



Ten-year Causes of Cerebral Venous Sinus Thrombosis in Patients Referred to Ghaem Hospital from 2009 to 2019

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Received: October 13, 2023

Revised: December 13, 2023

Accepted: December 27, 2023

ABSTRACT

Objective: Cerebral Venous Sinus Thrombosis (CVST), a complex and infrequent cerebrovascular disorder characterized by the formation of clots within the cerebral venous sinuses, occurs as a result of multiple risk factors and casualties, and its epidemiological picture should be investigated.

Methods: This descriptive study was conducted retrospectively on patients with a final diagnosis of cerebral vein thrombosis, who were referred to the emergency room of Ghaem Hospital (Mashhad, Iran) between 2009 and 2019. The study included all patients with cerebral vein thrombosis who were older than 18 years. Clinical symptoms and causes were documented and contrasted according to demographics.

Results: During the 10 years of this study, 749 cases of cerebral vein thrombosis were observed, with women accounting for the majority (72.8%). The most prevalent symptom was headache (554 cases; 74.0%), followed by seizures (23.1%), blurred vision (16.0%), nausea (7.5%), vomiting (6.9%), double nose (4.9%), and dizziness (3.3%). There was no significant difference in the frequency of symptoms between the two genders ($p < 0.05$). The most commonly identified risk factors were OCP (110 cases; 14.7%), followed by infection (103 cases; 13.8%), malignancies (78 cases; 10.4%), and fasting (15 cases; 2.0%). There was no significant difference in risk factors between the two genders, with the exception that all cases of fasting were in women, and the differences were significant ($p = 0.015$). The most common site of involvement according to Magnetic Resonance Venography (MRV) was the upper sagittal sinus (427 cases; 57.0%). There was no significant difference in terms of the site of the conflict between the two genders ($p < 0.05$).

Conclusion: The findings of the present study showed that deep vein thrombosis occurred mainly in women and manifested itself mostly as a headache. Moreover, the upper sagittal sinus was the most common site of involvement.

Keywords: Cerebral vein thrombosis; OCP; Headache; Magnetic Resonance Venography.

Please cite this paper as:

Pishbin E, Ziyaei M, Vafadar Moradi E, Foroughipour M, Javadzadeh R, Foroughian M. Ten-year Causes of Cerebral Venous Sinus Thrombosis in Patients Referred to Ghaem Hospital from 2009 to 2019. *Bull Emerg Trauma*. 2024;12(1):8-14. doi: 10.30476/BEAT.2024.100510.1472.

Introduction

Cerebral venous sinus thrombosis (CVST or CVT) is a type of stroke caused by blood clot formation in the brain's venous sinuses, which drain the blood from the brain [1, 2]. Severe cases might cause brain parenchymal damage, such as brain swelling, edema, venous infarction, or venous hemorrhagic infarction [2]. CVT is considered an infrequent condition. CVT incidence estimates ranged from 2.83 to 5.27 per 100,000 in individuals aged 18-64 years, highlighting age-related variability [3]. It is three times more prevalent in women [4] and affects clinical presentation and risk factors [5]. Gender-specific risk factors could explain why CVST is more common in women [6]. In adults, CVT tends to occur at a younger age than arterial thrombosis. An international study in 2004 found that the average age of CVT patients is 37 years, with only 8% being over the age of 65 [7].

The incidence of CVST is estimated to be between two and five occurrences per million annually

[8]. According to a more recent analysis, there may have been an influence of the pandemic on CVST hospitalizations, as seen by the crude rate of hospitalizations for CVST rising from 14.33 in the pre-COVID-19 era to 22.92 during the COVID-19 period per 1,000,000 individuals [9]. CVST is less common than most strokes; however, it presents diagnostic challenges [10]. Previous studies identified significant gender-based variations in the presentation, course, and risk factors of CVST [11]. Although the age and sex distribution of CVST patients varies, women often make up a sizable majority of those with this ailment [12]. CVST is regarded as a condition primarily affecting childbearing women, while a significant proportion of cases also occur in men [13, 14]. The incidence of CVST varies with identifiable risk factors found in approximately 73% of patients [15]. CVST exhibits a notable sex-based distribution, with a higher incidence in women. Studies indicate that approximately 75% of CVST patients are female, as observed in the International Study on Cerebral Venous and Dural Sinus Thrombosis (ISCVST) [16]. Fasting during the Islamic holy month of Ramadan was associated with an increased incidence of CVST. Studies suggested that fasting may contribute to dehydration, particularly in women using oral contraceptive pills [2]. Previous research indicated a higher frequency of CVST during fasting, which could be attributed to dehydration and impaired hemostasis [17].

Women with CVT were significantly younger than men, with an average age of 34 years versus 42 years for men [18]. The manifestations of cerebral venous sinus thrombosis are varied and can present in a variety of ways, including acute, subacute, or chronic. Common symptoms include new headaches, isolated intracranial hemorrhage (ICH) syndrome,

focal neurological deficits, encephalopathy, or seizures [19, 20]. The signs and symptoms of CVT can be classified into three main groups: 1. Isolated ICH syndrome (headache, with/without vomiting, papilledema, and visual problems) [21]; 2. Focal syndrome (focal lesions, seizures, or both); 3. Encephalopathy (changes in mental function or decreased level of consciousness, and coma) [19]. Neuroimaging findings in CVT patients might include focal edematous areas, venous infarction, venous hemorrhagic infarction, diffuse cerebral edema, or in rare cases, isolated subarachnoid hemorrhage [22]. In these individuals, 30-40% suffer from cerebral hemorrhage (ICH) [23, 24]. The cause of cerebral hemorrhage in 25% of cases was related to upper sagittal sinus obstruction [24]. To date, several studies investigated risk factors related to CVT, as well as clinical and paraclinical symptoms. However, considering that no similar study has been conducted in Iran, the findings of this study, which determine the underlying causes and common symptoms of cerebral venous sinus thrombosis in a subset of the Iranian population, can lead to early diagnosis and timely treatment of patients, thereby reducing mortality and controlling disease costs in more advanced stages. This study aims to address the following question: What are the underlying causes of cerebral venous sinus thrombosis in patients referred to Ghaem Education, Research, and Treatment Center in Mashhad? Investigating the causes of CVST might help identify potential risk factors. This knowledge is essential for establishing preventive measures and identifying individuals at higher risk, allowing for timely interventions to mitigate the risk of developing CVST. There are gaps in the current understanding of the causes of CVST. This study aims to fill these gaps by presenting additional information on specific cases in Iran.

Materials and Methods

This retrospective descriptive study was conducted on patients diagnosed with cerebral vein thrombosis (CVT), who were referred to the emergency department of Ghaem Hospital (Mashhad, Iran) between 2009 and 2019.

Due to the limited number of CVT cases, a census sampling method was employed, and all CVT patients who were over the age of 18 were included in this study. Patients with incomplete information or unrecorded clinical symptoms in their files and unconfirmed diagnoses were excluded from the study. The participant's clinical symptoms, causes of venous sinus thrombosis, and demographic information were extracted from the patient's files. The diagnosis of CVT was confirmed through MR venography, which is considered the gold standard method.

Patient files served as the primary source of data.

A standardized data extraction form was developed to systematically collect relevant information. This form included sections for demographic information such as age and gender, as well as clinical symptoms, risk factors, and diagnostic confirmation details. All the required information including demographic data and clinical symptoms, causes of venous sinus thrombosis, and risk factors, as well as symptoms such as headache, nausea, dizziness, vomiting, blurred vision, double vision, seizures, and information on risk factors like oral contraceptive pill (OCP) consumption, fasting, malignancies, and infection, were meticulously recorded [25].

The diagnosis of cerebral venous thrombosis in this study adhered to the criteria outlined by the American Heart Association/American Stroke Association, as defined by Saposnik *et al.*, [21]. As a result, the diagnosis and confirmation of CVT were based on these two previously mentioned diagnostic subgroups:

1. History and clinical examination were consistent with thrombosis diagnosis.

2. Presence of partial or complete venous occlusion in MR venography.

The data were analyzed using SPSS software version 22 (SPSS Inc., Chicago, Illinois, United States). Descriptive statistics, including mean and standard deviation for quantitative data, and frequency and percentage for qualitative data, were calculated. The Chi-square and Fisher's exact tests were used to compare the qualitative data. $P < 0.05$ was considered statistically significant.

Results

In the present study, 749 confirmed cases of cerebral venous sinus thrombosis were identified during the decade from 2009 to 2019. Among these cases, 545 (72.8%) patients were women, and 204 (27.2%) were men. The mean age of these patients was 38.11 ± 14.66 years, ranging from 20 to 88 years. Table 1 presents detailed demographic information, clinical symptoms, and risk factors associated with thrombosis in the studied patients. The most prevalent symptom was headache, which affected 554 patients (74.0%). Additional data are available in Table 1.

Figure 1 focuses on the locations of venous sinuses within the brain. The upper sagittal sinus was the most frequently affected site, accounting for 427 cases (57.0%).

The findings of the comparison between the clinical symptoms and thrombosis risk factors in men and women are shown in Table 2. There were no significant differences in terms of clinical symptoms between genders ($p < 0.05$). However, all causalities of fasting were among women, and there was a statistically significant gender difference ($p = 0.015$).

The Chi-square test was used to compare the two groups based on the CVT location. Furthermore, there were no significant differences in the location of the lesion between male and female patients ($p = 0.649$). Table 3 provides detailed information about these cases.

Table 1. Demographic information, clinical symptoms, and risk factors for thrombosis in the studied patients

Characteristic		Frequency	Percentage
Gender	Female	545	72.80%
	Male	204	27.20%
Headache	Present	554	74.00%
	Absent	195	26.00%
Nausea	Present	56	7.50%
	Absent	693	92.50%
Dizziness	Present	25	3.30%
	Absent	724	96.70%
Vomiting	Present	52	6.90%
	Absent	697	93.10%
Blurred Vision	Present	120	16.00%
	Absent	629	84.00%
Double Vision	Present	37	4.90%
	Absent	712	95.10%
Seizures	Present	173	23.10%
	Absent	576	76.90%
OCP Consumption	Yes	110	14.70%
	No	639	85.30%
Fasting	Yes	15	2.00%
	No	734	98.00%
Malignancies	Yes	78	10.40%
	No	671	89.60%
Infection	Yes	103	13.80%
	No	646	86.20%

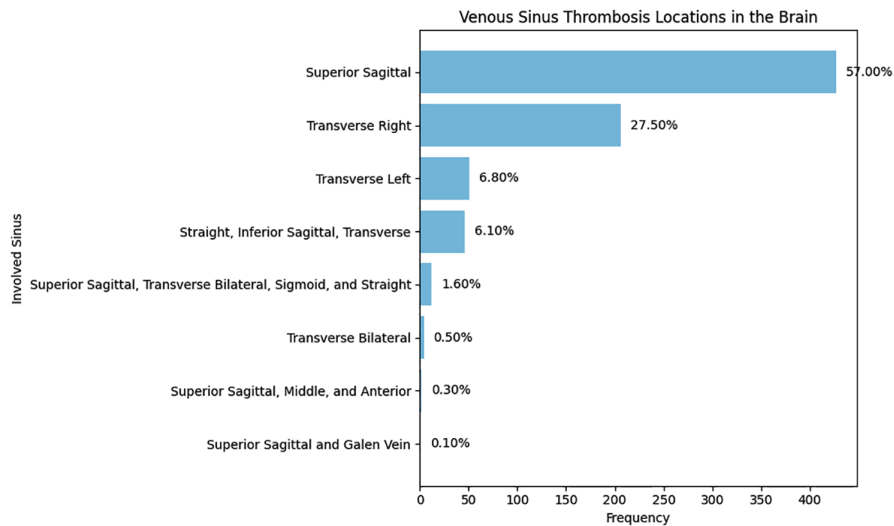


Fig. 1. Locations of involved venous sinuses in the brain

Table 2. Gender disparities in the prevalence of symptoms and risk factors of CVT

Variables		Female Prevalence (%)	Male Prevalence (%)	p value
Headache	Present	405 (74.3)	149 (73.0)	0.779
	Absent	140 (25.7)	55 (27.0)	
Nausea	Present	40 (7.3)	16 (7.8)	0.876
	Absent	505 (92.7)	188 (92.2)	
Dizziness	Present	20 (3.7)	5 (2.5)	0.499
	Absent	525 (96.3)	199 (97.5)	
Vomiting	Present	37 (6.8)	15 (7.4)	0.75
	Absent	508 (93.2)	189 (92.6)	
Blurred Vision	Present	94 (17.2)	26 (12.7)	0.147
	Absent	451 (82.8)	178 (87.3)	
Double Vision	Present	28 (5.1)	9 (4.4)	0.85
	Absent	517 (94.9)	195 (95.6)	
Seizures	Present	127 (23.3)	46 (22.5)	0.922
	Absent	418 (76.7)	158 (77.5)	
Fasting	Yes	15 (2.8)	0 (0.0)	0.015
	No	530 (97.2)	204 (100.0)	
Malignancy	Yes	58 (10.6)	20 (9.8)	0.831
	No	487 (89.4)	184 (90.2)	
Infection	Yes	71 (13.0)	32 (15.7)	0.754
	No	474 (87.0)	172 (84.3)	

Table 3. Comparison of the location of the lesion in male and female patients

Location of Lesion	Female Prevalence (%)	Male Prevalence (%)	p value
Suprasellar Sagittal	313 (73.3)	114 (26.7)	0.649
Right Transorse	151 (73.3)	55 (26.7)	
Left Transorse	39 (76.5)	12 (23.5)	
Streit, SubSagittal, and Transorse	28 (60.9)	18 (39.1)	
Suprasellar, Bilateral Transorse, Sigmoid, and Streit	8 (66.7)	4 (33.3)	
Bilateral Transorse	3 (75.0)	1 (25.0)	
Suprasellar, Midline, and Anterior	2 (100.0)	0 (0.0)	
Suprasellar and Galen Vein	1 (100.0)	0 (0.0)	

A chi-square test was used to compare the two groups.

Discussion

In total, 749 confirmed cases of venous thrombosis were identified in the present study, with women accounting for almost 70% of the total cases.

Overall, the most prevalent symptom was headache, which affected nearly 3 out of 4 individuals. Seizures (23.1%) were the most common symptom, followed by blurred vision (16.0%), nausea (7.5%), vomiting (6.9%), double vision (4.9%), and dizziness (3.3%).

There were no significant differences in clinical symptoms between the two genders. Additionally, approximately 15% of the study participants had a history of OCP use, which was a risk factor. However, fasting was only identified as a risk factor in 2.0% of the study participants, and all cases of fasting were among women, with significant differences observed. Malignancy and infection were also identified as risk factors for thrombosis in 10.4% and 13.8% of individuals, respectively, with no significant gender differences.

Based on MRV, the upper sagittal sinus was the most frequently affected site, accounting for 57% of cases. The right transverse sinus, left transverse sinus, striate sinus, inferior sagittal and transverse sinus, superior sagittal sinus, bilateral transverse sinus, sigmoid sinus, and striate sinus, bilateral transverse sinus, superior sagittal sinus, middle and anterior sagittal sinus, and the vein of Galen were among the other involved sites, arranged in order of prevalence. The site of involvement did not differ significantly between the two genders.

The characteristics of CVST were evaluated in several studies [26-30]. The average age of these patients in the present study was 38.11 ± 14.66 years. While CVST can happen at any age, the average age is frequently between 37 and 39 years old [31]. A previous study indicated a mean age of 33 years for young adults with CVST, with a two-thirds female preponderance [32]. Older patients (≥ 55 years) with CVT have a median age of 43 years [33]. Another study mentioned a mean age of 37 years for patients with CVST, with a range of 18 to 80 years [34]. In terms of age, the findings of all the research were comparable to ours.

Shakibajahromi *et al.*, conducted a similar study between 2012 and 2016, examining cases of cerebral thrombosis at Namazi Hospital in Tehran [26]. During their study, a total of 174 patients were admitted, with 128 (73.6%) being women, and the remaining patients being men. The average age of the subjects in their study was 37.8 years, ranging from 18 to 78 years. The most common symptom in their study, as in ours, was headache. Other symptoms included double vision, focal neurological deficits, decreased level of consciousness, and papillary edema. While there were no significant differences in terms of various symptoms between the two genders in the present study, their study found a significant difference mainly in cases of focal neurological deficits. The present study found no significant differences between the two genders in terms of symptoms. According to their findings, the most common risk factor was OCP use, followed by thrombophilia, fasting, and infections. In the present retrospective study, we could only examine OCP use and fasting. The findings of the present study, similar to theirs, 72.8% of the population were women, and the mean age was 38.11 years. Singh *et al.*, [27] also conducted a similar study

between 2018 and 2020 at a tertiary hospital center in India. They included a total of 40 patients aged between 18 and 55, with an average age of 32.45 years. In contrast to the participants of this study, in their study, approximately 60% of the participants were men. However, the present study had a larger sample size ($n=749$), which provided more precise findings. Similar to this study, the most prevalent symptom in their study was headache. Additionally, in both studies, the upper sagittal sinus was the most common site of involvement, with a prevalence of 67.5%. Krishnan *et al.*, conducted a study on 50 cases of cerebral vein thrombosis between 2017 and 2019 [28]. Similar to the findings of the present study, the majority of the participants in their study were female, accounting for 78.0%. The age range in their study was 14 to 72 years. In this study, headache was the most prevalent symptom, affecting 96% of the participants. Following headache, the most common symptoms were paresis, convulsions, papillary edema, impaired level of consciousness, and aphasia. Pregnancy was the leading risk factor, followed by OCP usage, malignancy, and infection. In terms of the site of involvement, their findings confirmed ours, with the upper sagittal sinus being the most commonly affected site, followed by the transverse and sigmoid sinuses. The present study indicated that all causalities of fasting were among women. A previous study showed that men and women experience similar rates of cardiovascular events during Ramadan [35]. The impact of intermittent fasting on CVST in Ramadan may differ between men and women [36]. A retrospective study in Iran found a higher prevalence of CVST during Ramadan than in other months [37]. Coutinho *et al.*, also conducted a study between 2008 and 2010, focusing on 53 cases of cerebral vein thrombosis [29]. Similar to the findings of the present study, 72% of their participants were women. The average age of their patients was 41 years. Among the risk factors, 52% were using oral contraceptive pills (OCPs), 18% were pregnant, and 44% had parenchymal problems. In contrast to our study, the upper sagittal sinus was not the most common site of involvement, with 43% of cases affecting this region. The sigmoid sinus (53%) and the transverse sinus (70%) were the most frequently involved sites in their study. A smaller percentage of individuals had sinus tract involvement. Khealani *et al.*, conducted a study spanning from 1991 to 2007 [30]. During their study period, a total of 109 cerebral thrombosis patients were admitted, with 53% being women. The average age of the subjects in their study was 37.63 years. Headache was the most common symptom in their patients, followed by focal neurological deficits, seizures, changes in the level of consciousness, papilledema, fever, and dysarthria. Regarding the involvement of different sinuses in their study, as in ours, the upper sagittal sinus had the highest involvement at 71%, followed by the transverse sinus, sigmoid sinus, and

straight sinus.

Perhaps one of the important limitations of this study was its retrospective nature, which caused challenges in data collection procedures and sometimes file defects. However, the period of the study was 10 years, and it had a large sample size, which was not comparable with other studies and could be considered an important strength of the present study. Furthermore, since the present research was conducted on the Iranian population, it would be preferable to conduct studies on other racial groups to investigate racial and genetic factors.

In conclusion, our extensive ten-year investigation of cerebral venous sinus thrombosis (CVT) revealed important patterns. An apparent gender disparity was observed, with females having a higher proportion of cases than males. The mean age of the patients was 38.11 years. The predominant observed symptom was headache, which affected a significant majority of cases. Although there were no significant gender-based differences in clinical symptoms and the general site of blood clot formation, a clear gender-specific pattern was detected in the relationship between fasting and cerebral venous thrombosis (CVT), which was only observed in women. This finding emphasized the significance of taking into account gender-specific variables when determining the risk of CVT. The prevalence of CVT in different sinuses was similar between men and women, with the upper sagittal sinus being the most commonly affected location. These findings enhanced our understanding of CVT epidemiology by underscoring the importance of taking gender-specific factors into account in both research and therapeutic settings. The results of the present study can be applied in two ways. First of all, this information can be provided to clinicians at the bedside; so that they can have a better view of the management of these patients. Second, this study has the potential to shed light on future research on this subject. Additional research is required to clarify the fundamental mechanisms and practical implications of these gender-specific interactions.

Declaration

Ethics approval and consent to participate: All patient information was anonymized to maintain confidentiality. The study adhered to the ethical principles of the Helsinki Declaration. Additionally, it received approval from the Ethics Committee of

Mashhad University of Medical Sciences. This research was conducted on 10/24/2019 and was approved by the Ethics Committee of Mashhad University of Medical Sciences under the title “Investigation of the causes of cerebral venous sinus thrombosis in patients referred to Ghaem Hospital between 2009 and 2019,” with license number 980446 and code IR.MUMS.MEDICAL.REC.1399.009.

Consent for Publication: We, the authors, collectively grant consent for the publication of our content.

Conflict of Interest: The authors declare no conflict of interest.

Funding: The research presented in this paper has been made possible through the generous funding support from Ghaem Hospital. The financial backing provided by the hospital has played a crucial role in facilitating the necessary resources, equipment, and personnel required for the successful execution of our study. We extend our sincere appreciation to Ghaem (AJ) Hospital for their commitment to advancing research initiatives and contributing to the dissemination of valuable knowledge in the medical field. Their support underscores the collaborative efforts between the academic and healthcare sectors, fostering an environment conducive to impactful scientific exploration.

Authors' Contribution: The contributions of the authors to this paper are as follows: EP and EVM were primarily responsible for the conception and design of the study, as well as the acquisition and analysis of data. MZ and MF played key roles in drafting and critically revising the manuscript for intellectual content. MF contributed significantly to the interpretation of data and provided valuable insights throughout the research process. RJ participated in the statistical analysis and data interpretation. All authors have read and approved the final version of the manuscript, demonstrating a collaborative effort in the development of this research work.

Acknowledgment: The authors would like to thank the Clinical Research Development Unit of Peymanieh Educational and Research and Therapeutic Center of Jahrom University of Medical Sciences for revise manuscript

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