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Original Article

The Effects of Temperature and Prothrombotic Conditions on Cerebral Venous Sinus Thrombosis Frequency: An Institutional Experience

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Abstract

Objectives: The pathogenesis of cerebral venous sinus thrombosis (CVST) is complex and involves the interplay of underlying provocative factors. Upon observing a higher frequency of CVST cases presenting to our hospital in summer, we hypothesized that CVST may be influenced by variations in climate. **Materials and Methods:** A retrospective review of all patients who were diagnosed with CVST at a tertiary care hospital in Pakistan between January 2010 and December 2019 was conducted. After dividing patients into groups based on the type of risk, the frequency of CVST in these groups between four seasons (spring, summer, fall, and winter) was compared. **Results:** A total of 256 patients diagnosed with CVST were included, of which 129 were female and 127 were male. The mean age was 41.7 ± 15.2 years. Of the total patients, 91.4% had some sort of risk factor, either systemic (162 patients) or local (72 patients), while 22 patients did not have any identifiable risk factor. The number of patients with more than one known risk factor was 93 (36.3%). Of the total number of patients, 96 (37.5%) patients had hyperhomocysteinemia, followed by 85 patients (33.2%) with a prothrombotic risk factor other than hyperhomocysteinemia and 44 (17.2%) patients with central nervous system infections. The most commonly affected sinuses were a combination of the transverse sinus and sigmoid sinus (21%), There was a statistically significant seasonal variation in CVST cases among all patients ($P = 0.03$) and in the systemic risk factor group ($P = 0.05$), with the highest number of cases occurring in the summer season. **Conclusions:** CVST may be influenced by seasonal changes in atmospheric temperatures and humidity, especially in patients with underlying prothrombotic risk factors.

Keywords: *Cerebral venous sinus thrombosis, prothrombotic, temperature*

Introduction

Cerebral venous sinus thrombosis (CVST) is a rare cause of stroke that includes thrombosis of the dural venous sinuses and cortical or deep cerebral veins. CVST is a separate clinical entity from arterial stroke with some key differences – it is markedly less frequent than arterial stroke, affects younger female patients, has a variable clinical presentation, is more difficult to diagnose, and has a distinct set of provocative factors.[1] The global annual incidence of CVST was estimated to be 3–5 cases per million;[2,3] however, more recent data suggest higher rates of 12–16 cases per million from high-income countries (HICs)[4,5] and low- and middle-income countries (LMICs)[6-8] alike. The increased incidence can be ascribed to the emergence of improved diagnostic and imaging modalities for CVST, especially in HICs.[4,9] Differences in the quality of postpartum care, persistence of infectious etiologies,[10] genetic variability and variation in seasons,[6] temperature, humidity, and altitude[11] might explain the higher incidence of CVST in LMICs.

A variety of congenital and acquired risk factors for CVST have been identified [Table 1].

The International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) revealed thrombophilia (genetic or acquired) and the use of oral contraceptives to be the most common risk factors for CVST. Only 12.5% of patients did not have any identifiable risk factors.[12]

While the pathogenesis of CVST is complex, it likely involves elements from Virchow's triad (i.e., venous stasis, vascular injury, and hypercoagulability) that are implicated

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Table 1: Risk factors for cerebral venous sinus thrombosis

Local risk factors
Brain tumor
Central nervous system infection
Other head-and-neck infections (mastoid, ear, sinus, nose, face, skull)
Head and/or neck trauma
Recent neurosurgical procedure
Systemic risk factors
Acquired
Malignancy (other than the brain)
Systemic infection
Oral contraceptive use and hormone replacement therapy
Pregnancy and/or puerperium
Hyperhomocysteinemia
Autoimmune disease (e.g., Systemic lupus erythematosus)
Antiphospholipid antibody positive
Vasculitides (e.g., Behcet disease)
Inflammatory bowel disease
Nephrotic syndrome
Inherited
Factor V leiden mutation
Protein C deficiency
Protein S deficiency
Antithrombin III deficiency
APC resistance

APC – Activated protein C

in the development of deep venous thrombosis (DVT).[13] Dehydration may promote venous stasis through mechanisms such as hemoconcentration. While dehydration has been widely assumed to play a role in the pathogenesis of DVT, it has also been identified as a potential risk factor for CVST.[10,14,15] People living in arid and hot regions such as Karachi may be susceptible to dehydration. Over the last few years, we have observed more cases of CVST being diagnosed at our hospital in the summer months. We aim to explore this relationship further and determine if the frequency of CVST cases follows a seasonal pattern.

Materials and Methods

After approval and exemption from our institution's Ethical Review Committee a retrospective chart review of patients who were diagnosed with CVST at the Aga Khan University Hospital (AKUH), Karachi, Pakistan, was conducted. Medical record numbers of all adult (>18 years of age) patients with an International Classification of Diseases (ICD)-9 coded diagnosis (disease code 325: Phlebitis and thrombophlebitis of intracranial sinuses) of CVST from January 2010 to December 2019 were obtained from the health information management systems department. All adult patients with the first episode of CVST diagnosed at AKUH were included. The diagnosis of CVST was made on clinical grounds (presenting symptoms and neurological examination) and supported by imaging findings on magnetic resonance imaging, magnetic resonance venography, computed tomography venography, and angiography. Patients who had a history of prior CVST episode(s), those who were diagnosed outside of AKUH, and those who did not have convincing evidence of CVST on imaging were excluded from the study.

Patients were divided into different groups based on the risk factors they possessed [Table 1]. Patients who did not have any identifiable risk factors for the development of CVST were placed in the group titled "None." Those who had any local risk factors were placed in the group titled "Local," while those with acquired or inherited prothrombotic conditions were placed in the group titled "Systemic" [Table 1].

Seasons were divided according to the Gregorian calendar into spring (March, April, and May), summer (June, July, and August), fall (September, October, and November), and winter (December, January, and February). The average temperature and dew point (which is a measure of humidity) were extracted for each month from January 2010 to December 2019 from historical climate data acquired from the Jinnah International Airport Station, Karachi.

Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) was used for statistical analysis of the data. P <0.05 was considered significant. Pearson's Chi-squared test was used to determine if the difference in frequency of CVST was significant between different seasons and months. The Chi-squared test was used to evaluate differences in sex and presenting symptoms between seasons. Analysis of variance was used to evaluate differences in age between seasons.

Results

Patient characteristics

A total of 293 patients were identified through the initial search of AKUH's patient database using the relevant ICD codes. We excluded 37 patients based on the exclusion criteria. Of the 256 patients that were included, 127 were men and 129 were women. Their mean age was 41.7 years ± 15.2 years, with a minimum age of 19 years and maximum age of 85 years. Age and sex were computed for each risk group and are displayed in Table 2. Although age and sex varied significantly across the different risk groups, they were not statistically different when analyzed according to seasons and months (not shown in Table 2).

There were 234 patients (91.4%) with underlying risk factors and 22 patients (8.6%) without any identifiable risk factors; 162 patients (63.2%) had systemic prothrombotic risk factors and 72 patients (28.1%) had local risk factors.

Involvement of sinuses

Over 60% of patients had involvement of more than one cerebral venous sinus. The most common combination of

sinuses was transverse sinus and sigmoid sinus (21%), followed by superior sagittal sinus, transverse sinus, and sigmoid sinus (18%) and superior sagittal sinus and transverse sinus (12%). Some patients had involvement of a single sinus – 7% of patients had involvement of the transverse sinus, followed by the sigmoid sinus (6%) and cavernous sinus (6%).

Seasonal, annual, and monthly variations in the frequency of cerebral venous sinus thrombosis

The frequency of CVST cases according to the season is shown in Table 3 and Figure 1. Summer had the highest number of cases, followed by winter, fall, and spring in all patients and the systemic risk factor group. This result was statistically significant in both the groups (P = 0.03 and P = 0.05, respectively). When considering all patients, approximately 1.35 times more CVST cases occurred in summer compared to winter. The order of seasons after summer was different in the local risk factor group and the group without risk factors, but summer still had the highest number of cases. However, these results were not statistically significant (P = 0.6 and P = 0.2).

Even though CVST frequency was highest in the summer months of June, July, and August and, to a lesser extent, in the winter months of October, November, and December, the difference in CVST frequency across individual months was not statistically significant.

We also observed an increase in the number of hospital admissions for CVST in our hospital over the study period [Figure 2], with frequent annual peaks in the summer season.

Table 2: Patient demographics according to risk group

Variable	All patients	Systemic	Local	None
Gender, *n* (%)				
Male	127	65	52	10
Female	129	97	20	12
Age, years, mean±SD	41.7±15.2	38.5±13.0	46.5±17.8	49.1±15.5

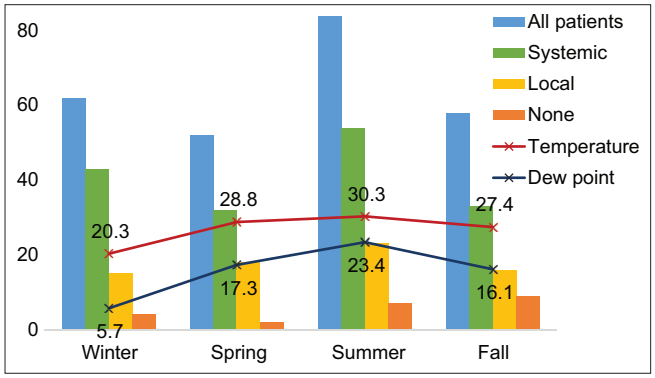

Figure 1: Distribution of cerebral venous sinus thrombosis cases according to seasons. The bar graph indicates a significantly higher value during summer as compared to the other seasons

Climate data

The mean temperatures for each season are presented in Table 3. Summer was the hottest season with a temperature of 30.3°C, followed by spring which was 1.5°C cooler (P = 0.001). Similarly, the dew point was highest in the summer season (P = 0.001). May, June, and July were the only 3 months with a temperature above 30°C, but June, July, and August were the only months with a dew point above 23°C.

Risk factors

There were 93 (36.3%) patients who had more than one risk factor. The most common risk factor in our patient population was increased levels of homocysteine which was present in 96 (37.5%) patients. Furthermore, 85 (33.2%) patients had an acquired or inherited prothrombotic condition other than hyperhomocysteinemia and 44 (17.2%) patients had a central nervous system (CNS) infection. Of the women, 6 (4.7%) had a documented history of oral contraceptive (OCP) use and 26 (20.2%) were either pregnant or in puerperium.

Discussion

There are two main mechanisms by which CVST has deleterious effects on the brain parenchyma. First, occlusion of the cerebral veins leads to localized brain edema and venous infarction. The second mechanism involves occlusion of the major venous sinuses which impairs the absorption of cerebrospinal fluid, leading to increased intracranial pressure.[2] It is challenging to categorize CVST risk factors into discrete subsets because of the complex nature of CVST pathogenesis and presence of multiple risk factors. The percentage of patients with multiple risk factors has ranged from 36% to 44% in the literature.[12,16] We found a similar percentage of 36.3%. While systemic prothrombotic states may contribute to all three elements of hypercoagulability, venous stasis, and vascular endothelial injury, the mechanism of CVST development after local or mechanical injury may be different. Mechanical causes such as head injury can lead to injury to the sinus endothelial lining and compression or deformation of the

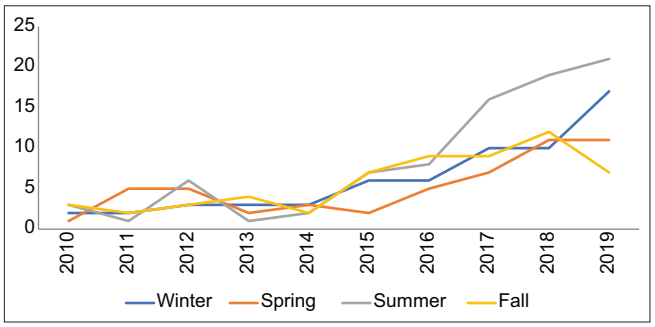

Figure 2: Plot of annual frequency of cerebral venous sinus thrombosis cases over the study period (2010–2019) according to seasons, indicating an increase in the overall number of cerebral venous sinus thrombosis cases over time and peaks in the summer season

Table 3: Seasonal frequency of cerebral venous sinus thrombosis cases; temperature, and dew point

Risk factor group	Frequency per group	Frequency of CVST cases per season				*P*
		Winter	Spring	Summer	Fall	
All patients	256	62	52	84	58	0.03
Systemic	162	43	32	54	33	0.05
Local	72	15	18	23	16	0.6
None	22	4	2	7	9	0.2
Temperature (°C)		20.3	28.8	30.3	27.4	0.001
Dew point (°C)		5.7	17.3	23.4	16.1	0.001

CVST – Cerebral venous sinus thrombosis

venous walls.[17,18] CNS and head-and-neck infections can lead to thrombosis of the adjacent sinuses and impair the absorption of cerebrospinal fluid.[2] Therefore, we divided patients based on systemic prothrombotic states (both acquired and inherited) and local/mechanical CVST risk factors to best assess the additive effect of dehydration (because of high temperatures and humidity).

Seasonal variation in incidence has been reported for diseases such as cellulitis, appendicitis, diverticulitis, cholecystitis, and surgical site infections.[19-22] Similarly, there are a handful of studies examining the seasonal variation in the frequency of CVST with varying results, however none with divisions based on risk factors. Our data show a significant seasonal association of CVST cases among all patients and among the patients within the systemic risk factor group. This association was not significant in the local risk factor group and among the very small percentage (8.6%) of patients without any identifiable risk factors. The highest number of CVST cases was observed in the summer season, with a smaller peak in the winter season. An analysis of two main hospitals in Tehran, Iran, showed the greatest frequency of CVST cases from July to September and the lowest frequency from December to April.[23] However, another study in a different Iranian city (Isfahan) showed the highest frequency of CVST cases in autumn.[6] Ferro *et al*. similarly found that the highest number of CVST cases occurred in autumn and winter in Portugal.[24] In their analysis of a German cohort of patients with CVST, Stolz *et al*. observed a bimodal trend with peaks in both summer and winter.[25] More recently, Aaron *et al*. have also observed a significantly higher frequency of CVST cases in the summer in India.[26]

It has been suggested that the winter peak can be explained by the increase in viral or bacterial upper respiratory tract infections triggering CVST in susceptible individuals.[24] Some studies examining factors associated with pulmonary, coronary, and cerebral thromboses have shown higher blood levels of C-reactive protein, D-dimer, platelets, fibrinogen, and Factor VII and increased blood viscosity during winter.[27,28] Lim *et al*. found a U-shaped association between temperature and markers of dehydration (serum blood urea nitrogen/creatinine, urine specific gravity, plasma tonicity, and blood hematocrit) with an increased risk of dehydration in both hot and cold temperatures.[29] On the other hand, summers in Karachi are notorious for extremely high ambient temperatures and increased morbidity and mortality from heatstroke and severe dehydration.[30-32] In addition to dehydration, hyperthermia resulting from passive exposure to heat leads to the release of endotoxins from intestinal mucosal cells. Hyperthermia also causes release of certain interleukins (IL-1 and IL-6). These chemical mediators are released into the systemic circulation, causing systemic inflammatory response syndrome.[33] The widespread inflammatory response along with the direct effects of heat causes injury to the endothelial cells of blood vessels[34] and may predispose susceptible patients to developing CVST.

Our study revealed almost equal number of men and women who were diagnosed with CVST, although we noticed a female to male ratio of 1.5:1 in the systemic risk factor group. This could be because the systemic risk factor group included women who were pregnant or had recently delivered, as well as those who were using OCPs. While the ISCVT[12] reported a female dominance of 70%, a large multinational study of CVST in Asia[35] showed a lower percentage of female patients.

Several CVST studies have found a significant proportion of patients (between 20% and 40%) with hyperhomocysteinemia,[10,35,36] with an estimated fourfold increased risk of CVST.[37] The reported rates of women diagnosed with CVST during pregnancy or puerperium in India, Pakistan, and the Middle East have been between 30% and 31%,[10,36] while 14% had a history of OCP use.[36] In the West, the incidence of peripartum CVST is 5%–26% and the association with OCP use is found to be between 54% and 71%.[12,38,39] Our study showed that 20% of women were diagnosed with CVST during pregnancy or puerperium and only 4.6% had documented OCP use. These differences in findings can be attributed to various factors such as cultural and traditional practices involving pregnancy (home births in unhygienic conditions and traditions involving water deprivation during the postpartum period),[36] higher birth rates, and lack of OCP awareness and use in the South Asian region.

Our study has certain limitations, partly due to its retrospective nature. We cannot exclude the possibility that

there was incomplete ascertainment of some cases – such as patients who were miscoded and those who were excluded due to incomplete medical history. On the other hand, carrying out this study at a tertiary care hospital was advantageous for several reasons. Our patients underwent evaluation (including imaging) according to best practices and current technology. In addition, most of the patients with suspected underlying risk factors went through a uniform hypercoagulability workup. This allowed us to search for risk factors extensively and accurately, reflected by the fact we were able to identify risk factors in more than 90% of our patients.

Conclusion

Our data and observations show that seasonal effects play a role in the development of CVST and may enhance the effects of other predisposing conditions, such as systemic prothrombotic states. We believe that our study adds information to the relatively small pool of data studying seasonal variations in CVST frequency. More studies are needed from countries around the world to assess the effects of climate and geography on CVST pathogenesis as this may aid physicians in anticipating the diagnosis of CVST during certain months and seasons.

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Conflicts of interest

There are no conflicts of interest.

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