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Risk Factors and Outcome Variables of Cerebral Venous and Sinus Thrombosis in a Tertiary Care Hospital

Aasish, Vidyasagar Sudha**, Dantuluru Muralidhar V***, B Nandakrishna****, Holla Avinash*****, Cynthia Amrutha*****

Abstract

Introduction: Cerebral venous and sinus thrombosis (CVT) is one of the common causes of stroke in young people. It is a relatively uncommon neurologic disorder that is potentially reversible with prompt diagnosis and appropriate medical care. The purpose of this study is to identify the risk factors and outcome determinants.

Methods: A prospective observational study was conducted at a tertiary care centre in coastal Karnataka from November 2015 to May 2017. Demographic details, symptomatology and history pertaining to risk factors were noted. Outcome and prognosis were assessed by Modified Rankin Scale (mRS) at the time of admission and follow-up after 4 to 6 weeks. Chi-square test was used to compare mRS score at admission and follow-up in relation to outcome variables.

Results: A total of 45 adults with CVT were included. Males (53.3%) were more affected than females (46.7%), mostly in the 3rd decade. The most common risk factors were polycythaemia (31.1%) followed by oral contraceptive pill intake (17.7%). Based on mRS score at admission, 23 patients were functionally independent (mRS≤2) and 22 were functionally dependent (mRS > 2). At 6 weeks' follow-up 73.3% of the patients were functionally independent. Nine patients (20%) underwent decompressive craniotomy, of which seven patients improved, one deteriorated and one expired. The mortality rate was 2.2 %. Two patients were lost to follow-up.

Conclusion: The most common risk factors were polycythaemia followed by intake of oral contraceptive pills. Functional independence was achieved in 73.33% of patients at follow-up. The determinants of poor outcome were altered level of consciousness, presence of neurological deficits and intracerebral haemorrhage at the onset of illness.

Key words: Cerebral venous and sinus thrombosis, stroke, polycythaemia, mRS score.

Introduction

Cerebral venous and sinus thrombosis (CVT) is a type of cerebrovascular disease marked by thrombosis of blood in the cerebral veins, or dural sinuses, and cortical veins. CVT accounts for 0.5% of all strokes and its annual incidence is estimated to be 3 - 4 cases per 1 million population[1]. Strokes in the young account for nearly 30% of all cases of stroke in India and CVT accounts for 10 - 20% of these cases[2]. The mortality is relatively lesser compared with arterial stroke and most of the patients have a good long-term prognosis[3]. There are only few Indian studies on the risk factors, outcome and prognostic factors of cerebral venous thrombosis. The present study will assess the risk factors and outcome determinants of CVT.

Meterial and methods

This was a prospective observational study conducted at Kasturba Hospital, Manipal from November 2015 to May 2017. Data collection was commenced after obtaining ethical clearance certificate (IEC 635/2015) from Kasturba Medical College and Hospital Ethics Committee. A total of 56 patients diagnosed with CVT were considered for screening and enrolment into the study. Of these, 11 patients were excluded based on the exclusion criteria (patients with arterial infarcts and arterial malformations and those that developed as a result of diagnostic and treatment procedures that pierce the dura mater) and 45 patients with CVT of age greater than 18 years, radiologically proven either by CT/MRI brain with MR venography were included in our study after taking written informed consent.

Information regarding baseline patient characteristics, history pertaining to risk factors of CVT, such as intake of oral contraceptive pills, were compiled. All the patients underwent MRI brain with MR venography and treated in the intensive care unit with anti-epileptics, anti-oedema measures (mannitol, furosemide, and glycerol) and anticoagulation as per standard guidelines and protocols. Modified Rankin Scale (mRS) was used for measuring the degree of disability or dependence in the daily activities of living in our study. This scale describes 6 grades of disability (grade 6 denotes death; and grade 0 denotes no symptoms

**Junior Resident, **Professor, ***Associate Professor, ****Assistant Professor, *****Senior Research Fellow, Department of Medicine, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Udupi District, Karnataka - 576 104.*
Corresponding Author: Dr Sudha Vidyasagar, Professor Department of Medicine, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Udupi District, Karnataka - 576 104. Tel: 9880083580, E-mail: vsagar33@yahoo.com.

at all). mRS score of ≤ 2 was considered as functionally independent and score of > 2 was considered as functionally dependant. mRS score was documented at admission, at discharge and follow-up at 6 weeks.

Laboratory tests such as haemogram, serum homocysteine levels, antinuclear antibody tests and coagulation studies were done to identify the thrombophilia risk factors. Diagnosis of Polycythaemia Vera was made based on the WHO 2016 criteria[4]. Diagnosis of Antiphospholipid syndrome (APS) was made based on the revised Sapporo APS Classification Criteria (also called the Sydney criteria)[5]. Cut-off values for raised serum homocysteine levels were taken as > 15 mg/100 ml in those below 60 years, and > 20 mg/100 ml in those above 60 years of age[6].

Statistical methods

Data analysis and interpretation was done with Statistical Package for the Social Sciences (SPSS) version 15.0. The mean, standard deviation and Chi-square test was used to analyse the data and p value < 0.05 was taken as statistically significant. Chi-square test was used to compare mRS score at admission and follow-up in relation to age, gender, Glasgow Coma Scale (GCS) at presentation, presence of neurological deficits and intracerebral haemorrhage.

Results

A total of 45 patients were included in the study, of which 24 (53.3%) were males and 21 (46.7%) were females. Mean age of the patients was 36.13 ± 13.47 years with 31 (68.9%) patients below 40 years and 14 (31.1%) patients above 40 years of age.

The most common aetiology was polycythaemia (31.1%, n = 14) followed by intake of oral contraceptive pills (17.7%, n = 8), Antiphospholipid syndrome, pregnancy and puerperium, and hyperhomocystinaemia as shown in Fig 1. Out of 14 patients with polycythaemia, 7 (50%) were diagnosed with polycythaemia vera. The others had secondary polycythaemia with 5 (35.7%) having history of cigarette smoking and 2 (14.3%) having history of chronic obstructive pulmonary disease (COPD).

Outcome analysis

Based on mRS score at admission, 23 patients were functionally independent (mRS≤2) and 22 were functionally dependent (mRS>2) as shown in Table I. At 6 weeks, 100% of patients with mRS ≤ 2 at admission remained functionally independent with 65% (n = 15) returning from mRS 2 to mRS 0. Forty-five per cent (n = 10) of the patients with mRS >2 at admission recovered to mRS≤ 2 and were functionally

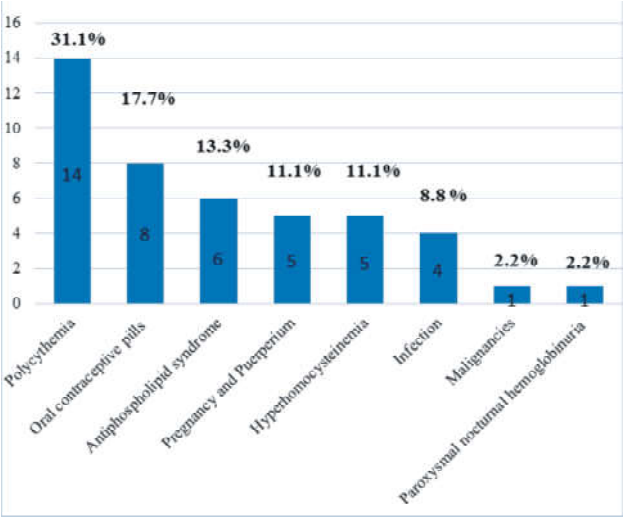

Fig. 1: *Risk factor analysis.*

independent at 6 weeks. Nine patients (20%) underwent decompressive craniotomy, of which seven patients improved, one deteriorated and one (2.2%) expired, which was probably due to cerebral oedema with transtentorial herniation. Two patients (4.4%) were lost to follow-up during the study. Last documented mRS score was taken for evaluation of patients lost to follow-up.

Table I: mRS scores of patients at admission and 6 weeks follow-up.

mRS score	At admission	Follow-up after 6 weeks
	No. of patients (%)	No. of patients (%)
≤2	23 (51.1%)	33 (73.3%)
> 2	22 (48.9%)	12 (26.6%)
Total	45	45 (93%)

In patients with baseline mRS ≤ 2 at admission, irrespective of age group, 100% remained functionally independent at 6 weeks follow-up. In patients with mRS > 2 at admission, age cut-off of 40 years was not a predictor of functional independence at 6 weeks follow-up. Age and gender showed no association with outcome as shown in Table II.

There were 15 patients (33.3%) with altered level of consciousness (2 patients in comatose state) at admission. Altered level of consciousness at presentation (i.e., GCS < 15) was associated with poor prognosis as the p value (0.003) was statistically significant. There were total of 19 patients (42.2%) with neurological deficits (11 had hemiparesis, 6 had paraparesis and 2 had quadriparesis). Presence of neurological deficits was associated with poor prognosis as the p value (0.034) was statistically significant. 13 patients (28.8%) had intracerebral haemorrhage at

admission. Presence of intracerebral haemorrhage was associated with poor prognosis as the p value (0.034) and was statistically significant.

Table II: Prognosis based on age and gender.

Demographic characteristics		mRS* ≤ 2	mRS* > 2	p value
Age < 40 years	Admission	18	13	p = 0.468
	Follow-up	24	7	
Age ≥ 40 years	Admission	5	9	
	Follow-up	9	5	
Males	Admission	8	16	p = 0.5
	Follow-up	16	8	
Females	Admission	13	8	
	Follow-up	17	4	

**Modified Rankin scale.*

Table III: Outcome based on GCS, neurological deficits and intracerebral haemorrhage status at admission.

		mRS ≤ 2	mRS > 2	p value
GCS < 15		6	10	p = 0.00005
GCS = 15		27	2	
Neurodeficits	Yes	9	102	p = 0.0007
	No	24	2	
ICH*	Yes	9	10	p = 0.0007
	No	24	10	

*ICH: Intracerebral haemorrhage

Discussion

The study revealed that a significant number of patients affected by CVT were in the 3rd decade of life with mean age being 36.13 ± 13.47 years, which was similar to the observations from various Indian and Western studies such as Pai *et al*[7], Narayan *et al*[8], Wassay *et al*[9] and Ferro *et al*[1]. Most of the earlier case series from India and Western studies like Wassay *et al*[9] and Ferro *et al*[1] have reported a higher proportion of women suffering from CVT, than men. This gender bias was usually attributed to gender specific risk factors like the usage of oral contraceptive pills (OCPs) and the influence of other factors such as pregnancy, puerperium, and hormone replacement therapy. In our study male gender was predominant (53.3%) which was consistent with the observations of recent Indian studies like Pai *et al*[7] (M: F - 3: 2) and Narayan *et al*[8] (M: F - 1.16: 1). The plausible reason for this change in gender trends over the last two decades could be due to usage of less thrombogenic oral contraceptive pills containing levonorgestrel and norethisterone in the recent years[7] or difference in healthcare availability to females.

The most common identified risk factors in our study were polycythaemia (31.1%) followed by intake of oral contraceptive pills (17.7%). Eight patients (17.7 %) had a history of intake of oral contraceptive pills (OCP) with mostly norgestimate and drospirenone as progestins. The incidence of oral contraceptive pills in the causation of CVT is gradually decreasing over the recent years due to the usage of less thrombogenic oral contraceptive pills (containing levonorgestrel and norethisterone).

Six patients (13.3%) were identified having antiphospholipid syndrome as a risk factor, of which 5 patients had primary antiphospholipid syndrome and 1 patient had secondary antiphospholipid syndrome with history of SLE in the past. There were a total of 5 pregnant and puerperal patients (11.1%) and all these patients developed CVT in their third trimester and puerperium, i.e, 6 weeks after delivery. The plausible reason was pregnancy being a hypercoaguable state, which induces several prothrombotic changes in the coagulation system and it worsens after delivery as a result of volume depletion and trauma. During the puerperium, additional risk factors which contribute to causation of CVT include infection and instrumental delivery or caesarean section.

Five patients (11.1%) were detected having hyperhomocysteinaemia and four patients (8.8%) were found to have infection as a risk factor and these infections were identified as paranasal sinusitis, tuberculous meningitis, chronic suppurative otitis media and severe dengue fever with hemoconcentration. One patient (2.2%) had essential thrombocytosis and one patient (2.2%) had paroxysmal nocturnal haemoglobinuria (PNH).

Pai *et al*[7], Narayan *et al*[8], Wassay *et al*[9] have shown that polycythaemia was the most common risk factor for the development of CVT. Ferro *et al* study[1] showed that oral contraceptive pills were the commonest risk factor. The risk of CVT among pregnant and puerperal patients in our study was almost similar to the above studies. The risk of infections leading to CVT was slightly higher than other Indian studies such as Pai *et al*[7] and Narayan *et al*[8]. The reason could be due to our hospital being situated in a rural area and lack of awareness about the significance of these infections among the people.

The risk of malignancy in the causation of CVT in our study was comparable with the other Indian studies such as Pai *et al*[7] and Narayan *et al*[8]; however, western studies like Wassay *et al*[9] and Ferro *et al*[1] have shown higher risk in comparison to Indian studies and the reason could be due to various dietary habits and malignancies being detected more common in developed countries than developing

countries. The incidence of hyperhomocysteinaemia in our study was almost similar with the results of other Indian studies such as Pai *et al*[7] and Narayan *et al*[8]; however, western studies such as Wassay *et al*[9] and Ferro *et al*[1] have shown lower risk and the reason could be due to higher incidence of vitamin B12 deficiency in the Indian population.

In our study, genetic thrombophilia markers such as protein C deficiency, protein S deficiency, antithrombin deficiency, and factor V Leiden (FVL) mutation were not tested due to the financial constraints of our patients, as the hospital being situated in a rural area and majority of patients belonged to low socio-economic standards. However, Pai *et al*[7], Narayan *et al*[8], Wassay *et al*[9] and Ferro *et al*[1] studies have showed that genetic thrombophilia contributes up to 18%, 12.3%, 10% and 22.4% for the causation of CVT, respectively.

Functional independence (assessed by mRS score ≤ 2) was achieved in 73.33 % of patients at 6 weeks of follow-up in our study. 9 patients (20%) underwent decompressive craniotomy, of which seven patients improved, one deteriorated and one expired probably due to cerebral oedema with transtentorial herniation. 14 patients (31.1%) required mechanical ventilation during the hospital stay. 2 patients (4.4%) were lost to follow-up during the study.

Patil *et al*[10] have shown that 84% of patients were discharged with partial and/or total recovery from illness in the form of hemiplegia or monoplegia. 3 patients (6%) underwent decompressive surgery, of which 2 patients improved and 1 succumbed. Eight patients (16%) died with cerebral oedema with transtentorial herniation. Thota Naveen *et al*[11] have shown that 20% of patients underwent decompressive craniectomy as the part of the treatment. 35 (70%) of the 50 patients had complete functional recovery, 9 (18%) had partial recovery independent, 3 (6%) had partial recovery dependent, whereas 3 (6%) died during the hospital stay.

Natarajan *et al*[12] have shown that 43 out of 48 patients (89.6%) recovered without any neurological disability; 2 out of 48 patients (42%) were discharged with minimal residual paresis. Total mortality in their study was 6.2%, i.e., 3 patients expired. Ferro *et al* have shown that 86.6% of the patients recovered without any neurological disability (mRS score ≤ 2). 52 patients (8.3%) had expired. 9 patients (1.4%) had decompressive craniotomy or hematoma evacuation and 7 (1.1%) required mechanical ventilation.

Our study has shown that gender and age have no association with the outcome of patients with CVT. Altered level of consciousness at presentation, presence of neurological deficits and intracerebral haemorrhage were associated with poor outcome. Ferro *et al* also showed that important prognostic factors for poor outcome were age > 37 years, male sex, coma on admission, mental status disorder, intracerebral haemorrhage on admission CT scan of the brain, which were similar to our study. Wassay *et al* study[9] also showed that altered level of consciousness at presentation and intracerebral haemorrhage were the strongest predictors of poor outcome in CVT.

Conclusion

The most common identified risk factors were polycythaemia followed by the intake of oral contraceptive pills. Functional independence, assessed by mRS score of ≤ 2, was achieved in 73.33 % of patients at follow-up. The mortality rate was 2.2%. The determinants of poor outcome in CVT were altered level of consciousness at presentation, presence of neurological deficits and intracerebral haemorrhage.

Strengths of study: All the patients in our study underwent MRI brain with MR venography and the abnormalities in the cerebral venous system were documented and confirmed by qualified radiologists. Majority of the patients were followed-up for 4 to 6 weeks and their functional neurological status was reassessed.

Limitation of study: Our hospital being situated in a rural area and most of the patients belonged to low socio-economic standards, genetic prothrombotic factors leading to cortical vein thrombosis was not evaluated due to financial constraints.

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