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Evaluation of Risk Factors, Clinical Characteristics, and Prognosis in Cerebral Venous Thrombosis: A Single Tertiary Center Experience

Serebral Ven Trombozunda Risk Faktörleri, Klinik Özellikler ve Prognozun Değerlendirilmesi: Üçüncü Basamak Tek Merkez Deneyimi

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Abstract

Objective: We evaluated the demographic and clinical characteristics, risk factors, involved vasculature, and prognosis in cerebral venous thrombosis.

Materials and Methods: We included 53 patients with cerebral venous thrombosis (CVT) who were followed up in our neurology inpatient clinic and neurology intensive care unit in the study. The demographic and clinical characteristics on admission, risk factors, results of laboratory tests and neuroimaging studies, treatment, outcomes at discharge, and 6th-month follow-up were reviewed.

Results: The mean age of the patients was 44.1±13.7 (19-71) years. Thirty-one (58.4%) of the patients were female. The most frequent symptom was headache (69.8%). Puerperium and malignancy were the most common risk factors for patients under 45 years of age; whereas anemia and malignancy were the most common risk factors for patients over 45 years of age. The most common localization of CVT was found to be the transverse sinus (69.8%). The modified Rankin scale (mRS) scores at discharge were 0 for 47 patients (88.6%), 1 for 4 patients (7.5%) and 4 for 2 patients. In the 6th-month follow-up, 48 (90.5 %) of the patients had an mRS score of 0 with normal neurological examination.

Conclusion: Our study, representing the experience of a single tertiary referral center, showed that CVT mostly affected women of reproductive ages. More than 90% of patients in our study had an mRS score of 0 at the 6th-month follow-up. The results of our study suggest that early diagnosis of CVT with advanced neuroimaging techniques recently has improved the outcomes and reduced the disability.

Öz

Amaç: Bu çalışmada serebral ven trombozunun (SVT) demografik ve klinik özelliklerinin, risk faktörlerinin, tutulan damar sisteminin ve prognozun değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Nöroloji polikliniğimizde ve nöroloji yoğun bakım ünitemizde takip edilen SVT'li 53 hasta çalışmaya dahil edildi. Başvurudaki demografik ve klinik özellikler, risk faktörleri, laboratuvar testleri ve beyin görüntüleme çalışmalarının sonuçları, tedavi, taburculuk sonuçları ve 6. ay takipleri gözden geçirildi.

Bulgular: Hastaların yaş ortalaması 44,1±13,7 (19-71) yıl idi. Hastaların 31'i (%58,4)

kadındı. En sık görülen semptom baş ağrısıydı (%69,8). Kırk beş yaş altı hastalarda lohusalık ve malignite en sık görülen risk faktörleri iken, 45 yaş üstü hastalarda anemi ve malignite en sık görülen risk faktörleri idi. SVT'nin en sık yerleşim yeri transvers sinüs (%69,8) olarak bulundu. Taburculuk mRS skoru 47 hastada (%88,6) 0, 4 hastada (%7,5) 1 ve 2 hastada 4 idi. Altıncı ay takibinde hastaların 48'inde (%90,5) normal nörolojik muayene ile mRS skoru 0 olarak bulundu.

Sonuç: Tek bir üçüncü basamak sevk merkezi deneyimini temsil eden çalışmamız, SVT'nin çoğunlukla üreme çağındaki kadınları etkilediğini göstermiştir. Çalışmamızdaki hastaların %90'ından fazlasının 6. ay takibinde mRS skoru 0 idi. Çalışmamızın sonuçları, son yıllarda gelişmiş nörogörüntüleme teknikleri ile SVT'nin erken teşhisinin sonuçları iyileştirdiğini ve özürlülüğü azalttığını göstermektedir.

Introduction

Cerebral venous thrombosis (CVT) is a subtype of stroke which involves cerebral venous sinuses and cortical veins leading to hemorrhage or venous infarcts (1,2). It affects the young population with a female predominance. Previously, the frequency of CVT was underestimated because of diagnostic complexities; however, the development of advanced imaging modalities in recent decades allowed for prompt and accurate diagnosis of CVT, even in mild cases (3). Clinical features of CVT include headache, visual disturbances, epileptic seizures, focal neurological deficits, movement disorders, altered mental status related to involved cerebral venous structures (4). CVT can be provoked or unprovoked, and multiple risk factors can be present in patients. Most of the patients with CVT are known to have prothrombotic risk factors and thrombophilias are identified in more than one-third. In the young population, sex-specific risk factors including pregnancy, puerperium, and oral contraceptives are the most striking predisposing conditions, whereas malignancy is more common in the advanced ages (5). There are no certain blood parameters pathognomonic for CVT, but higher D-dimer levels strengthen the diagnosis. When the diagnosis of CVT is considered in the presence of cerebral hemorrhage or ischemic lesions on the initial radiological examination, advanced neuroimaging techniques should be performed in order to evaluate venous structures. Computed tomography (CT) venography and magnetic resonance venography (MRV) can be used alternatively to digital subtraction angiography for diagnosis. However, magnetic resonance imaging (MRI) is superior to CT for demonstration of the thrombosis and parenchymal lesions in suspected CVT (4,6). The goal of the treatment in CVT is to reverse the thrombosis and prevent cerebral herniation, as well as parenchymal injury (6,7).

In the present study, we aimed to evaluate the demographic and clinical characteristics, risk factors, clinical presentation, involved cerebral venous sinuses, and prognosis of CVT in a university hospital.

Materials and Methods

Fifty-three patients diagnosed with CVT in the neurology inpatient clinic and neurology intensive care unit of Gazi University Hospital between 2006 and 2015 were included in this retrospective study. Demographic and clinical characteristics, potential risk factors, neurological examination findings, modified Rankin Scale (mRS) scores at discharge and follow-up were reviewed. The laboratory studies including complete blood count, anticardiolipin antibodies, antiphospholipid antibodies, proteins C-S, antithrombin-III (AT-III), activated protein C resistance, Factor V Leiden and *methylenetetrahydrofolate reductase* (*MTHFR*) gene mutations, serum homocysteine levels were recorded when available. Patients were screened for Behçet's disease (BD) and the pathergy test was applied to patients, since BD is a prevalent chronic inflammatory disease in Turkey. Cranial MRI and MRV studies were conducted in our hospital (1.5 and 3 Tesla Magneton Aera and Verio; Siemens, Erlangen, Germany) and assessed by two experienced neuroradiologists (M.U., N.T.). Laboratory and radiological data were obtained from our hospital information management system. Ethical approval was obtained from the clinical research Ethics Committee of Gazi University Faculty of Medicine Hospital for the study (decision no: 252, date: 12.05.2014).

Statistical Analysis

Analysis of the data was performed by using IBM SPSS 21.0 statistical package program. Continuous variables were expressed as mean ± standard deviation or as median (interquartile range). Categorical variables were presented as frequencies and percentages. The normality of data was assessed

by the Kolmogorov-Smirnov test. Pearson chi-square (χ^2), Yates (χ^2), or Fisher's Exact (χ^2) tests were used to compare qualitative data where appropriate. The Independent Samples t-test (t-test in independent groups) was used to compare quantitative data in the study. A p-value smaller than α=0.05 was considered statistically significant.

Results

The mean age of 53 patients included in the study was 44.1±13.7 (19-71) years. Thirty-one (58.4%) patients were female and 22 (41.6%) were male. Clinical characteristics of the patients and potential risk factors for CVT are summarized in Table 1.

When risk factors were evaluated according to gender; the most frequent risk factor was anemia in women and local infections in men. Multiple risk factors were identified more frequently in women. Puerperium and malignancy were the most common risk factors for patients under 45 years of age, while anemia and malignancy were found to be the most common risk factors for patients over 45 years. The presence of multiple risk factors was notable for patients over 45 years of age.

The most common localization of CVT was found to be transverse sinus in 37 patients (69.8%) (Table 2). Venous infarction was detected in 28 of the patients, the majority of which were in the right hemisphere (35.7%). A statistically significant difference was found between the two genders regarding the presence of hemorrhage or hemorrhagic infarction ($p<0.05$) (Table 2). Mortality due to CVT was not observed in our cohort. The mRS score at discharge was 0 in 47 patients (88.6%). In the 6th month follow-up, 48 (90.5 %) of the patients had a mRS score of 0 with totally normal neurological examination.

Discussion

In this retrospective study of 53 patients with CVT at a tertiary hospital in Turkey, we evaluated the demographic and clinical characteristics, risk factors, clinical presentation complaints, involved cerebral venous structures, and short-term follow-up findings of CVT. The median age of patients was 44 years similar to large cohorts in which onset age distribution was found to be 3rd to 4th decades (2,8,9). Our findings demonstrating female predominance (58.7%) were also in accordance with previous studies (9-11). Female superiority in CVT is mainly attributed to sex-specific risk factors [puerperium, pregnancy, and the use of obsessive-compulsive disorder (OCD)] acting as both predisposing and precipitating conditions for CVT (11,12). The International Study on cerebral vein and dural sinus thrombosis (ISCVT) study showed that the prognosis of female patients with sex-specific risk

Table 1. Clinical characteristics and potential risk factors of the patients with CVT (n=53)

	Total n (%)
Age (mean ± SD) standard deviation	44.1±13.7 (19-71)
Female sex, n (%)	31 (58.4%)
Potential risk factors, n (%)	
Anemia	19 (33.9%)
Activated protein C resistance	16 (30.2%)
MTHFR gene mutation (heterozygous)	15 (28.3%)
Protein C/S deficiency	14 (26.4%)
Malignancy	8 (15%)
Puerperium	6 (11.3%)
Local infections	5 (9.4%)
Factor V Leiden mutation	3 (5.7%)
MTHFR gene mutation (homozygous)	2 (3.8%)
History of cerebral venous thrombosis	2 (3.8%)
Pregnancy	1 (1.8%)
Anti-thrombin III deficiency	1 (1.9%)
Trauma	1 (1.9%)
Dehydration	1 (1.9%)
Post lumbar punction	1 (1.9%)
Behçet's disease	1 (1.9%)
History of venous thromboembolism	1 (1.9%)
Neurological signs and symptoms, n (%)	
Headache	37 (69.8%)
Papilledema	20 (37.7%)
Seizures	19 (35.8%)
Nausea and vomiting	15 (28.3%)
Cranial nerve palsies	10 (18.9%)
Motor deficits	10 (18.9%)
Altered mental status	9 (17.0%)
Sensory deficits	2 (3.7%)
Dysarthria	2 (3.7%)
Gait disturbances	1 (1.8%)

CVT: Cerebral venous thrombosis, SD: Standard deviation, *MTHFR*: Methylenetetrahydrofolate reductase

Table 2. Radiological findings of patients with CVT				
	Total n=53 n (%)	**Female n=31**	**Male n=22**	
Involved venous structures, n (%)				
Transverse sinus	37 (69.8%)	23 (74.2%)	14 (63.6%)	
Sigmoid sinus	29 (54.7%)	17 (54.8%)	12 (54.5%)	
Superior sagittal sinus	20 (37.7%)	12 (38.7%)	8 (36.4%)	
Internal juguler vein	17 (32.1%)	8 (25.8%)	9 (40.9%)	
Cortical veins	5 (9.4%)	3 (9.7%)	2 (9.1%)	
Inferior sagittal sinus	1 (1.9%)	0 (0%)	1 (4.5%)	
Sinus rectus	1 (1.9%)	0 (0%)	1 (4.5%)	
Multiple sinus involvement	32 (60.4%)	19 (61.3%)	13 (59.1%)	
Parenchymal lesion n (%)				**p-value**
No lesion	25 (47.1%)	12 (38.7%)	13 (59.1%)	0.143
Venous infarcts	28 (52.8%)	13 (59.1%)	9 (40.9%)	
Hemorrhage or hemorrhagic infarcts	23 (43.4%)	17 (54.8%)	6 (27.3%)	0.046
CVT: Cerebral venous thrombosis				

factors was better than in other conditions (12). Nasr et al. (13) showed that pregnancy and puerperium were risk factors for 24.6% of 11,400 CVT patients who were followed between 2001 and 2008 and these patients had lower mortality rates when compared to others. In our study, no significant difference in terms of prognosis was found between patient groups according to risk factors. When we compared the risk factors according to gender in our study, the most common risk factor was anemia in 25.8% of women and local infection in 22.7% of men. In Coutinho et al.'s (12) study, the most common risk factors for CVT were genetic thrombophilia affecting 25% of men, and use of OCD affecting 46% of women. Duman et al. (2) found that prothrombotic conditions were the second causative risk factor for CVT after reproductive health-related factors in the Turkish population. Although the clinical impact of heterozygous (*MTHFR*), FV Leiden, and prothrombin gene mutations on CVT is uncertain, these mutations may contribute to the multifactorial causality in CVT.

In our study, we accepted anemia (hemoglobin <12 g/dL) and thrombocytosis (platelets >450x10.e3/uL) as risk factors for CVT. Hemogram abnormality was found in 45.2% of women and 22.7% of men with CVT. We suggest that the higher incidence of iron deficiency anemia among women in low-middle income countries contributes to the higher proportion of anemia in patients with CVT. However, the relationship between anemia and cerebrovascular diseases, particularly CVT, is not fully understood (14-16); several mechanisms have been proposed to date (15). Decreased iron levels induce megakaryocyte activity paradoxically, which provoke secondary thrombocytosis, thus leading to a hypercoagulable state (17). In addition, iron deficiency was found to cause increased levels of factor VIII as a prothrombotic risk factor (15,18). Although the relationship between iron deficiency and venous thromboembolism is controversial, anemia should be considered as a precipitating risk factor for CVT with underlying predisposing conditions. Eventually, CVT is a multifactorial disease, which means that the identification of a risk factor or cause should not interrupt the complete diagnostic workup (17). Patients diagnosed with CVT should be screened for all risk factors; especially for reproductive health-related risk factors (puerperium, pregnancy, use of OCD) which are important in terms of recurrence.

At least one serologic marker for vasculitis was detected in 11.3% of the patients. One of our patients had a previous diagnosis of BD. In the ISCVT study, 3% of patients were found to have systemic vasculitis especially systemic lupus erythematosus and BD. Hyperhomocysteinemia was detected as a risk factor for SVT in 11.3% of the patients included in our study. In the ISCVT study, less than 1% of CVT

cases had hyperhomocysteinemia (8). Although some meta-analyses showed a higher risk of venous thromboembolism with hyperhomocysteinemia (19,20), the latest study from the Netherlands failed to confirm this relationship (21).

The clinical picture of CVT varies broadly from mild headache to encephalopathy which can present with acute, subacute, or chronic symptoms. There are four important syndromes of CVT: isolated intracranial hypertension, focal neurological deficits, epileptic seizures, and encephalopathy (22). In the ISCVT study, the headache was observed in 88.8% of patients, which is followed by seizures with a rate of 39.3% and motor deficit with 37.2% (8). In our study, headache was the most common symptom with 69.8%, followed by multiple symptoms in 64.2% of patients; 35.8% of patients had seizures, and 18.9% of patients had motor deficits. Similar to large cohorts, the most common symptom was headache in both genders (2,12). The initial neurological examination revealed papilledema in 37.7% of our patients, whereas 18,9% had motor deficits. The most common finding in the neurological examination of the ISCVT cohort was a motor deficit in 37.2% of patients, which was followed by papilledema in 28.3% (8). When neurological signs of our study population were compared according to gender; papilledema was the most common finding in both groups. The corresponding parameter was reported to be motor deficit for either sex in the study of Coutinho et al. (12).

Cranial MRI followed by MRV is the most sensitive diagnostic tool while demonstrating the venous thrombus and parenchymal lesions in acute, subacute, and chronic stages in CVT (22). We detected transverse sinus thrombosis in 69.8% of the patients, sigmoid sinus thrombosis in 54.7%, and superior sagittal sinus thrombosis in 37.7% of the patients. In the ISCVT study, the most common localization was the superior sagittal sinus with 62% (8). Duman et al. (2) reported transverse and sigmoid sinuses were the most frequently involved cerebral veins in CVT among the Turkish population.

In the ISCVT study, mortality was observed in 8.3% of the patients and found to be associated with underlying risk factors such as malignancy (8). Coutinho et al. (9) reported a rate of 0-28% for CVT-associated deaths after 2000 in a systematic review of literature. Recently, Duman et al. (2) reported no death due to CVT in 1144 patients. In our cohort, no death was observed either at discharge or in 6 months. We found patients with CVT had a better prognosis and 96.2% were functionally independent with favorable mRS scores (0-1) at discharge; while the proportion of patients with mRS 0-1 at discharge was 65.7% in the ISCVT cohort (8). Reduced mortality and disability in CVT can be explained by higher recognition of CVT and advances in modern neuroimaging techniques. Furthermore, experiences in treatment options might result in less mortality together with a better prognosis.

There are some limitations to our study. First, the study population was small since it consisted of cases from a single center with a relatively rare diagnosis. Second, the retrospective design of the study might give rise to some missing clinical and laboratory data. Third, the follow-up period was relatively short to observe recurrences. And last, the lack of follow-up MR imaging studies restricted the interpretation of vascular recovery showing recanalization of thrombosed sinuses.

Conclusion

In conclusion, CVT is a rare subgroup of cerebrovascular diseases with a relatively better prognosis, of which early diagnosis is essential. Our study reflecting a single-center experience from a tertiary hospital showed that CVT affected mostly women of reproductive ages. The patients are often in the 3rd to 4th decades but CVT can be seen at any age from childhood to late adulthood. CVT is typically multifactorial and the identification of all precipitating and predisposing risk factors is essential to avoid recurrences. The clinical symptomatology comprises a broad spectrum varying from headache to coma. The most commonly involved venous structure in CVT was found to be transverse sinus in our study. Venous infarcts, hemorrhages, and hemorrhagic infarcts as parenchymal lesions occurred in nearly half of the patients during the clinical course. More than 90% of our patients had mRS score of 0 at the 6th-month follow-up. We suggest that early diagnosis of CVT with advanced neuroimaging techniques improved the outcomes and reduced the disability.

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Ethics

Ethics Committee Approval: Ethical approval was obtained from the clinical research ethics committee of Gazi University Faculty of Medicine Hospital for the study (decision no: 252, date: 12.05.2014).

Informed Consent: Retrospective study.

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Authorship Contributions

Surgical and Medical Practices: H.M.M., H.Z.B.Ç., B.N., N.T., M.U., Concept: H.M.M., H.Z.B.Ç., B.N., N.T., M.U., Design: H.M.M., H.Z.B.Ç., B.N., N.T., M.U., Data Collection or Processing: H.M.M., H.Z.B.Ç., B.N., N.T., M.U., Analysis or Interpretation: H.M.M., H.Z.B.Ç., B.N., N.T., M.U., Literature Search: H.M.M., H.Z.B.Ç., B.N., N.T., M.U., Writing: H.M.M., H.Z.B.Ç., B.N., N.T., M.U.

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