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Cerebral venous thrombosis with clinical, etiological and radiological findings

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ABSTRACT

Aims: Thrombosis of the cerebral veins is a disease that can be caused by many factors and puts clinicians in a difficult situation during diagnosis and treatment. Our study investigated clinical findings, etiological causes, localization of thrombosis detected by neuroimaging tests, and the treatments received by the patients with cerebral venous thrombosis who were followed up as inpatients in our clinic.

Methods: We retrospectively analyzed 44 patients between the ages of 18-80 years who were hospitalized with a diagnosis of cerebral venous thrombosis. Age, duration of admission, initial symptoms, neurological examination findings, Glasgow Coma Scale values at admission, etiological causes, topographic areas of involvement in neuroradiological examinations, and inpatient medical treatment were analyzed.

Results: Forty-four patients (26 females, 18 males) with cerebral venous thrombosis were included in our study. According to the duration of presentation, 47.7% presented in the subacute period. Headache was the most common presenting symptom, with a rate of 90.9%, while nausea and vomiting (68.2%) and papilledema (54.5%) were the other common symptoms. Multiple vein and/or sinus involvement was present in all 17 patients with seizures. The most common etiological factors were thrombophilia (54.5%), pregnancy and the postpartum period (18.8%), and oral contraceptive use (15.9%). Multiple sinus involvement was observed in 41 patients (93.2%), while three had single sinus involvement. The rate of sinus involvement was 86.4% (38 patients) in the transverse sinus, 77.3% (34 patients) in the sigmoid sinus, and 52.3% (23 patients) in the superior sagittal sinus.

Conclusion: Cerebral venous thrombosis has many etiological causes that can be overlooked due to the variety of clinical manifestations and changes in the prognosis when treated. Early treatment is essential because it can reduce the risk of death and severe disability. Our study is critical because it covers a relatively large number of cases.

Keywords: Sinus vein thrombosis, etiology, topography

INTRODUCTION

Cerebral venous thrombosis (CVT), which is caused by thrombosis of dural veins and sinuses, is a rare form of cerebrovascular disease and incidence between 14 and 20 cases per million population. Still, this fatal disease is observed more frequently in the young age group and women.[1]

While many intracranial and extracranial causes may lead to CVT, prothrombotic state, venous stasis, and direct involvement of the venous wall may be considered as the three primary mechanisms in the formation of clinical findings of the disease. Still, the cause cannot be determined in 20-25% of patients despite all investigations.[2] Depending on the location of the thrombus and the rate of thrombus formation, the spectrum and onset of clinical findings are quite variable. Increased intracranial pressure or focal brain damage is frequently responsible for the findings.[3] The disease's recognition is tricky because it may mimic many neurological diseases.

Cranial computed tomography (CT) may give a quick idea when the clinician suspects CVT, but cranial magnetic resonance imaging (MRI) and cranial MRI venography (MRV) are recommended for definitive diagnosis.[3] Treatment of CVT mainly consists of anticoagulant agents in addition to treatment of symptoms and etiological causes. Despite treatment, mortality is observed at a rate of 3-15%, especially in the acute phase of the disease.[4]

In our study, patients with CVT who were followed up in our clinic were retrospectively analyzed, and clinical findings,

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etiological factors, localization of thrombosis detected by neuroimaging examinations, and the treatments they received were examined.

METHODS

Our study analyzed patients with CVT diagnosed by MRI and/or MRV between January 2008 and December 2014. Approved by the Ethics Committee of İzmir Katip Çelebi University Atatürk Training and Research Hospital (Date: 12.11.2015, Decision No: 212). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Age, gender, initial symptoms and findings (headache, nausea/vomiting, pupil edema, focal deficit, focal and generalized seizure, confusion, abducens nerve palsy), Glasgow Coma Scale (GCS) values at the time of initial presentation to our clinic, Topographic areas of involvement in neuroradiological examinations such as CT, CTV, MRI, MRV, conventional angiography and medical treatments used during hospitalization were retrospectively reviewed from patient files and patient information management system. The presence of focal neurological deficit (hemiparesis and/or hemihypoalgesia) and accompanying focal or generalized seizures were determined from the records. Possible etiological causes evaluated in the clinic during the treatment of the patient: hereditary thrombophilia panel (prothrombin G20210A mutation, factor V leiden mutation, protein C deficiency, protein S deficiency, antirombin III mutation, MTHFR C667T mutation, and homocysteinaemia), malignancy, surgical intervention, lumbar puncture, trauma, oral contraceptive drug use, presence of infection, pregnancy and the postpartum period, iron deficiency anemia, connective tissue disease, inflammatory bowel disease thrombocytosis, chronic renal failure were recorded. Patients were accepted as acute (<48 hours), subacute (48 hours-30 days), and chronic (>30 days) according to the duration of onset. Patients whose data could not be accessed from the hospital information system were excluded.

Statistical Analysis

Statistical analysis of the data was performed in SPSS 22.0 for the Windows package programme with 95% confidence. Chi-square and Fisher exact tests were used to compare categorical variables between groups, and independent two-sample test statistical analyses were used to compare continuous data between groups. $p<0.05$ was considered statistically significant, and $p\geq0.05$ was considered statistically insignificant.

RESULTS

Between January 2008 and December 2014, 49 patients who were hospitalized with a prediagnosis of sinus vein thrombosis in the Neurology Clinic of İzmir Katip Çelebi University Atatürk Training and Research Hospital were identified. Five of them were excluded from the study due to incomplete data. 18 of 44 patients were male, and 26 were female. The ages of the patients at the time of the event ranged between 18 and 80 years. The age distribution of the patients according to gender is shown in Figure 1.

When the onset of symptoms at presentation was analyzed, the rate of presentation in the acute period was 31.8% (<48 hours), in the subacute period 47.7% (48 hours-30 days), and in the chronic period 20.5% (>30 days).

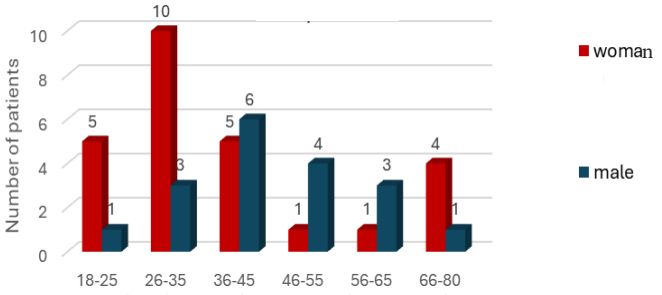

Figure 1. Age distribution of cases according to gender

The distribution of symptoms and signs detected in the patients is shown in Figure 2.

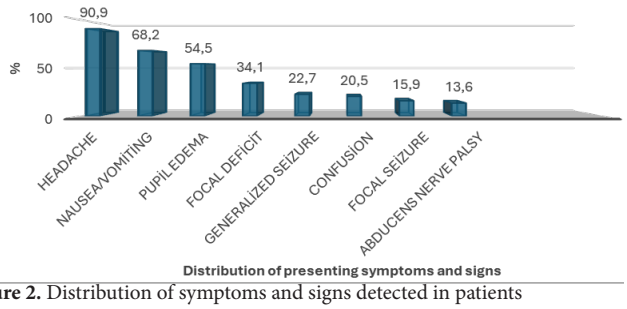

Figure 2. Distribution of symptoms and signs detected in patients

While multiple complaints and findings were found simultaneously in all patients, headache was the most common symptom in 90.9%. Isolated headache without any neurological deficit was not found in any patient. A total of 24 patients had papilledema, 3 of whom presented in the acute, 16 in the subacute, and 5 in the chronic phase. In 22 patients, papilledema was accompanied by headache, while headache was absent at presentation in 2 patients.

Focal neurological deficit (hemiparesis and/or hemihypoalgesia) was found in 34.1% (15 patients). The frequency of focal and generalized seizures in patients with focal neurological deficits is shown in Table 1.

Table 1. Frequency of focal and generalized seizures in patients with focal neurological deficit

		Focal seizure	Generalize seizure	Non-seizure	Total
Focal neurological deficit	yes	5 (11.3%)	7 (15.9%)	3 (6.8%)	15 (34.1%)
	no	2 (4.6%)	3 (6.8%)	24 (54.5%)	29 (65.9%)
Total number of patient		7 (15.9%)	10 (22.7%)	27 (61.3%)	44

The possible etiological causes found in the patients are briefly summarised in Table 2.

Table 2. Possible etiological causes detected in patients

Etiological factor	Number of patients
Hereditary thrombophilia	24 (54.5%)
Malignancy	8 (18.2%)
Surgical intervention, lumbar puncture, trauma	7 (15.9%)
Oral contraceptive drug	7 (15.9%)
Infection	4 (9.1%)
Pregnancy	4 (9.1%)
Postpartum period	4 (9.1%)
Iron deficiency anemia	3 (6.8%)
Connective tissue disease	2 (4.6%)
Inflammatory bowel disease	2 (4.6%)
Thrombocytosis	1 (2.3%)
Chronic renal failure	1 (2.3%)

While clouding of consciousness was present in 20.5% of the patients, GCS values at admission were analyzed. GCS>12 in 88.6% of the patients, GCS 9-12 in 11.4%, and GCS≤8 in no patient.

The rates of hereditary thrombophilia detected in patients are summarised in Table 3.

Table 3. Rate of hereditary thrombophilia detected in patients

Hereditary thrombophilia	Number of patients
MTHFR C667T	11 (25%)
Faktor V leiden	5 (11.4%)
Protein C deficiency	3 (6.8%)
Prothrombin G20210A	2 (4.6%)
Homocysteine	2 (4.6%)
Protein S deficiency	1 (2.3%)
Total	24

Among 11 patients with homozygous MTHFR gene mutation, 1 patient had simultaneous factor V leiden (FVL), 1 patient had homozygous protein C deficiency mutation and 1 patient had homozygous protein S deficiency mutation.

Four of twenty-six female patients (15.3%) were pregnant at presentation. It was learned that one of them was in the 1st trimester, 1 in the 2nd trimester, 2 in the 3rd trimester, and 4 patients (15.3%) presented in the postpartum period. There were seven patients who were using oral contraceptive drugs (OCS), and when the accompanying aetiological factors were examined, methylene tetrahydrofolate reductase (MTHFR) C667T gene mutation was homozygous in 2 patients and heterozygous in 2. factor V leiden mutation was detected in 1 patient.

MRI and MRV were performed together for diagnostic purposes in 38 of forty-four patients. Three patients were diagnosed with CT and MRI evaluations, and three patients were diagnosed with CT and MRI together. The number of patients with direct and indirect thrombosis on neuroimaging is shown in Figure 3.

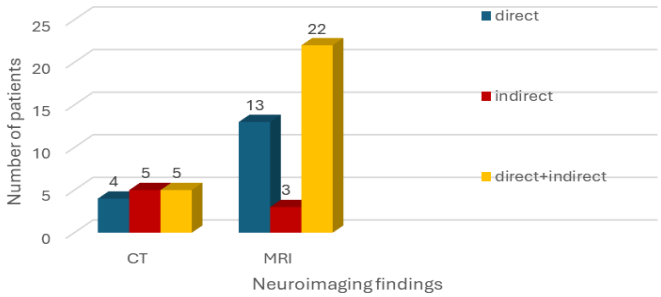

Figure 3. Number of patients with direct and indirect thrombosis detected on neuroimaging

MRI and/or MRV results of 44 patients included in the study were evaluated together, and the localization of thrombosis was defined. Multiple sinus involvement was observed in 93.2% of the patients. The topographic distribution in patients with CVT is shown in Figure 4.

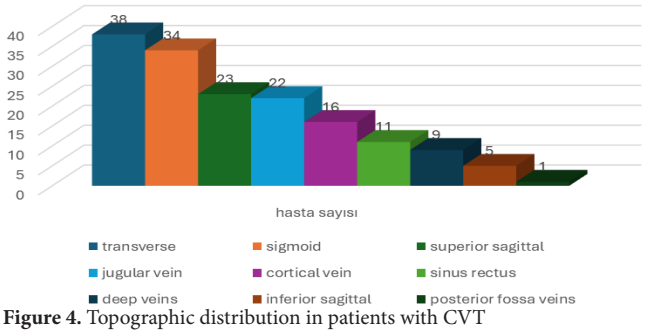

Figure 4. Topographic distribution in patients with CVT

CVT: Cerebral venous thrombosis

DISCUSSION

CVT is a complex disease to diagnose because of the variability of clinical signs and symptoms, which frequently affects young adults and children.[5] The estimated incidence is 3-4 per million population.[3] While a homogeneous distribution is observed at all ages in males, it is observed more frequently in females between the ages of 20-35 years in relation to pregnancy, puerperium, and OCS drug use.[6] In our study, the mean age was found to be 41.8±15.8 years, but the mean age of female patients was younger than that of male patients. It was thought that this may be related to gender-specific risk factors observed in women at younger ages.

In the literature, CVT is grouped as acute (2 days or less, 20-30%), subacute (2 days-1 month, 50-80%), or chronic (more than two months, 10-20%) according to the time from onset to diagnosis.[7] A study conducted in our country found that 33% of the patients presented in the acute, 40% in the subacute, and 27% in the chronic period.[8] When the duration of the presentation was analyzed in our study, it was observed that patients presented most frequently in the subacute period, followed by the acute period, and least frequently in the chronic period, similar to the literature.[8]

The mode of onset and clinical manifestations of CVT have a broad spectrum due to the diversity of collateral venous drainage, and it is known that it can mimic many neurological diseases. Headache caused by distension of pain-sensitive structures (veins and sinuses) or increased intracranial pressure is the most common symptom of CVT. Headache does not have a typical characteristic or temporal profile, is usually severe and progressive, and may mimic other primary causes of headache.[6] In two studies conducted with 624 and 1144 patients, the most common presenting symptom was headache.[9,10] Although the incidence of papilledema in sinus vein thrombosis varies between 45-86%, it has been reported to be less frequent in acute cases.[11] At the same time, papilledema was found in 24 cases; 3 of these patients presented in the acute, 16 in the subacute, and 5 in the chronic period. While focal deficit, seizure, and confusion were observed at a rate of 50-75% in the old series, they are now observed in 1/3 of the cases with early diagnosis enabled by neuroimaging methods.[12] Focal brain damage caused by venous ischemia or hemorrhage may lead to neurological signs and symptoms related to the affected area, most commonly hemiparesis and aphasia.[13] Epileptic seizures are observed with a rate of 35-40%, and literature analyses show that focal motor deficit, cortical vein thrombosis, and supratentorial parenchymal lesions are associated with the risk of early seizure development.[14,15] In a series of 100 patients with seizure accompanying thrombosis, a GCS below 8, focal damage, presence of hemorrhagic infarction, frontal lobe involvement, and superior sagittal sinus thrombosis and high D-Dimer levels were reported as risk factors for acute seizure development.[16] In our study, focal seizures were observed in 5 of 15 (34.1%) patients with focal neurological deficits, while generalized seizures were observed in 7 patients. In patients

without focal neurological deficits, 2 had focal seizures, and 3 had generalized seizures. Changes in consciousness in CVT frequently occur when deep venous structures are affected.[14] Our study found clouding of consciousness in 20.5% of the patients (9 patients), whereas cavernous sinus syndrome, recognized by painful ophthalmoparesis, chemosis, and proptosis findings, was not found.

When etiological causes are examined, the main cause cannot be found in 20-30% of patients.[2] Pregnancy, puerperium, OCS use, coagulopathies, intracranial infections, cranial tumors, penetrating head traumas, lumbar puncture, malignancy, dehydration, inflammatory bowel disease, connective tissue diseases, Behçet's disease, sarcoidosis, nephrotic syndrome, parenteral infusions, and various drugs lead to CVT.[9] In the ISCVT study, the most common cause was reported as OCS use (54.3%), followed by hypercoagulation (34.1%), pregnancy, and the postpartum period (20.1%).[9] In the VENOST study, gynecological causes were the most common cause in women and prothrombotic conditions in men, followed by infections in both sexes.[10] In our research, the most common cause in both sexes was thrombophilia (54.5%), while pregnancy and puerperium were found to be 18.8% and OCS use 15.9% in women. Compared with the literature, it is noteworthy that coagulation disorders were found at a high rate in our patients.

Pregnancy, puerperium, and OCS use are common in women, especially between the ages of 20-35 years. In the ISCVT study, pregnancy was found in 6.3% and puerperium in 13.8% of women under 50 years of age.[9] In the VENOST study, 41.7% of gynecological causes were found in our country.[10] Among 26 female patients included in our study, 4 (15.3%) were pregnant, 4 (15.3%) were in the postpartum period, and 7 (26.9%) were using OCS drugs.

In the literature, it has been reported that OCS use increased the risk of CVT from 13% to 34% in patients with hereditary thrombophilia.[17] In 7 patients with OCS use, the finding of homozygous MTHFR C667T gene mutation in 2, heterozygous in 2, and Factor V Leiden mutation in 1 (3.8%) patient is compatible with the literature.

Prothrombotic factors are among the well-defined etiological factors with a frequency of 15-35%.[18] Thrombophilic conditions including factor V Leiden mutation (FVL), protein C, protein S, antithrombin III deficiencies, factor II gene mutation, and hyperhomocysteinemia, which can be genetically demonstrated, cause a predisposition for CVT.[19] In the ISCVT study, hereditary thrombophilia was found in 22.4% of patients, and acquired thrombophilia was found in 15.7% of patients.[9]

FVL mutation is frequent in patients with CVT, and the risk increases in the presence of concomitant OCS use, pregnancy, or puerperium. In a series of 55 patients by Lüdemann et al.,[20] the presence of FVL mutation was found with a rate of 14.5%, which was significant compared with the control group. In our study, the presence of factor V Leiden mutation was found in 5 (11.4%) of 44 patients. Three of these patients were female, and 1 case had concomitant OCS use. In a study, the frequency of prothrombin G20210A mutation was reported to be 11% in patients with a diagnosis of CVT. The association of this mutation with OCS use increases the risk of CVT 10.2-fold. In patients with prothrombin G 20210 A mutation, the risk of thrombosis increased from 14.7 to 19.8 in the presence of concomitant protein C mutation.[21,22] Factor II mutation was found in 2 of our patients, one female, and one male, and there was no concomitant OCS use. Hyperhomocysteinaemia is among the causes defined in the etiology of CVT. In a case-control study published by Martinelli et al.[17] in patients with CVT, hyperhomocysteinemia was found in 33 of 121 patients and 21 of 242 healthy controls. In our study, methylene tetrahydrofolate reductase (MTHFR) C667T gene mutation was found to be homozygous in 11 patients (25%) and heterozygous in 6 patients (13.7%). In 2 patients (4.6%), homocysteine level was found to be isolated high. When compared with the literature, the reason for the lower homocysteine level in our study was thought to be inadequacies in the sampling conditions. Although protein-C, protein-S, and antithrombin III deficiency are well-known causes of venous thromboembolism, their role in CVT is unclear. Publications are reporting an association. In our study, antithrombin III deficiency was not found, protein C deficiency was found in 2 patients, and protein S deficiency was found in 1 patient.

Due to its practicality and prevalence, brain CT is used as a diagnostic method, especially in patients presenting to emergency departments with headaches. On brain CT, hyperdense appearance due to acute thrombosis in the affected sinus region, filling defects in contrast-enhanced images (delta sign), hyperdense tentorium, findings secondary to congestion in cortical veins or cerebral edema may be detected, or it may be completely normal.[23] CT shows direct findings of CVT in approximately one-third of the cases. Indirect findings are observed in 60% to 80% of cases. Small ventricles are encountered in 20% to 50% of cases. Contrast uptake in the falx and tentorium is observed in 20% of cases, and CT is normal in up to 30% of cases.[24] In our study, direct evidence of thrombosis was found in 4 (28.6%), indirect evidence in 5 (35.7%), and the presence of direct and indirect thrombosis indicators in 5 (35.7%) of 14 patients who underwent CT scans, similar to the literature.

Cranial MRI and MRV are the first choice non-invasive examinations in diagnosing CVT. Cranial MRI may show infarcts, especially hemorrhagic infarcts, which do not fit into the arterial irrigation area, and the absence of signal in venous sinuses is also diagnostic. The thrombosed sinus is best visualized on T1, T2, and FLAIR sequences and MR angiography with T2 sequence addition. Diagnosis is easy when the occlusion is complete; however, it may be difficult in partial occlusions where the flow is still present but irregular. Intraarterial angiography, previously accepted as the gold standard in the diagnosis of CVT, is currently performed only in cases in which the diagnosis cannot be confirmed by MRI and MRV.[25,26] In our study, MRI and MRV were performed together for diagnostic purposes in 38 of 44 patients. While the diagnosis of 3 patients was made by CT and MRI evaluations, the diagnosis of 3 patients was made by CT and MRV evaluation. MRI was performed in 41 cases (93.2%), and MRI revealed direct thrombosis in 13 cases (31.7%), indirect thrombosis in 3 cases (7.3%), and direct and indirect thrombosis in 22 cases (53.7%). In 3 patients (7.3%), no direct or indirect thrombosis was found, and the diagnosis was made based on the presence of thrombosis on MRV. The presence of direct and indirect thrombosis findings is similar to the literature.

In the most extensive series of 624 cases in the literature, the superior sagittal sinus (62%) was reported as the most common site of involvement. The left transverse sinus (44.7%) and the right transverse sinus (41.2%) followed, respectively.[9] In a study

conducted by Cantu et al.[27] with 113 patients, involvement was found to be 97.8%, involvement 43.4%, thrombosis of deep venous structures 21.7%, and thrombosis of cortical veins 30.4%.

MRI and/or MRV results of 44 patients included in our study were evaluated together, and the localization of thrombosis was defined. More than one sinus was observed in 41 patients (93.2%), while a single sinus was found in 3 patients. In order of frequency, transverse sinus 86.4%, sigmoid sinus 77.3%, superior sagittal sinus 52.3%, jugular vein 50%, cortical veins 36.4%, sinus rectus 25%, deep veins 20.5%, inferior sagittal sinus 11.4%, posterior fossa veins 2.3%. When compared with the literature, it is noteworthy that the transverse sinus was most commonly involved in our patients, and the superior sagittal sinus was thrombosed at a lower rate.

Treatment of CVT consists of reversal of an identifiable cause, control of seizures and intracranial hypertension, and antithrombotic therapy. Anticoagulation is the mainstay of treatment for CVT in the acute and subacute setting. Currently, most centers start treatment with subcutaneous low molecular weight heparin or intravenous heparin as soon as the diagnosis is made, even if hemorrhagic infarcts are found, and continue treatment with warfarin.[28] When the anticoagulant therapies received by the patients during follow-up in our clinic were analyzed, it was found that 56.9% started intravenous heparin and 27.3% started low molecular weight heparin. In 88% of the patients in whom heparin was initiated after the acute period, warfarin was continued in 88%, and low molecular weight heparin was continued in 12%. Among the 12 patients who received low molecular weight heparin, 66.7% of 8 patients received warfarin in the long term, and 33.3% did not. Only warfarin was given to 13.6% of the patients. In 1 case (2.3%), anticoagulant treatment was not started because of hematological contraindications.

CONCLUSION

Nowadays, with the development of new diagnostic tests, CVT recognition rates are increasing, and we have more information about the disease. Especially in the presence of an identifiable etiological cause, the mortality and morbidity of the disease can be reduced with cause-oriented treatments. It is necessary to carefully examine the coagulopathy conditions,which were especially frequently detected in our studay. Therefore, more studies on CVT are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ethics Committee of İzmir Katip Çelebi University Atatürk Training and Research Hospital (Date: 12.11.2015, Decision No: 212).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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