....
 - D. Change in mentation A. YES B. NO C. NOT MENTIONED
 - E. Visual impairment A. YES B. NO C. NOT MENTIONED
 - F. Others (specify)
4. Duration of symptoms
 - A. < 2 weeks
 - B. 2- 4 weeks
 - C. > 4 weeks

5. Identified medical/ surgical condition (More than one answer is possible)
- A. Pregnancy / puerperium
 - B. Oral contraceptive use
 - C. Malignancy
 - D. CNS Infection
 - If present, type of CNS infection.....
 - E. Pro thrombotic conditions
 - F. Head injury/ mechanical precipitants
 - G. Risk factor unidentified
6. Other investigations done
- I. PICT A. REACTIVE B. NONREACTIVE C. NOT DONE
 - II. Stool occult A. NEGATIVE B. POSITIVE C. NOT DONE
 - III. CBC A. NORMAL B. LEUKOCYTOSIS/ ANEMIA C. NOT DONE
 - IV. Coagulation profile A. NORMAL B. ABNORMAL C. NOT DONE
7. Treatment with anticoagulation A. GIVEN B. NOT GIVEN
- If given, type of anticoagulation.....
 - If given, day of starting anticoagulation from diagnosis.....
8. Outcome of the patient
- A. Completely recovered
 - B. Had motor weakness on discharge
 - C. Same condition
 - D. Died