Original Article

Relevance of Geographical and Biochemical Factors in Causation of Cerebral Venous Sinus Thrombosis: An Observational Analytical Study

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Abstract

Objectives: There is a higher prevalence of cerebral venous sinus thrombosis (CVST) in more recent times, owing to increased awareness, clinical diagnostic skills, and advancements in neuroimaging modalities. This study aimed to identify and characterize the geographical, clinical, and etiological profiles of patients with CVST that may be relevant to planning appropriate diagnostic and therapeutic strategies to improve functional recovery. **Methods and Results:** A retrospective observational study was carried out at a tertiary care hospital between March 2014 and October 2018. The demographics and clinical profile of the hospitalized patients were extracted from the Medical Record Division. Choropleth maps were created to present the geographic distribution of the patients with CVST admitted to our hospital. A total of 145 patients with CVST were included in the study. Etiological factors revealed striking abnormalities in red blood cells counts and serum homocysteine. Analyzing the geographical distribution of the patients with CVST showed most of the patients hailed from Central Karnataka Plateau 106 (73%). Polycythemia was most commonly seen in patients residing in the Central Karnataka Plateau 21 (62%). **Conclusion:** It is inferred that large scale community-based studies to identify a genetic abnormality like a mutant erythropoietin gene should be undertaken to plan effective diagnostic, therapeutic, and preventive measures.

Keywords: Choropleth maps, CVST, genetic predisposition, polycythemia

Introduction

Cerebral venous sinus thrombosis (CVST) is an infrequent cause of stroke in the developed world with ~0.5% of all stroke types.[1] But it is not so rare in India.[2] CVST most commonly affects young adults and children[3] and is responsible for 10-20% of young strokes in India.[4]

Many acquired causes like anticardiolipin antibodies, systemic lupus, antiphospholipid syndrome, thrombophilia, inflammatory bowel disease, pregnancy, puerperium, oral contraceptives, substance abuse, and head trauma predispose to CVST.[5,6] Inheritance of prothrombotic conditions like Factor V Leiden mutation, Protein C and S deficiency, antithrombin III and prothrombin gene mutation explain 10-15% of cases of CVST.[7] There is a huge knowledge gap in the elucidation of etiological factors in respect of CVST. In 2004, the largest international multicenter trial of CVST consisted of very few patients from Asia and Africa.[8] Enhanced clinical diagnostic skills and advances in neuroimaging have heightened awareness and enabled early diagnosis of CVST.[9,10]

Genetic makeups of an individual and geographical location are the two important epidemiologic variables. There is a lack of well-designed large-scale population-based studies from the South Asian region in general and the Indian subcontinent in particular. It is very important to correlate CVST prevalence with the geographical location so that further studies can focus on high prevalent areas to study genetic mutations and other important variables. In this retrospective study, the geographical location and other important predisposing factors of CVST were analyzed. The correlation between geographical location and predisposing factors in that location was developed to identify potential issues for future studies.

Methodology

This is a retrospective observational study carried out at a tertiary care hospital. All CVST patients of either gender diagnosed by magnetic resonance imaging (MRI) of the brain

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Submitted: 24-Dec-2021 **Revised:** 22-Apr-2022 **Accepted:** 23-Apr-2022
Published: 14-Jul-2022

DOI: 10.4103/aian.aian_1109_21

with magnetic resonance venography (MRV) between March 2014 and October 2018 were evaluated retrospectively. The profile of the study patients was extracted from the Medical Records Division (MRD) registry using the International Classification of Disease (ICD) code G08. Individuals with no record of neuroimaging and those with other forms of stroke were excluded. The study protocol was approved by the Institutional Ethics Committee (IEC 367/2018).

A total of 145 patients were evaluated. A Case Record Form (CRF) was developed and checked by local experts for its appropriateness. Patient's demographical characteristics, medical history, medication history, time of onset of symptoms, vital signs, reports of laboratory investigations, imaging reports Computed Tomography (CT), MRI/MRV, and prognosis at discharge were recorded in the CRF.

Statistical analysis

Choropleth maps were created to present the geographic distribution of the patients with CVST admitted to our hospital in the state of Karnataka, India. Choropleth maps were created using freely available software R version 3.5.2. Statistical Package for the Social Sciences (SPSS) version 15.0 (SPSS South Asia, Bangalore) was used to analyze all relevant variables, except for creating the choropleth maps. Quantitative and qualitative variables were described using Mean ± Standard Deviation (SD) and frequency (percentage), respectively.

Results

A total of 145 patients with CVST were evaluated. Mean age of the individuals was found to be 34.51 ± 11.59 years (Mean ± SD). Mean length of hospitalization was observed to be 11.04 ± 5.12 days (Mean ± SD). Gender-wise distribution showed a male predominance of 102 (70%). It was shown that 75 (52%) of the patients were presented to this institute within 1-10 days of symptoms onset [Table 1]. In 35 (24%) of the patient's alcohol consumption history was elicited.

The geographical distribution of patients with CVST in the state of Karnataka is depicted in [Table 2]. The district-wise distribution of cases, percentage spatial distribution of polycythemia cases, and gender distribution are shown in Figure 1(a, b, c, and d).

Important clinical features included headache in 117 (81%), papilledema in 64 (44%) and seizures in 49 (34%) patients [Table 1]. Polycythemia and Hyperhomocysteinemia (Hhcy) emerged as an important risk factor [Table 3]. Janus Kinase 2 (JAK-2) mutation assessment could be done in only seven patients with polycythemia (7 out of 34), and it was found positive in two patients. The inability to perform mutation assessment in the rest of the patients is because of the financial constraints as this investigation is outsourced.

Various sinuses involved in disease processes are illustrated in [Figure 2] and superior sagittal sinus involvement is observed more often. One hundred and twenty-nine patients (89%) were treated with oral anticoagulants. A total of 129 (89%) of the patients showed good functional outcomes on the modified rankin scale (mRS) score and 15 (10%) of the patients had an unfavorable outcome (mRS -5). Recurrent CVST was seen in 13 (9%).

Discussion

The key findings of this study are 1) majority of the patients with CVST admitted hailed from Central Karnataka Plateau, 2) polycythemia and Hhcy were more frequently associated with CVST, and 3) polycythemia was found to be more prevalent in 21 (62%) of the patients residing at the Central Karnataka Plateau (altitude >500 m).

The etiological factors for CVST are more than one and they vary from region to region. CVST is frequently encountered at higher altitudes and polycythemia is observed in these cases. High Altitude Polycythemia develops in residents in the plateau of the hypoxia environment (>3200 meters) and is mostly attributed to hypoxia but the underlying molecular mechanisms are not clear.[11,12] Some molecular mutations are likely to confer a protective mechanism and others more susceptibility. In these cases, polycythemia could be due to relative hypoxia and/or genetic predisposition (JAK-2 Mutation).[13] The Chorographic (physiographic) distribution of the state of Karnataka can be divided into four landforms: The Northern Karnataka Plateau; The Central Karnataka Plateau (Districts: Bellary, Chikmagalur, Chitradurga, Davanagere, Haveri, Shimoga); The Southern Karnataka Plateau (District: Mysore); and The Coastal Karnataka Region (Districts: Udupi, Dakshina

Table 1: Demographic Characteristics of 145 patients with Cerebral Venous Sinus Thrombosis (CVST)

Demographic Characteristics	Number of Patients (%)
Age in Years	34.51±11.59 (Mean±SD)
Gender	
Male	102 (70.3%)
Female	43 (29.7%)
Mean Length of Hospitalization	11.04±5.12 days
Symptoms Duration Before Diagnosis (days)	
1-10	75 (51.7%)
11-20	13 (8.96%)
21-30	10 (6.89%)
>30	14 (9.65%)
Social Habits	
Alcohol Consumption History	35 (24.1%)
Smoking History	13 (9%)
Tobacco Chewing History	6 (4.13%)
Clinical Features	
Headache	117 (80.7%)
Papilledema	64 (44.1%)
Seizures	49 (33.8%)
Altered Sensorium	15 (10.3%)
Aphasia	3 (2.06%)

SD=Standard Deviation

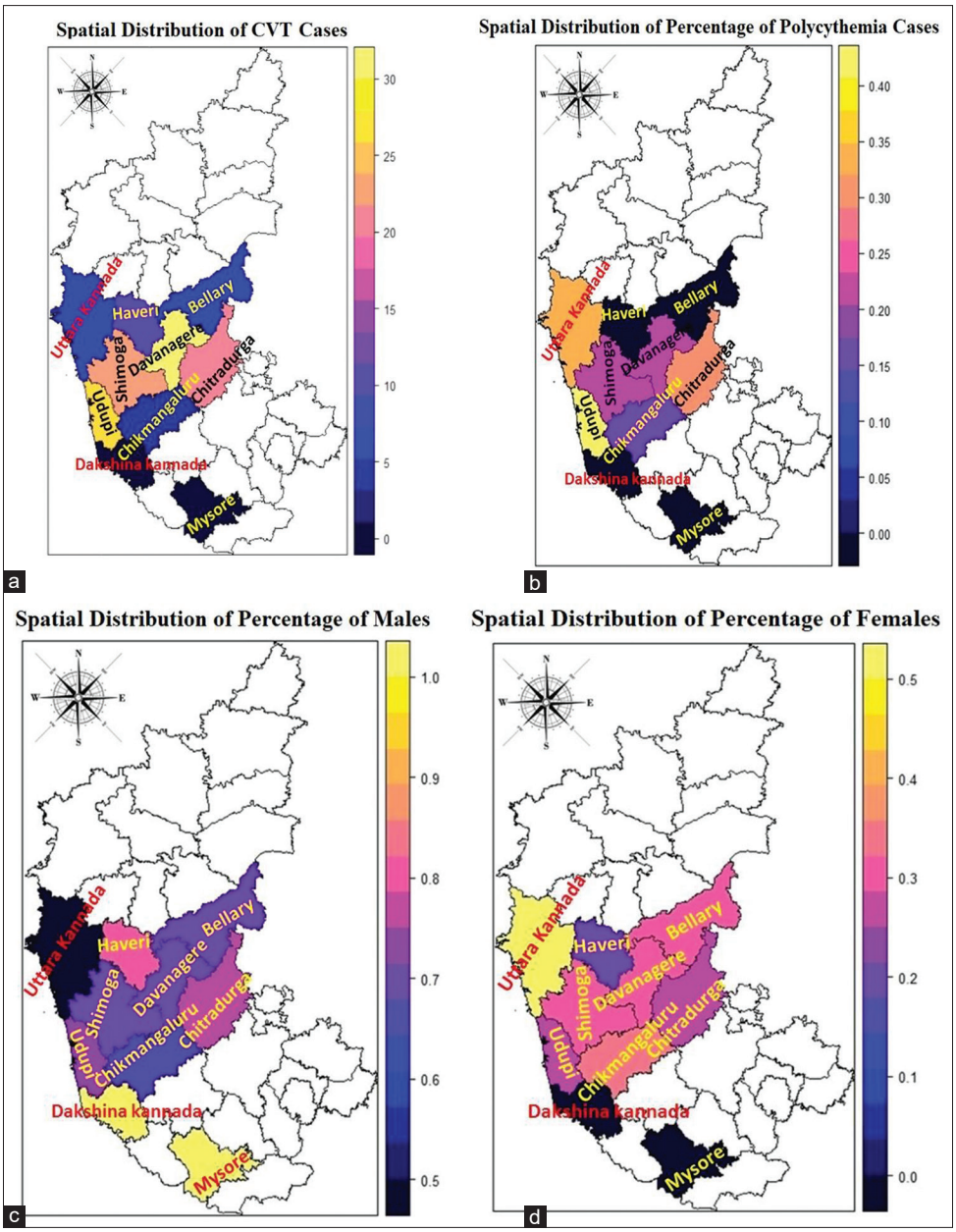

Figure 1: a, b, c, d: Geographical Distribution of 145 Patients with CVST

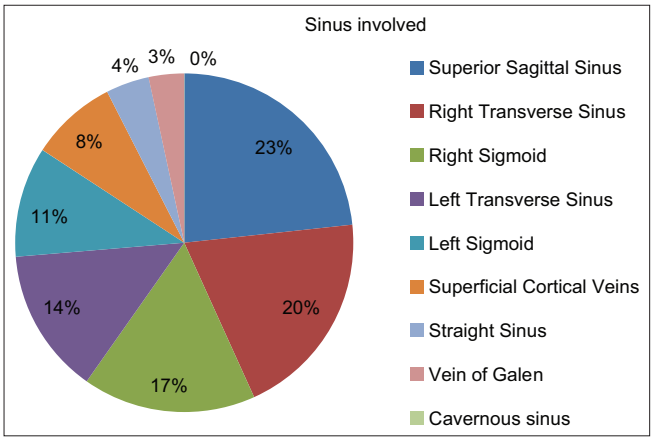

Figure 2: Distribution of Involvement of Various Sinuses in patients with CVST

Kannada &Uttara Kannada).[14] Analyzing the geographic distribution of the patients with CVST in the present study showed that 73% hailed from Central Karnataka Plateau and 23% from the Coastal Karnataka Region.

CVST is a disease of young adults and in observational analytical studies both from India and the west including the present study, the mean age is falling between 30-45 years.[9,10,15] Sex-specific differences in risk factors and increased use of oral contraceptives were traditionally explained by female preponderance in the ratio of 2.2:1.[7,15,16] However, there is a striking male preponderance in the current study. Only referral bias could not account for it. In addition, is there any non-modifiable gene mutation in Esp. Erythropoietin gene which could account for this striking variability in

Table 2: 145 CVST cases: Geographical location and altitude above sea level

Physiographic Distribution – State of Karnataka	Districts	Altitude (meters) Above the Sea Level	Number of Patients (%)
The Northern Karnataka Plateau	Nil	--	Nil
The Central Karnataka Plateau	Chikmagalur	1,090	6 (4.13%)
	Chitradurga	732	20 (13.79%)
	Davanagere	587	40 (27.58%)
	Haveri	571	10 (6.89%)
	Shimoga	569	23 (15.86%)
	Bellary	485	7 (4.82%)
The Southern Karnataka Plateau	Mysore	763	1 (0.68%)
The Coastal Karnataka Region	Udupi	27	27 (18.6%)
	Dakshina Kannada	22	1 (0.68%)
	Uttara Kannnada	500	6 (4.13%)

CVST=Cerebral Venous Sinus Thrombosis

Table 3: The Risk Factor Profile Observed in 145 Cases of CVST

Risk Factors	Number of Patients	Percentage
Polycythemia	34	23.4%
High Homocysteine Levels	28	19.31%
ANA - Profile	12	8.27%
ANA - Global	07	4.82%
Puerperium	07	4.82%
APLA	04	2.8%
ANCA	02	1.37%
OCP Use	01	2.3%

CVST=Cerebral Venous Sinus Thrombosis, ANA=Antinuclear Antibody, APLA=Antiphospholipid Antibody, ANCA=Antineutrophil Cytoplasmic Antibodies, OCP=Oral Contraceptive Pills

gender distribution differences? CVST has varied clinical presentations from headache to stupors or comatose.[17] Aneesh *et al*.[18] reported the most common presenting symptom in men was seizures followed by headache and in women, it was headache followed by vomiting. In the current study, headache was the most common presenting symptom in both men and women. High altitude dwelling means more than 3000 meters and where hypoxia conditions predispose to polycythemia, Ferro *et al*.[8] reported thrombosis as a serious complication of polycythemia. It is very well established that hypoxia that occurs at high altitude promotes venous thromboembolism (VTE) by coagulation activation with an increase in systemic inflammation. In the present study, significant polycythemia was associated with CVST at less than 1000 meters altitude. The highest altitude seen in this study was 1,090 m above the sea level and100 (69%) of patients with CVST hailed from altitudes between above 500 and 1000 meters, and this preponderance could not be ascribed only to secondary causes of polycythemia. Is there any gene mutation (mutant erythropoietin gene) that confers a protective mechanism and less susceptibility to polycythemia?

The normal serum homocysteine level ranges between 5.46 – 16.20 µmol/L. Hhcy is an independent and strong risk factor for CVST, which is present in 27-43% of the patients and in 8-10% of people in the community.[19-21] Martinelli *et al*.[19] concluded that Hhcy increases the risk of CVST by approximately four-folds. The prevalence of Hhcy is 19-24% in Indian studies.[22] Similarly in the present study, Hhcy was present in 28 (19.31%) patients. Since there was no history of thrombosis in abnormal sites or positive family history, the procoagulant factors like Protein C, Protein S, and Antithrombin III were not done in all the patients and were performed only in two patients which were normal.

The major limitation of this study could be selection bias in that esp. Berkson's bias. The study patients do not reflect the true rate or severity of the condition in the population. Though the relationship between exposure and the disease is likely to be unrepresentative of the population, there is still a strong trend toward the geographic and mutant gene connection which suggests more studies to identify the culprit gene. The other bias that could affect the inferences of this study could be the Incidence/Prevalence bias (Nyman bias). It affects the study as there is a time gap between exposure and the actual selection of the study population in this retrospective analysis. It is possible that some individuals with exposure are not available for analysis. Despite the setbacks of a retrospective study, there is a strong suggestion requiring large scale community-based genetic studies of CVST in this geographical location.

Conclusion

The main inference that can be drawn from this study is that a hitherto unknown genetic influence is predisposing to polycythemia and Hhcy in a geographical location with an altitude up to 1000 meters. It is observed that hypoxia or other secondary factors alone cannot explain the high prevalence of these two risk factors which may have a genetic influence. A large community-based genetic study of CVST cases may help to elucidate the mutant gene paving way for planning effective diagnostic, therapeutic, and preventive strategies.

Acknowledgement

Dr. Kurupath Radhakrishnan, Department of Neurosciences, Avitis Institute of Medical Sciences, Nemmara, Palakkad - 678 508, Kerala, India.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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