Original Article

Etiologic and Clinical Features of Cerebral Venous Sinus Thrombosis in Saudi Arabia

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Abstract

Objective: Our study aims to evaluate the etiologic and clinical features of cerebral venous sinus thrombosis (CVST) in Saudi Arabia, and secondarily whether gender plays a role in CVST. **Materials and Methods:** Data were collected retrospectively from the stroke registry during the period from January 2008 to April 2018, and the patients with the diagnosis of CVST were identified, and data were analyzed for any gender-specific differences in clinical presentation and etiology of cerebral venous thrombosis. **Results:** There were 15 females while 11 males with a female:male ratio of 1.4:1. The mean age was 29.4± standard deviation 8.9 with the age range of 15–49. Headache was the most common and usually the first presenting symptoms present in 65% followed by hemiparesis and cranial nerve palsies. The first neurological examination was normal in 9/26 (34.6%) of the patients, while the common abnormality was cranial nerve palsies. Infections and trauma played an important part in risk factor analysis of our patient after the pregnancy- and hormone-related conditions. Some significant differences between the clinical presentation and risk factors among males and females were noted as age at presentation was higher in females while trauma and infections were common in male patients, although the involvement of the sinuses and response to treatment did not prove to be statistically significant. **Conclusion:** The results of this study were similar to the available literature with few differences. The relatively higher proportion of males in our study can be explained partly with more cases of traumatic CVST. Some important differences were noted between the risk factors and clinical presentation among genders. Large-scale prospective studies are needed to further clarify these differences.

Keywords: *Cerebral venous thrombosis, etiology, gender, risk factors*

Introduction

Cerebral venous sinus thrombosis (CVST) has been considered to be a rare cause of stroke previously with the reported ratio of venous strokes in comparison to arterial stroke to be 1:62.5, but now with the increased awareness about the disorder and improvements in the imaging modalities, CVST has been reported more often as cerebral venous thrombosis (CVT) was reported in 9% out of 182 autopsy cases by Towbin in 1973,[1] while the frequency of CVT from Saudi Arabia was reported to be seven cases per 100,000 hospital patients by Daif in 1995.[2] CVST might affect any age and sex; however, it is more prevalent in younger adults. In the largest international study on CVST, the mean age of the patient was estimated to be 39.1 and female comprised 75% of the total cohort.[3]

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Clinical manifestations are very diverse, and usually, this is a major reason to delay the diagnosis. The common reported symptom is headache that is present in approximately 70%–95% of cases.[4,5] Other common presentations include altered mental status, seizures, cranial nerve palsies, and focal neurological deficits.[6] According to the international study on CVT (ISCVT), inherited prothrombotic conditions are the leading cause of CVST (34%), although, in the Middle East and Pakistan, infections and postpartum states are the main etiologies of CVST (5% and 17%, respectively).[3] Significantly higher preponderance has been reported among females that have been attributed to the peripartum state and the use of oral contraceptive pills.[7] Coutinho *et al*., in their gender-specific analysis from ISCVT study, have also mentioned the gender-specific differences in risk factor profile and response to treatment among males and females.[8] The physician should have a high index of suspicion to diagnose it promptly. Noncontrast computed tomography (CT) is usually the most frequent performed modality in emergency setting, although only in 1/3rd of the cases, unenhanced CT reveals the direct sign of CVST.[9] In comparison with arterial or hemorrhagic stroke, CVT has better prognosis.[6]

Materials and Methods

This study was carried out in the Department of Neurology at King Fahd Hospital of University (KFHU) in retrospective manner from January 2008 to April 2018. KFHU is teaching, tertiary care hospital and has an established neurology team of residents, specialist, and consultants providing round the clock services for adult neurology patients.

A total of 1800 patients were admitted under neurology service. Out of these, 775 (41%) patients were diagnosed with acute stroke. After excluding the patients with ischemic stroke, hemorrhagic stroke, and transient ischemic attack, 26 (3.3%) patients with a final diagnosis of CVT were included in the study. The preliminary diagnosis was based on clinical grounds in patients presenting with features suggestive of CVT as headache, new-onset seizures, focal neurological deficits, cranial nerve palsies, blurred vision, and alteration of conscious level and supported by imaging studies as CT scan head and brain/and CTV (venogram)/and magnetic resonance imaging (MRI)/and magnetic resonance venography (MRV) (venogram)/and conventional four-vessel cerebral angiogram if indicated. The diagnosis was based on clinical grounds and confirmed by radiological investigations either CTV or MRV or in certain cases by both.

Table 1: Clinical characteristics of the patients with cerebral venous sinus thrombosis (*n*=26)

Demographics	Number of patients (%)
Age	29.4 (15-49)
Gender	
Male	11 (42.3)
Females	15 (57.7)
Clinical presentation	
Headache	17 (65.4)
Unilateral weakness	14 (53.8)
Vomiting	7 (26.9)
Seizures	7 (26.9)
Visual symptoms	2 (7.7)
Cranial nerve palsies	10 (38.5)
Altered level of consciousness	5 (19.2)
Neuro exam findings	
Nonfocal	9 (34.6)
Abnormal	15 (57.7)
Not known	2 (7.7)
Risk factors	
OCP/postpartum	6 (23)
Infections	4 (15.3)
Trauma	3 (11.5)
Hereditary thrombophilia	3 (11.5)
Others	2 (7.7)
Workup completed	16 (61.5)
No risk factor identified	3 (11.5)
More than one risk factor identified	7 (26.9)
Acquired thrombophilia	3 (11.5)
New cases of hereditary thrombophilia	4 (15.3)
Treatment	
Warfarin	10 (38.5)
Low-molecular-weight heparin	6 (23.1)
New oral anticoagulants	7 (26.9)
Other	3 (11.5)

OCP: Oral contraceptive pills

Out of 26 patients, 20 were admitted to neurology service and 6 patients were seen as consultation in neurosurgery and internal medicine and later on transferred to the neurology department. Complete blood count, routine blood biochemistry, and coagulation profile were performed in all patients as well as routine laboratory screening for hypercoagulable states included protein C, protein S, antithrombin III, factor V Leiden, homocysteine, antinuclear antibodies, anticardiolipin antibodies, antiphospholipid antibodies, lupus anticoagulant, and antibodies to double-stranded DNA. Other investigations were done where required.

A structured preformat designed comprising details regarding demographic characteristics as age, gender, nationality, symptoms, and signs at time of presentation 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 inquired for pregnancy, puerperium, and usage of oral contraceptive pills as well. The statistical analysis was performed using IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, NY, USA). The mean and standard deviation (± standard deviation [SD]) were computed for age and scaled data. Frequencies and percentages were calculated for categorical data. $P < 0.005$ was considered to be statistically significant.

Results

During the study period, a total of 26 patients with the diagnosis of CVST were included in this study.

11 (42%) were male while 15 (58%) were female with a female-to-male ratio of 1.4:1.

Data about the ethnic background were available in 20 patients, out of these, majority of the patients (58%) were Saudis. Their age ranges were between 15 and 49 (mean age 29.4 ± SD 8.9. Their demographics and clinical characteristics are summarized in Table 1. Out of these 26 patients, three patients were already known to have protein S deficiency, and three patients had venous sinus thrombosis secondary to head trauma and initially treated under neurosurgical team and later transferred to the neurovascular services. Six patients were either postpartum or using hormonal contraception, one patient was diagnosed with a case of ulcerative colitis, and one with Behcet's disease (BD) before presentation with CVST.

Noncontrast CT was the preferred first-line brain imaging and was performed in 23 patients, and 22 patients had CTV. In three patients, the brain MRI was done as the first-line imaging while in, majority of the patients, either it was done as a follow-up imaging to confirm the diagnosis if in doubt or to see the extent of the brain insult. The radiological findings are summarized in Table 2. Most of the patients had multiple sinuses involved at presentation, and the most common sinus involved was transverse sinus. Some patients have dual or multiple mechanisms for CVST. Workup for hereditary thrombophilia was done in 16 patients, out of those, three patients did not found to any known risk factor for CVST, while two new patients diagnosed to have protein S deficiency and antiphospholipid antibody syndrome and anticardiolipin were documented in four patients, one patient had hyperhomocysteinemia. One patient was post-partum, but as her systemic review, her symptoms were suggestive of ulcerative colitis; hence, it was worked up, and the diagnosis of ulcerative colitis was confirmed, another patient, after the first presentation to the neurology department with CVST, was diagnosed with neuro Behcet's syndrome and further workup and treatment was instituted. Follow-up imaging was available in 15 patients, out of these, 10 patients had complete recanalization, and partial recanalization was observed in three patients while two patients did not recanalize. In comparison between males and females, the mean age was higher in females with significant $P = 0.02$. The other differences between males and females have been summarized in Table 3.

Table 2: Radiological findings and details of thrombosed sinuses and veins

Radiological findings	*n* (%)
CT/MRI findings	
Hemorrhagic venous infarction	11 (40)
Nonhemorrhagic infarction	6 (23.1)
Subarachnoid hemorrhage	2 (7.6)
No parenchymal changes	9 (34.6)
Dural venous sinuses involved	
Transverse	19 (73)
SSS	15 (57.7)
Sigmoid	15 (57.7)
Others	8 (30.7)
Single sinus involved	
SSS	3 (11.5)
Two sites involvement	
Transverse + sigmoid	9 (34.6)
Transverse + SSS	8 (30.7)
SSS + sigmoid	3 (11.5)
Sigmoid + ISS	1 (3.8)
More than two sites involvement	2 (7.7)
Follow-up imaging available	15 (57.6)
Complete recanalization	10 (38.5)
Partial recanalization	3 (11.5)
No recanalization	2 (7.7)

CT: Computed tomography, MRI: Magnetic resonance imaging, SSS: Superior sagittal sinus, ISS: Inferior sagittal sinus

Discussion

CVST prevalence is now being increasingly found to be high, that seems secondary to increasing awareness among the physicians and availability of more sophisticated imaging modalities to diagnose the condition in the earlier stages.[1] It is more prevalent in females,[7] and few studies have pointed out some specific differences in the clinical presentations, etiological risk factors, and response to treatment;[8] however, still data are sparse from the Middle Eastern countries especially regarding the differences between males and females risk factor profile for CVST.

In this study, we aimed to identify the etiological and clinical parameters of CVST and specifically looking

Table 3: Demographic and clinical differences among males and females

Gender	Females (15)	Males (11)	*P*
Age	32.33±9.93	25.45±5.55	0.02
Clinical presentation			
Headache	12	3	0.067
Vomiting	2	5	0.069
Unilateral weakness	11	3	0.026
Seizures	4	3	0.65
Dec level of consciousness	1	4	0.08
Visual symptoms	2	0	0.32
Cranial nerve palsies	9	1	0.01
Other	4	2	0.49
Intracranial hemorrhage	8	3	0.17
Infarction	6	0	0.02
Known premorbid etiology			
Hereditary thrombophilia	3	0	0.06
Postpartum + OCP	6	N/A	
Trauma	0	3	
Complete etiological workup was done			
Hereditary thrombophilia	4	2	0.49
Acquired prothrombotic condition	3	3	0.50
Infection	1	4	0.06
Posttrauma	0	3	0.06
Other	5	2	0.34
Dural venous sinuses involve			
SSS	9	6	0.54
Sigmoid	8	7	0.45
Transverse	10	9	0.34
Other	6	4	0.58
Treatment			
Warfarin	6	4	0.58
Low-molecular-weight heparin	5	1	0.16
New oral anticoagulants	4	3	0.65
Other	0	3	0.06

SSS: Superior sagittal sinus, OCP: Oral contraceptive pills

for any specific differences in the etiologies or clinical features in males and females.

Our patients' clinical profile showed insignificant female predominance 1.4:1, while in most of the studies including ISCVT,[3,4] female dominance of up to 70% has been reported, and CVST is mainly considered to be a diseases mainly affecting females that has been attributed to gender-specific risk factors;[8] however, male dominance in CVST has been reported by other authors as well, where 63% were males,[10] as well as Rim *et al*. study from South Korea in 2016 also showed male comprising 45% of the CVST cases.[11]

This difference could partially be explained as in our study, posttraumatic CVST cases found in 11.5% of the patients as previously the posttraumatic cases were usually being managed under neurosurgery and now since the introduction of neurovascular unit, we had cases referred from neurosurgery and trauma is worldwide more common in males. In other studies, where trauma was common also conducted in neurosurgical or neurovascular services, and male predominance was noted. The most common symptom was headache, present in up to 65% of the patients, that is also the case in almost all the studies of CVST as headache has been reported in various studies of CVST in the range of 70%–90%.[4,5] The mean age in most large studies of CVST has been reported between 37 and 39 years, though all ages can be affected.[3,12]

In this study, the mean age was 29.4, which is lower as compared to other international studies; however, in other study from the similar geographical region, the mean age was also 29.5, however, they included the pediatric patients as well.[13]

Other common presentations, in this study, were also in accordance with the current literature as again focal neurological findings, and cranial nerve palsies are usually the common findings in almost all the series of CVST as well as the risk factor profile was almost similar to other studies done in Saudi Arabia as well as internationally. In this study,[3-7] mortality in our case was 3.8%, only one patient died secondary to diabetic ketoacidosis rather than the direct effect to his central nervous system (CNS) condition. Mortality rates have been significantly variable among different studies on CVST ranging from 9% to 44%,[14,15] ISCVT also mentioned death or dependency of 13%;[3] however, they measured the combined outcome of death and dependency and the gender-specific analysis in subgroup of ISCVT patients showed mortality to be as low as 2%.[8] Our patients were relatively younger, and none of the patients was found to have malignancy, this could explain the relatively low mortality in our patients.

We tried to find if there were any significant gender differences between the etiological or clinical characteristics among our patients. In our cases, the mean age was significantly higher in females as compared to males that is in contrast to the study[8] where the female presentation was at younger age than the males, headache was more common in females than males (P = 0.067) that is similar to the comparison study[8,16] while vomiting and decreased level of consciousness were more common among male patients presenting with CVST (P = 0.069 and 0.082, respectively) that is contrary to the other study but that could be explained as all these patients presented secondary to road traffic accidents and had posttraumatic CVST secondary to severe head trauma, two patients

needed intubation in the emergency department secondary to low Glasgow Coma Scale. Focal findings, including unilateral weakness and cranial nerve palsies, were also more significant in female counterpart that has previously been noted by Jonathan *et al*. as well.

Among the etiological factors, trauma and infections ($P = 0.063$) were significant in favor of males, this finding is also similar to the studies[6,8] while in other study comparing gender differences, none of the risk factors reached statistical significance.

Literature search reveals that a known etiological factor can be identified in 75%–85% of cases.[3,4,12] We were able to find the likely etiology in 88% of the patients, as summarized in Table 1.

In our patients, two patients 7.9% had ulcerative colitis, which is similar to the literature[17] and the same no had Behcet's syndrome. BD is more common in Middle Eastern countries, and it can present in many ways. CNS involvement is considered to be the most severe sequelae of BD. The prevalence of CVST in all populations with Behcet's has been reported in literature to be between 10% and 20%.[18]

The brain lesions were more common in females than males. This study had many limitations, major limitation being the retrospective data collection in majority of the patients, where further workup, if indicated, could not be performed. Another limitation was smaller sample size, especially in subgroup analysis, follow-up study was not available in almost half of the patients either as some patients lost to follow-up, but despite all these limitations, we think it provides good insight about the etiologies and clinical features of CVST and some important gender differences between males and females. Further prospective designed studies are recommended.

Conclusion

Most of the results of our studies were in accordance with the similar studies from our region as well as the international studies with some differences. Male predominance can be explained partly because of the inclusion of the neurosurgical posttraumatic cases in our study. Few differences among the clinical features and etiological causes in general as well as between genders were noted; however, most of these did not reach the statistical significance that could be the result of small sample size. Prospective, large-scale studies are needed to be conducted to better clarify this issue.

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Conflicts of interest

There are no conflicts of interest.

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