

ORIGINAL ARTICLE

ÖZGÜN ARAŞTIRMA

**CEREBRAL VENOUS THROMBOSIS IN PATIENTS WITH AND WITHOUT FEMALE SPECIFIC SEX FACTORS -
A SINGLE-CENTER EXPERIENCE**

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ABSTRACT

INTRODUCTION: Certain female sex specific factors (SSFs) including pregnancy, puerperium and oral contraceptive (OC) use have been associated with cerebral venous thrombosis (CVT). We aimed to determine if there are differences between female patients with and without SSFs regarding the clinical characteristics, neuroimaging findings and the prognosis of CVT.

METHODS: This is a retrospective study that included consecutive female inpatients with CVT admitted to our hospital between January 1, 2012 and December 31, 2021. The demographic and clinical characteristics, neuroimaging findings and the outcome data were collected from the patient files.

RESULTS: Fifty-three female patients were included into the study. Thirty-one (58.5%) of the patients had SSFs including pregnancy (n=2), puerperium (n=20), and OC use (n=9). The mean age of patients with SSFs was lower than that of the patients without SSFs (30.7 and 44.0, respectively, p=0.002). The mode of disease onset, clinical manifestations, epileptic seizures, parenchymal lesions, thrombosed veins, length of hospital stay did not differ between the patients with and without SSFs. Predisposing factors, including cancer, were more common in the patients without SSFs. The median of the modified Ranskin scale score of the patients with SSFs was lower than that of the patients without SSFs. The OC users were older and had a more slow disease onset than the postpartum patients. All patients were treated with anticoagulants, decompressive surgery was performed in one patient.

DISCUSSION AND CONCLUSION: The majority of the female CVT patients had SSFs, most commonly puerperium. The mean age is lower and prognosis is better in the patients with SSFs.

Keywords: Cerebral venous thrombosis, female sex, postpartum, pregnancy, oral contraceptive, neuraxial anesthesia.

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KADIN CİNSİYETE ÖZGÜ FAKTÖRLERİ OLAN VE OLMAYAN HASTALARDA SEREBRAL VENÖZ TROMBOZ - TEK MERKEZ DENEYİMİ

ÖZ

GİRİŞ ve AMAÇ: Gebelik, puerperium ve oral kontraseptif (OK) kullanımından oluşan, kadın cinsiyete özgü faktörler (CÖF) serebral venöz trombozla (SVT) ilişkilendirilmiştir. Bu çalışmada, CÖF'lerine sahip olan ve olmayan kadın SVT hastaları arasında klinik ve nörogörüntüleme özellikleri ve prognoz açısından fark olup olmadığını araştırmayı hedefledik.

YÖNTEM ve GEREÇLER: Bu retrospektif çalışmaya, 1 Ocak 2012 ve 31 Aralık 2021 tarihleri arasında kliniğimize başvuran ve hospitalize edilen ardışık kadın SVT hastaları dahil edildi. Demografik ve klinik özellikler, nörogörüntüleme bulguları ve sonlanım verileri hasta dosyalarından elde edildi.

BULGULAR: Çalışmaya 53 kadın hasta dahil edildi. Otuz bir hastada (%58,5) CÖF mevcuttu: gebelik (n=2), puerperium (n=20) ve OK kullanımı (n=9). CÖF olan hastaların ortalama yaşı, CÖF olmayan hastalardan daha düşüktü (sırasıyla 30,7 ve 44,0, p=0.002). Hastalık başlangıç şekli, klinik özellikleri epileptik nöbetler, parankimal lezyonlar, tromboze venler ve hospitalizasyon süresi açısından CÖF olan ve olmayan hastalar arasında fark yoktu. Kansere dahil predispozan faktörler CÖF olmayan hastalarda daha sıkı. CÖF olan hastalarda ortalama Rankin skoru daha düşüktü. OK kullananların yaş ortalaması postpartum hastalardan daha yüksekti ve hastalık başlangıcı daha yavaştı. Tüm hastalar antikoagülanlarla tedavi edildiler, bir hastaya dekompresif cerrahi uygulandı.

TARTIŞMA ve SONUÇ: Kadın SVT hastalarının büyük kısmında, en sık puerperium olmak üzere CÖF vardır. CÖF olan hastalarda ortalama yaş daha düşük ve prognoz daha iyidir.

Anahtar Sözcükler: Serebral venöz tromboz, kadın cinsiyet, postpartum, gebelik, oral kontraseptif, nöroaksiyel anestezi.

INTRODUCTION

Cerebral venous thrombosis (CVT) is a rare but important cause of stroke in young adults, more commonly in females of reproductive age than males (1-3). The mean age of patients with CVT has been reported to be 32.9, with a female to male ratio of 2:3 (3). Risk factors for CVT include hereditary thrombophilia, acquired prothrombotic diseases, infectious and inflammatory disorders, diagnostic or therapeutic procedures and female sex specific factors (SSFs) such as pregnancy, puerperium, oral contraceptive (OC) and hormone replacement therapy (HRT) use (1).

The incidence of CVT varies between 1.32/100000/year to 2.02/100000/year with female preponderance, the most recent publications reporting higher incidence than previously reported (4-7). During the last decades, the proportion of female patients has increased, possibly due to increased OC use (8). In the VENOST study comprising 1144 CVT patients, 68% of the patients were female and 41.7% of all patients had SSFs including puerperium, OC use or pregnancy (9). Significant demographic, clinical and prognostic differences between female patients with and without SSFs were reported (10).

In this retrospective study, we aimed to determine the demographic, clinical, imaging and the prognostic characteristics of the female CVT

patients with and without SSFs admitted to our hospital during the last ten years.

METHODS

This is a retrospective study that included consecutive female patients with CVT admitted to Cumhuriyet University Faculty of Medicine, Department of Neurology, between January 1, 2012 and December 31, 2021. Patient files, electronic medical record system and imaging system were retrospectively reviewed and the following data were retrieved and collected: the demographic characteristics of the patients, the mode and type of onset, neuroimaging (magnetic resonance imaging, MRI; computerized tomography, CT; MRI venography and CT venography) findings, predisposing factors including pregnancy, puerperium, OC and HRT use, cancer, hereditary and acquired severe prothrombotic conditions, diagnostic and therapeutic procedures such as lumbar puncture, neuraxial analgesia, spinal or cranial surgery, central vein catheterization, duration of hospitalization, and outcome on follow-up using the modified Rankin scale (mRS) (11).

The mode of onset was categorized according to the method Boussier et al. (12) suggested: acute (<48 hours), subacute (≥48 hours and <30 days),

and chronic (≥ 30 days). Clinical manifestations at onset were arbitrarily divided into three main categories including (1) a focal syndrome with epileptic seizures and focal neurological deficits, (2) isolated intracranial hypertension characterized by headache, papilledema, and abducens nerve palsy, and (3) consciousness disturbance. Homozygous mutations of factor V Leiden and prothrombin G20210A, deficiencies of protein C, protein S, and antithrombin, antiphospholipid antibody syndrome (APAS) and combined thrombophilia were considered as severe thrombophilia (13).

The following neuroimaging findings were collected: the presence or absence of parenchymal lesions on CT or MRI including venous infarction, intracerebral hematoma, hemorrhagic infarction, and subarachnoid hemorrhage; thrombosed dural sinuses and/or cortical veins on CT venography or MRI venography: superior sagittal sinus, transverse/sigmoid sinuses, deep venous system, isolated cortical vein, internal jugular vein (IJV), and multiple venous sinuses. This study was designed and conducted according to The Declaration of Helsinki ethical principles and the study protocol was approved by Cumhuriyet University Non-interventional Clinical Research Ethics Committee (Date: November 14th, 2022; Number: 2022-09/32).

The results are presented as mean (\pm standard deviation, SD), median (interquartile range, IQR), number and percentage as appropriate. The Kolmogorov-Smirnov Goodness of Fit Test was used to determine if the data was normally distributed. Chi-Square test was used to compare the categorical variables between the groups. Student's t test, independent samples t test, Kruskal Wallis test and the one-way analysis of variance with post hoc Tukey test were used to compare non-categorical variables between the groups. A p-value less than 0.05 was considered statistically significant.

RESULTS

A total of fifty-three female patients with a diagnosis of CVT were included into the study. Thirty-one patients (58.5%) had SSFs including pregnancy (n=2, 6.5%), puerperium (n=20, 64.5%), and OC use (n=9, 29%). The mean (\pm SD) age of the patients with SSFs was 30.7 (\pm 6.4, minimum - maximum 19-44) and the mean (\pm SD)

age of the patients without SSFs was 44.0 (\pm 16.9, minimum-maximum 18-80) (p=0.002) (Table).

The majority of the postpartum patients had delivered via caesarean section (CS; n=16, 80%); only four patients (20%) had delivered via vaginal birth. The mean (\pm SD) number of days after birth was 11.7 (6.5) days. The anesthetic methods used for birth were as follows: general anesthesia (n=5, 25%), spinal anesthesia (n=10, 50%), epidural anesthesia (n=2, 10%); no anesthetic methods were used for three patients (15%) delivered via vaginal birth. More than half of the postpartum patients who had undergone neuraxial blockade (spinal or epidural anesthesia) for labor had had orthostatic headache prior to CVT symptoms and 42% of them had isolated cortical vein thrombosis (ICVT) and 33% had superior sagittal sinus thrombosis. Of the twenty postpartum patients with CVT, five patients (25%) had preeclampsia or eclampsia. There were three (15%) intrauterine fetal death.

The clinical manifestations did not differ between the patients with and without SSFs: the mode of onset (acute, subacute or chronic), clinical manifestations at onset and the rate of epileptic seizures were similar in the patients with and without SSFs (p=0.741, p=0.151, and p=0.228, respectively). The median (IQR) duration of hospital stay was also similar: 16 (11-20) days in the patients with SSFs and 15.5 (11.75-20.75) days in the patients without SSFs (p=0.935). However, the median (IQR) of the mRS score of the patients with SSFs was significantly lower than that of the patients without SSFs: 0 (0-0) and 2 (0-2), respectively (p=0.000) (Table). Two patients passed away during hospitalization, the mean age of the deceased patients was 62. One of them had IJV thrombosis and the cause of death was comorbid diseases. The other patient had a large deep intracerebral hemorrhage and midline shift. Despite undergoing decompressive surgery, the patient passed away after 11 days of intensive care unit follow-up.

Regarding the presence and the nature (infarction, hemorrhagic infarction, intracerebral and subarachnoid hemorrhage) of the parenchymal lesions or the thrombosed vein, there were no differences between the patients with and without SSFs (p=0.329, p=0.688 and p=0.290, respectively, Table). There were three isolated IJV thrombosis, all of them had undergone

Table. Demographic, clinical, radiological and prognostic characteristics of the patients with and without sex specific factors.

	Patients with SSFs	Patients without SSFs	p
Age, mean (\pm SD)	30.7 (6.4)	44 (16.9)	0.002*
Thrombosed veins/sinuses, n (%)			0.290
SSS	6 (19.4)	2 (9.1)	
TS and/or SS	12 (38.7)	9 (40.9)	
Deep veins	1 (3.2%)	0 (0)	
Multiple	6 (19.4%)	5 (22.7)	
ICVT	6 (19.4)	3 (13.6)	
IJV	0 (0)	3 (13.6)	
The mode of onset, n (%)			0.741
Acute	13 (41.9)	7 (31.8)	
Subacute	16 (51.6)	13 (59.1)	
Chronic	2 (6.5)	2 (9.1)	
Symptoms at onset, n (%)			0.151
Focal deficits/seizures	17 (54.8)	7 (31.8)	
IIH	13 (41.9)	12 (54.5)	
Consciousness disturbance	1 (3.2)	3 (13.6)	
Seizure, n (%)	15 (48.4)	7 (31.8)	0.228
Parenchymal lesions, n (%)	21 (67.7)	12 (54.5)	0.329
Venous infarction	13 (41.9)	6 (27.3)	0.688
ICH	4 (12.9)	3 (13.6)	
HI	3 (9.7)	3 (13.6)	
SAH	1 (3.2)	0 (0)	
Predisposing factors*, n (%)	6 (19.4)	14 (63.6)	0.001*
Prothrombin mutation†	2 (6.5)	0 (0)	
Factor V Leiden†	1 (3.2)	0 (0)	
APAS	2 (6.5)	2 (9.1)	
Behcet's disease	0 (0)	1 (4.5)	
Infections	0 (0)	3 (13.6)	
Catheterization	0 (0)	3 (13.6)	
Cancer	0 (0)	4 (18.1)	
Duration of hospital stay, days, median (IQR)	16 (11-20)	15.5 (11.8-20.8)	0.935
mRS score, median (IQR)	0 (0-0)	2 (0-2)	0.000

SSFs= sex specific factors, SD= standard deviation, SSS= superior sagittal sinus, TS= transverse sinus, SS= sigmoid sinus, ICVT= isolated cortical vein thrombosis, IIH= isolated intracranial hypertension, ICH= intracerebral hemorrhage, HI= hemorrhagic infarction, SAH= subarachnoid hemorrhage, APAS= antiphospholipid antibody syndrome, IQR= interquartile range. * significant at $p < 0.05$ level, † homozygous mutations.

catheterization of the thrombosed vein prior to CVT.

We compared the patients with and without SSFs regarding the predisposing factors for CVT and we found that these factors were more common in the patients without SSFs (19% in the patients with SSFs and 64% in the patients without SSFs, $p = 0.001$). In addition, there were significant differences between the patients with and without SSFs regarding the predisposing factors: homozygous prothrombin G20210A and factor V Leiden mutation and APAS were the predisposing factors in the patients with SSFs, whereas APAS, cancer, Behcet's disease, infections and vein catheterization were the predisposing factors in patients without SSFs (Table).

All patients except the pregnant women were treated with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) followed by warfarin. The pregnant patients were treated with

LMWH throughout the pregnancy and during the postpartum period. As there were only two pregnant patients treated with LMWH throughout the treatment period and the prognosis of almost all patients with SSFs was excellent, no statistical comparison could be made regarding the effect of treatment methods on outcome. The treatment was started as soon as possible after diagnosis was made. Briefly, therapeutic doses of UFH or LMWH were given in addition to warfarin until internationalized normalized ratio (INR) exceeds 2.0, then warfarin monotherapy was continued with a target INR of 2.0 to 3.0 for 3 to 6 months in patients with provoked CVT due to transient risk factors, 6 to 12 months in patients with unprovoked CVT and indefinitely in patients with severe thrombophilia.

We also compared the postpartum patients and the OC users and found that the mean (\pm SD) age of the postpartum patients was lower than

that of the OC users (28.7 ± 4.9 vs. 34.9 ± 8.1 , respectively, $p=0.049$). The mode of onset was also different between the postpartum patients and the OC users: all but one of the postpartum patients had acute or subacute disease onset, whereas all of the OC users had chronic disease onset ($p=0.001$). There were no differences between the postpartum patients and the OC users regarding the clinical manifestations at onset, duration of hospitalization or outcome.

DISCUSSION AND CONCLUSION

CVT has a wide spectrum of clinical manifestations and may have an acute, subacute or chronic disease course (1,2). Headache, focal neurological symptoms, epileptic seizures and consciousness disturbance are the main symptoms (1,9). Intracranial hypertension resulting from the obstruction of venous flow and venous infarction and/or hemorrhage are responsible for the neurological symptoms and signs (13). The diagnosis may be challenging due to more variable clinical picture and less acute onset than arterial stroke and is confirmed by neuroimaging methods, MRI venography and CT venography (1,2). Treatment methods include anticoagulation with UFH, LMWH and warfarin, antiepileptics in the presence of epileptic seizures, and endovascular treatment and decompressive surgery in selected cases (1). Pregnancy, puerperium and OC use are among the most common transient causes of CVT (13).

In this study, we found that female CVT patients with SSFs including pregnancy, puerperium or OC use, were younger than female CVT patients without SSFs. The mode of onset, clinical manifestations, hospitalization duration or the neuroimaging findings were not different between the patients with and without SSFs, however, the outcome was better in the patients with SSFs. Predisposing factors except SSFs were more common in the patients without SSFs; hereditary thrombophilia and APAS were the predisposing factors in patients with SSFs, whereas Behcet's disease, cancer, vein catheterization, infections, and APAS were the predisposing factors in the patients without SSFs. We also found that the OC users were older and they had a slower disease onset than the postpartum patients. The prognosis was quite good; almost all of the patients with SSFs returned

to their baseline functional levels, two patients without SSFs had deceased; the cause of death was due to comorbid diseases in one.

In accordance with our findings, the subgroups analysis of the multicenter VENOST study has showed that, female CVT patients with SSFs were younger and had a more favorable outcome when compared to female CVT patients without SSFs (10). They also found that OC users were older than postpartum and pregnant patients, as our results suggested (10). The authors reported that they did not find any differences between the patients with and without SSFs regarding the hematologic and genetic tests indicating a prothrombotic condition (10). However, we found that when predisposing factors were restricted to the conditions that a cause-and-effect relationship determined, such as homozygous factor V Leiden and prothrombin G20210A mutation, APAS, cancer, infections, Behcet's disease or certain diagnostic and therapeutic procedures, rather than including all genetic factors such as heterozygous methylenetetrahydrofolate reductase or plasminogen activator inhibitor-1 mutations, the patients without SSFs had higher predisposing factors than the patients without SSFs. Of note, cancer was more common in the patients without SSFs, as reported by Uluduz et al. (10). In terms of disease onset and clinical manifestations, Uluduz et al. (10) reported that acute disease onset, epileptic seizures and focal neurological deficit were more frequent in patients with SSFs than in patients without SSFs, we also found that the patients with SSFs tended to have a more acute presentation with focal deficits and/or seizures than the patients without SSFs. However, the differences did not reach statistical significance, probably due to the smaller case numbers in our study.

Almost one fifth of adult CVT cases are pregnant or postpartum women (14). The risk is highest during the first weeks postpartum, an almost 19-fold increased risk has been reported during this period (15). Hypertension, CS, certain infections have been reported to be significantly associated with peripartum and postpartum CVT (16). A pooled, systematic review including sixty-six patients with pregnancy and puerperium-related CVT, Kashkous et al. (17) reported that, the prognosis was good, 94% of the patients had mRS 0-2 at follow-up.

In our study, postpartum patients consisted the majority of the patients with SSFs (65%), 80% of the postpartum patients delivered via CS and more than half had had neuraxial blockage. CVT occurred mean 12 days after labor. Headache typical of intracranial hypotension resulting from cerebrospinal fluid leakage through the dural puncture prior to CVT symptoms was a frequent complaint in these patients. Obstetric neuraxial blockade has been associated with postpartum CVT; high rate of accidental dural puncture and post-dural puncture headache suggest a causal relationship (18). The proposed mechanism is cerebrospinal fluid depletion resulting from dural puncture, intracranial hypotension, compensatory venodilatation accompanied by the prothrombotic condition associated with puerperium (18). In these patients, superior sagittal sinus and cortical veins are the most common sites of thrombosis, as in our cases, 75% of whom had superior sagittal sinus thrombosis and ICVT (18).

Another striking finding of our study is that 25% of our postpartum patients had preeclampsia/eclampsia. Preeclampsia, a multisystemic inflammatory disorder, characterized by hypercoagulability, platelet activation, endothelial injury and venous thrombosis, complicates 2 to 5% of pregnancies (19, 20). Preeclampsia is considered to be a risk factor for CVT, as well as other cerebrovascular diseases during pregnancy and puerperium (20). The observed high frequency of preeclampsia/eclampsia in our patients may suggest a causal relationship.

Our study has several limitations including its retrospective design and small number of cases in some subgroups, for example pregnancy-related CVT.

In conclusion, we found that almost 60% of female patients with CVT have SSFs including pregnancy, puerperium and OC use. Women with SSFs are younger, have better prognosis and less predisposing factors for CVT and tend to have a more acute course with focal neurological deficits and/or seizures. Postpartum patients are younger and have more acute disease onset than OC users. Mean number of days between birth and CVT symptoms is 12 days. Preeclampsia/eclampsia, intrauterine fetal death, CS and neuraxial anesthesia procedures are common in postpartum patients with CVT. The majority of postpartum patients who have undergone neuraxial anesthesia

have orthostatic headache prior to CVT symptoms and superior sagittal sinus thrombosis and ICVT are common in these patients. Cancer, infections and vein catheterization are the most common predisposing factors in patients without SSFs. The prognosis is quite good in patients with SSFs, almost all of them return to their premorbid functional status on follow-up. However, patients without SSFs have worse prognosis.

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Ethics

Ethics Committee Approval: The study was approved by Cumhuriyet University Non-interventional Clinical Research Ethics Committee (Date: 14.11.2022, Number: 2022-09/32).

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