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Clinical Profile and Short-Term Outcome of Cerebral Venous Thrombosis in a Nepalese Population: A Retrospective Study

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ABSTRACT

Introduction: Cerebral venous thrombosis (CVT) is a rare cause of stroke. The increased awareness among the physicians and the suspiciousness for the myriad of its clinical presentation with increased availability of investigation modules and therapeutic options has led to the decrement of mortality and morbidity. The study intends to assess the clinical etiological profile of patients of CVT and also to assess short-term outcomes and if any factors are associated with it.

Methods: It was a hospital-based retrospective, observational cross-sectional study at a tertiary care center in Kathmandu among adult CVT patients from August 2019 to August 2021. Clinical, etiological, and radiological data, the outcome at discharge, and any factors influencing this were assessed where possible. Data were analyzed using SPSS 25 software. Analysis of the descriptive data was performed and independent factors influencing short-term outcome (admission date < 7 days) were analyzed.

Results: There were a total of 15 cases included in the study. The study showed female predominance (66.7%. The mean age of the patients was 48.87 years. Four (26.7%) patients had hypertension. The history of oral contraceptive pills (OCP) use was among five (33.33%) females. A significant association was present with direct signs in CT scan (p=0.02), and low erythrocyte sedimentation rate (ESR), p= (0.02).

Conclusions: OCP and hypertension are increasingly recognized as independent risk factor for CVT. The presence of direct signs in the CT head and the presence of high ESR have independent predictive value in assessing short-term outcomes.

Keywords: Cerebral; outcomes; thrombosis; venous.

INTRODUCTION

Cerebral venous thrombosis (CVT) is a relatively uncommon cause of stroke. It accounts for 0.5-1 % of all strokes and is more common in younger individuals.[1] However, current research suggests that CVT is more common than originally thought, affecting fewer than 5 people per million.[2] In addition, the number of cases recorded in national cross-sections revealed a slightly different and higher incidence of such occurrences. In Asia, the annual incidence is estimated to be 3-4 cases per million.[3] CVT was identified in 2% of all strokes by Yaqub et al.[4] Due to the rarity of CVT as seen in these figures, data on its clinical presentation, course, and prognosis is limited and mostly based on research with small sample sizes.[2] However, depending on the location of the thrombus, the clinical signs vary, which might cause a delay in identification. The most commonly reported symptom is headache (70-95 %). [5,6] Other symptoms include seizures, focal neurological impairments, cranial nerve palsies, and impaired mental status.[7]

CVT is caused by several modifiable and non-

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modifiable predisposing factors. Some of the most prevalent causal factors include female gender, congenital or acquired thrombophilia, and infections.[8] The peripartum period and the usage of oral contraceptive tablets have been linked to a significantly increased incidence among females (OCPs).[9] Physicians should have a high index of suspicion to make a prompt diagnosis. In the emergency department, non-enhanced computed tomography (NECT) is the most often used neuroimaging technology; yet, direct symptoms of CVT are only seen in one-third of patients.[10] As a result, some diagnoses were missed at first. When compared to arterial or hemorrhagic stroke, the prognosis for CVT is better.[11] Old age (>55 years), oral contraception, hormone replacement therapy, obesity, pregnancy and puerperium, dehydration, systemic illness, thrombophilic coagulopathy, local brain tumor, aneurysm, or arteriovenous malformation are just a few of the predisposing or risk factors.[12–14] The purpose of this study is to provide the clinical, radiological, and laboratory pattern of CVT along with the short-term outcome among the Nepalese population presenting to the tertiary center.

METHODS

The study was a hospital-based observational, retrospective cross-sectional study. Patients with the diagnosis of cerebral venous thrombosis in Tribhuvan University Teaching Hospital (TUTH), Neurology department of Kathmandu valley were included in the study. The study population included all patients who were admitted with the diagnosis of CVT from August 2019 to August 2021. The data were collected from the patient records kept at the record keeping department of the hospital. Only those patients whose complete data could be obtained were included.

Ethical approval was obtained from the Institutional Review Committee (IRC) of the Institute of Medicine (IOM). Official letter of cooperation from IRC were sent to the study center.

A structured preformat was created, which included details about demographic characteristics such as age, gender, and nationality, symptoms, and signs at the time of presentation such as headache, seizure, blurred vision, focal weakness or numbness, speech difficulty, cranial nerve palsies, and altered sensorium, blood investigations, and details of imaging modalities and radiological findings (location of thrombus, number of involved venous sinuses, venous infarction, and hemorrhagic transformation).

Female patients were asked about pregnancy, puerperium, and the usage of oral contraceptive tablets. Clinical signs in patients with features suggestive of a CVT, such as headache, new-onset seizures, focal neurological impairments, cranial nerve palsies, impaired vision, and altered consciousness level, were used to make the diagnosis. To confirm the diagnosis, a CT or MRI scan of the head and a CT venogram (CTV) or an MR venogram (MRV) of the brain were employed. T1, T2, fluid-attenuated inversion recovery imaging, diffusion-weighted imaging, apparent diffusion coefficient map, and gradient-echo sequences were used in the MRI and MRV, which were all done on a 1.5 or 3 Tesla MR imager.

The modified Rankin Scale (mRS) was used for assessing the degree of disability. The MRS discharge scores of less than or equal to 2 were grouped as "good functional outcome" while greater than 2 were grouped as "poor functional outcome". While a cut-off of one week was taken for total admitted days. The findings of complete blood counts, regular blood biochemistry, were examined in all patients to determine the frequency of predisposing factors. Antinuclear antibodies, anticardiolipin antibodies, antiphospholipid antibodies, lupus anticoagulant, coagulation profiles, and antibodies to double-stranded DNA were also sought as hypercoagulable conditions whenever indicated and according to patient's affordability.

Other tests, such as cerebrospinal fluid analysis,

were carried out if needed. Personal habits such as alcohol intake, smoking, and any substance abuse were also included. Glasgow coma scale was also noted. History of any chronic illness like hypertension, diabetes mellitus, known malignancy, hematological disorder, or connective tissue disease was also included.

The inclusion criteria were patients aged ≥18 years. According to established criteria,[15] patients were only included in the study if they had a CVT diagnosis confirmed by MRI, MRV, contrast-enhanced CT, and CT venography. Patients with incomplete evaluation and MRI tests were excluded.

All the patients were included with CVT as per established diagnostic criteria of CVT. Hence, sampling was not done for this study.

Basic data including age, gender, occupation, nature, duration of symptoms, and other relevant history was taken from all the study participants in the study. The data was collected in the proforma. Data was compiled, edited, and checked daily to maintain consistency. We used SPSS software for Mac, Version 25 (SPSS Inc., USA) to store and analyze the data. Continuous variables were presented in the form of mean and standard deviation. Univariate analyses (independent sample t-test for continuous variables, and $\chi 2$ test for categorical variables, as appropriate) were performed to assess the association of each of the independent variables and dependent variable. Fisher's exact test for categorical variable and independent-sample t-test for the continuous variable was used for the association of outcomes. For all statistical analyses, significance was accepted at $p< 0.05$.

RESULTS

Demographic variables

A total of 15 patients were included in our study, out of which 10 (66.7%) were female and 5 (33.33%) were male (Figure1). The mean age of patients was 48.87±16.80 years, ranging from 25 to 73 years. Among 15 patients, 4(26.7%) had hypertension, 1(6.7%) had diabetes mellitus and one patient had COVID-19 infection. The history of oral contraceptive pills (OCP) used was among five (33.33%) females while none of the patients had a history of a recent delivery. The admission GCS of the patients range from 9-15 (Figure 2). The common presenting symptoms at onset were headache (13, 86.7%) mainly throbbing type, vomiting (6, 40%), altered consciousness (6, 40%), seizures (focal among 5 cases, 33.3% and generalized among 4 cases, 26.7%), and hemiparesis (6,40%).

Abnormal CT scan findings were found in six (40%) patients. Among these, dense triangle sign and hemorrhagic infarct were found among 3 patients each. The lesion was localized in the frontal lobe in only two scans. Similarly, all patients have had their MRI-MRV scans done. Among MRI abnormal scans were found in six (40%) patients (five hemorrhagic and one non-hemorrhagic). In MRI, the lesion could be localized in the frontal and temporal region in five and one patient respectively. MRV revealed the sinus involved. Superior sagittal sinus, transverse sinus, sigmoid sinus, and deep vein were involved in 73.3%, 40%, 20%, and 6.7% of patients respectively.

The mean hemoglobin was found out to be 13.70±2.34 mg/dl. Similarly, the mean blood sugar and creatinine was found to be 102.57±16.72 mg/dl and 71.61±23.59 mmol/l respectively. The mean ESR were found to be 16.87±8.18 mm/ 1st hour.

OCP: oral contraceptive pills; CN: cranial nerve; GCS: Glasgow coma scale; ESR: erythrocyte sedimentation rate; SSS: superior sagittal sinus; SS: sigmoid sinus; TS: transverse sinus; mRS: modified Rankin scale; CT: computed tomography; MRI: magnetic resonance imaging; MRV: MRV: magnetic resonance venography

Outcomes

The median duration of hospital stay was 7 days ranging from 3 to 38 days (Figure 3). Complications were seen among 3 patients (2 patients developed

Table 1: Patient characteristics reported as mean ±SD, median (range) or number

Variables	All patients, n=15	Good outcome, n= 13	Poor outcome, n= 2
Age (mean± SD)	48.87±16.80	44.76±13.85	75.50±3.53
Sex			
Male (n)	5 (33.33)	4 (30.76)	1 (50.0)
Female (n)	10 (66.67)	9 (69.24)	1 (50.0)
History of OCP (n)	5 (33.34)	5 (38.46)	0
Comorbidities			
Hypertension (n)	4 (26.67)	4 (30.76)	0
Diabetes mellitus (n)	1 (6.67)	1 (7.69)	0
Smoking (n)	4 (26.67)	3 (23.07)	1 (50.0)
Median Interval between symptoms and admission (in days)	8	10	1
Clinical features			
Headache (n)	13 (76.5)	13 (100.0)	0
Vomiting (n)	6 (35.3)	5 (38.46)	1 (50.0)
Visual symptoms (n)	2 (11.7)	2 (15.38)	0
Seizures (n)	9 (52.9)	7 (53.84)	2 (100.0)
Altered Consciousness (n)	6 (35.3)	5 (38.46)	1 (50.0)
Weakness/Hemiparesis (n)	6 (35.3)	4 (30.76)	2 (100.0)
CN involved (n)	4 (23.5)	4 (30.76)	0
Examination			
Admission GCS	15 (9-15)		
Aphasia (n)	2 (11.7)	1 (7.69)	1 (50.0)
Papilledema (n)	2 (11.7)	2 (15.38)	0
Investigation			
Hemoglobin (mg/dl)	13.70±2.43	13.90±2.48	12.40±2.26
ESR (mm/ 1st hour)	16.86±8.18	16.38±8.73	20±0.00
Sodium (mEq/L)	138.60±2.97	138.84±3.02	137±2.82
Potassium (mEq/L)	3.84±0.25	3.86±0.25	3.75±0.35
Abnormal CT scan (n)	6 (35.3)	4 (30.76)	2 (100.0)
Direct signs in CT (n)	3 (20.0)	2 (15.38)	1 (50.0)
Indirect signs in CT (n)	3 (20.0)	2 (15.38)	1 (50.0)
Abnormal MRI/MRV (n)	6 (35.3)	4 (30.76)	2 (100.0)
SSS involved (n)	11 (73.3)	9 (69.24)	2 (100.0)
SS involved (n)	3 (20.0)	2 (15.38)	1 (50.0)
TS involved (n)	6 (35.3)	5 (38.46)	1 (50.0)
Outcome			
Median duration of admission (days)	7	5	23.50
Median Discharge mRS	0	0	4.5

pneumonia and 1 patient developed urinary tract infection). One person died during treatment. The median admission modified Ranking Scale (mRS) was 2 (0-4). 13 patients had good functional outcomes at discharge with median mRS 0 (0 to 6) while two patients had a poor outcome. The presentation was acute in 13 patients (86.7%) while subacute and chronic in one (6.7%) patient each.

Table 2: Patient characteristics reported as mean ±SD, median (range) or number with p value

Variables	All patients, n=15	Admission days ≤7, n=10	Admission days >7, n=5	P value
Age (mean± SD)	48.87±16.80	44.20±15.85	58.20±16.11	0.13
Sex				
Male (n)	5 (33.34)	3 (30.0)	2 (40.0)	1.00
Female (n)	10 (66.67)	7 (70.0)	3 (60.0)	
Co-morbidities				
Hypertension (n)	4 (23.5)	3 (30.0)	1 (20.0)	1.00
Diabetes (n)	1 (6.67)	1 (10.0)	0	1.00
Smoking (n)	4 (23.5)	2 (20.0)	2 (40.0)	0.56
Covid (n)	1 (6.67)	0	1 (20.0)	0.33
OCP use (n)	5 (33.34)	4 (40.0)	1 (20.0)	0.60
Median Interval between symptoms and admission (days)	8	10	1	0.15
Clinical Features				
Seizures (n)	9 (52.9)	5 (50.0)	4 (80.0)	0.30
Hemiparesis (n)	6 (35.3)	2 (20.0)	4 (80.0)	0.09
Examination				
Admission GCS	15 (9-15)	15 (9-15)	12 (9-15)	0.14
Aphasia (n)	2 (11.7)	0	2 (40.0)	0.10
Papilledema (n)	2 (11.7)	1 (10.0)	1 (20.0)	1.00
Investigation				
Hemoglobin (gm/dl)	13.70±2.43	14.16±2.70	12.80±1.64	0.32
ESR (mm/1st hour)	16.86±8.18	13.60±5.44	23.40±9.37	**0.02**
Sodium (mEq/L)	138.60±2.97	138.50±2.46	138.80±4.14	0.86
Potassium (mEq/L)	3.84±0.25	3.88±0.16	3.78±0.40	0.50
Abnormal CT (n)	6 (35.3)	2 (20.0)	4 (80.0)	0.09
Direct sign (n)	3 (20.0)	0	3 (60.0)	**0.02**
Indirect sign (n)	3 (20.0)	1 (10.0)	2 (40.0)	0.24
Abnormal MRI/MRV (n)	6 (35.3)	2 (20.0)	4 (80.0)	0.06
SSS involved (n)	11 (73.3)	6 (60.0)	5	0.23
TS involved (n)	3 (20.0)	5 (50.0)	1 (20.0)	0.58
SS involved (n)	6 (35.3)	2 (20.0)	1 (20.0)	1.00

Association between outcomes and variables

Admission days less than or equal to a week and more than a week were used as a dependent variable in a test of significance with other variables. Using Fisher's exact test for categorical variable and independent-sample t-test for a continuous variable, we found out the significant association with direct sign in CT scan (p=0.02), and erythrocyte sedimentation rate (ESR), p= (0.02). (Table 2) The most likely risk factor was an intake of OCP seen in 5 of the cases.

OCP: oral contraceptive pills; CN: cranial nerve; GCS: Glasgow coma scale; ESR: erythrocyte sedimentation rate; SSS: superior sagittal sinus; SS: sigmoid sinus; TS: transverse sinus; mRS: modified Rankin scale; CT: computed tomography; MRI: magnetic resonance imaging; MRV: MRV: magnetic resonance venography; COVID: corona virus disease.

Figure 1: Pie-chart showing sex distribution of CVT patients.

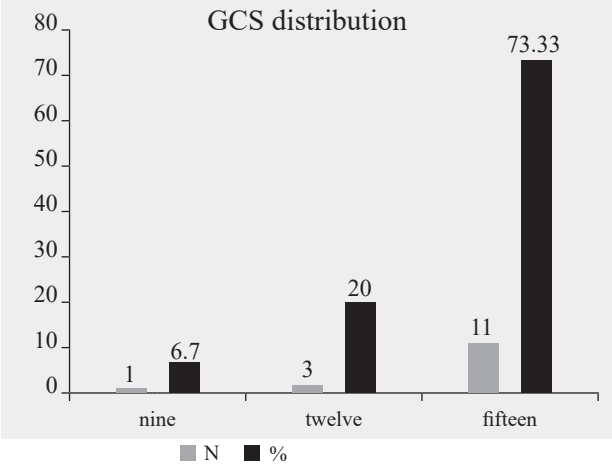

Figure 2: Bar diagram showing distribution of GCS.

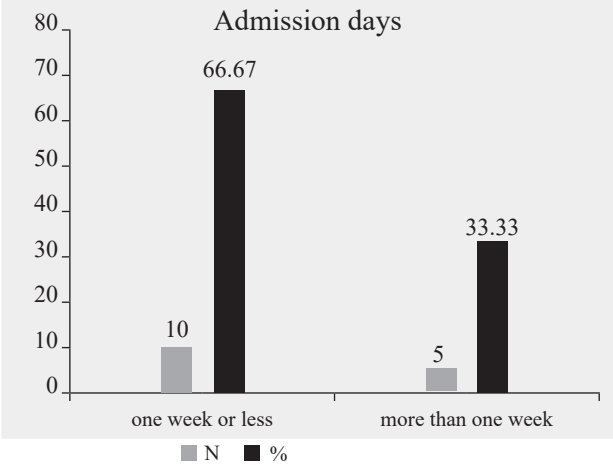

Figure 3: Bar diagram showing frequency of patients admitted for one week and more.

DISCUSSION

In this study, we provided the clinical, radiological, and laboratory patterns of CVT patients along with the short-term outcome at our center over two years period of time. As opposed to arterial strokes, CVT has a significantly higher incidence in women. The majority of patients in our study were female (66.7%), with a female-to-male ratio of 2:1 in the whole cohort consistent with all, except 1, previous studies which reported a 58%-79% woman preponderance[16–18]. During the reproductive years of women, this imbalance is more evident. This gender disparity in developing Asian countries could be linked to healthcare availability. Stroke in women is under-reported in South Asia, even though it is the top cause of mortality in women over the age of 60.[19] The mean age in our study was 48.87 years which was similar to study from Korea[20] and Italy[21] but was higher as compared to other larger studies.[22–25]

The onset type is variable among the studies. Many studies report acute onset to be more common, but Sidhom et al and Sassi et al demonstrate less often acute onset.[24,26,27] In a large number of patients, it may be the only complaint. 76.5 % of the 17 individuals had headaches, and it was the only symptom in 287 (25.1 %) of the patients in the previous studies.[30] Seizures are more common in CVT than in other forms of stroke, but the proportion varies between studies, ranging from 1.4 to 50.4 %.[25,31] Seizures occurred in 39% of participants in the ISCVT study, which is lesser than our results.[32] Seizures were documented less frequently in Terni et al's trials (6.9 %). [26]

MRI in combination with magnetic MRV has been proven to have the highest sensitivity and specificity in CVT diagnosis, despite CT being the basis of first examination and triage. Both MRI and MRV imaging was used as imaging modalities in our investigation. Digital subtraction angiography (DSA) although

is a gold standard for establishing the diagnosis of CVT, it was not used for diagnosis. The superior sagittal sinus (SSS) and sigmoid sinus were the most commonly impacted sinuses in our study, followed by the transverse sinus. This finding was in line with the findings of the ICVST study, which found that the SSS was the most usually impacted sinus (62%) followed by the transverse sinuses (41.2%) and the transverse sinuses (41.2%-44.7%), as well as some other studies.[13] Other studies, however, found that the transverse sinus with the sigmoid sinus (66.4 %) and the SSS were the two most common sites of thrombosis, similar to our findings (47.6%).[25] Multiple sinuses were found to be involved in 78.9% of cases, with the transverse sinus and sigmoid sinus being the most common combination.[33] Multiple sinuses were involved in 35.3 % of the individuals in our study.

Only one patient (6.67%) died of resistant raised intracranial pressure, while 86.7 % of those who were discharged had a good prognosis with a good functional outcome. This result is comparable to that of Wassay et al, who found that 3.3 % died and 55 % had a favorable functional outcome after discharge.[34] It was difficult to evaluate the long-term outcome because there were no reports of follow-up. In South Asian countries, stroke treatment and rehabilitation facilities, as well as follow-up mechanisms, are lacking. Despite these flaws, the result was satisfactory. Early detection and vigorous treatment, particularly endovascular thrombolysis, may help to reduce mortality and disability even more. In these emerging Asian countries, endovascular thrombolysis was essentially non-existent. Although there is no evidence from randomized trials, this method may have a role in patients who do not react to conventional anticoagulation[35,36].

Limitations: With all patients recruited from a single-center, it was a retrospective study with potential selection bias. Furthermore, the sample size was small. The disease's rarity could account for the small sample size. In diagnostic neuroimaging modalities, there is a lack of consistency. There was no follow-up information or imaging available. Furthermore, coagulation risk factors and prothrombotic diseases such as hyperhomocysteinemia and the prothrombin G20210A mutation were not explored in our patients due to their inability to pay for diagnostic tests. Despite these limitations, this is the first study from Nepal for over two years period of time. To highlight the overall characteristics of patients with CVT from Nepal, a large, prospective multicenter investigation is required.

CONCLUSIONS

CVT is an uncommon cerebrovascular disease. Although we could not find out various acquired or genetic reasons for CVT due to high cost, OCP usage, hypertension and systemic infections were the most common causes of CVT in this retrospective study. There was significant association of CVT with direct sign in CT scan (p=0.02), and ESR (p= 0.02).

Conflict of interest: None

NJHS

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