Research Article

Cerebral Venous Sinus Thrombosis in Women: Subgroup Analysis of the VENOST Study

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1. Introduction

Cerebral venous sinus thrombosis (CVST) is an uncommon form of stroke [1]. Several risk factors for CVST have been recognized including pregnancy, puerperium, oral contraceptive (OC) use, infections, inflammatory diseases, and thrombophilia. CVST is believed to be more common in women than in men [1, 2]. In addition, there is uniform age distribution in men, while 60% of women with CVST are clustered at 20-35 years old [1-4]. In some studies, one of third cases was clustered in periods of pregnancy and puerperium [5].

This study was performed to evaluate details about CVST among women and focused on reproductive health-related risk factors (RHRF) such as pregnancy, puerperium, and OC use.

2. Materials and Methods

This study includes 777 female CVST cases of the VENOST cohort. VENOST is a retrospective and multicenter observational study that includes 1144 patients with CVST diagnosed at 35 national neurology centers. In diagnosing CVST, the criteria defined in the VENOST study were used [1].

The patients were divided into two groups according to reproductive health-related risk factors (RHRF) such as oral contraceptive use, puerperium, and pregnancy as the RHRF (+) group and the RHRF (-) group. At the initial admission, both groups were evaluated according to demographics, clinical symptoms, and neurological signs. Radiological workup included brain computed tomography (CT), brain magnetic resonance imaging (MRI), MR venography, and/or digital subtraction angiography. Etiological factors, acute and
maintenance treatment, and follow-up results were evaluated for each group. Then, the RHRF (+) group was divided into three subgroups according to risk factors such as oral contraceptive use, puerperium, and pregnancy, and these subgroups were evaluated using the same risk factors. Putative etiological risk factors included the following: infections
Table 3: Comparison of demographic and clinical characteristics of subgroups according to reproductive health-related risks.

| Compared data of reproductive health-related risk factors | Pregnancy | Puerperium | Oral contraceptive use | p |
|-----------------------------------------------------------|-----------|------------|------------------------|---|
|                                                           | n = 74, 23% | n = 142, 44% | n = 108, 33% | |
| Age                                                       | 32.2 ± 6a | 32 ± 7a | 38 ± 9b | <0.001 |
| Mode of onset                                             |           |           |            |      |
| Acute                                                     | 70       | 85a       | 62         | 59a   | 56   |
| Subacute                                                  | 19       | 42a       | 31         | 26b   | 25   | <0.030 |
| Chronic                                                   | 11       | 10b       | 7          | 20a   | 19   |
| Clinical symptoms and signs                               |           |           |            |      |
| Isolated headache                                         | 22       | 24        | 17         | 26    | 24   | 0.361 |
| Headache                                                  | 93       | 117       | 82         | 96    | 89   | 0.062 |
| Nausea and vomiting                                      | 30       | 43        | 30         | 42    | 39   | 0.283 |
| Epileptic seizures                                        | 24       | 63b       | 44         | 29a   | 27   | 0.002 |
| Visual field defect                                       | 23       | 28        | 20         | 21    | 19   | 0.817 |
| Focal neurological                                        | 15       | 41        | 29         | 29    | 27   | 0.068 |
| Deficit                                                   | 22       | 34        | 24         | 17    | 16   | 0.277 |
| Altered consciousness                                     | 8        | 8         | 6          | 10    | 9    | 0.537 |
| Radiological workup                                       |           |           |            |      |
| Cranial MRI                                               | 4        | 6         | 12         | 9     | 7    | 7    | 0.975 |
| Cranial MRV                                               | 3        | 4         | 6          | 4     | 3    | 3    |
| Cranial MRI+MRV                                           | 65       | 89        | 122        | 86    | 97   | 90   |
| Cranial CT+MRV                                            | 1        | 1         | 2          | 1     | 1    | 1    |
| Number of sinuses involved                                |           |           |            |      |
| 1 sinus                                                   | 35       | 47        | 68         | 48    | 40   | 37   | 0.490 |
| 2 sinuses                                                 | 26       | 35        | 51         | 36    | 49   | 45   |
| More than 2 sinuses                                       | 13       | 18        | 23         | 16    | 19   | 18   |
| Involved sinuses                                          |           |           |            |      |
| Isolated transverse                                       | 21       | 28        | 34         | 24    | 23   | 21   | 0.547 |
| Sinuses                                                   | 11       | 15        | 20         | 14    | 13   | 12   | 0.838 |
| Isolated sagittal                                         | 2        | 3         | 3          | 2     | 2    | 1    | 0.926 |
| Sinuses                                                   | 1        | 1         | 9          | 6     | 1    | 1    | 0.051 |
| Isolated sigmoid                                          | 0        | 0         | 1          | 1     | 0    | 0    | 0.526 |
| Sinuses                                                   | 0        | 0         | 0          | 0     | 0    | —    |      |
| Isolated cortical veins                                   | 57       | 77        | 99         | 70    | 87   | 81   | 0.132 |
| Isolated jugular sinus                                    | 30       | 41        | 53         | 37    | 44   | 41   | 0.830 |
| Isolated cavernous                                        | 25       | 34        | 60         | 42    | 49   | 45   | 0.284 |
| Sinuses                                                   | 13       | 18        | 17         | 12    | 17   | 16   | 0.490 |
| Transverse sinuses                                        | 2        | 3         | 11         | 8     | 3    | 3    | 0.120 |
| Sigmoid sinuses                                           | 0        | 0         | 2          | 1     | 1    | 1    | 0.798 |
| Sagittal sinuses                                          |           |           |            |      |
| Internal jugular vein                                     |           |           |            |      |
| Cortical veins                                             |           |           |            |      |
| Cavernous sinuses                                         |           |           |            |      |

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3. Results

In this study, 58% (n = 453) of the total 777 female cases were classified as RHRF (-) and 42% (n = 324) of them as RHRF (+). The mean ages of the RHRF (+) group and the RHRF (-) group were 34 ± 9 and 43.2 ± 13, respectively, and were significantly different.

Acute onset is more frequent in the RHRF (+) group, whereas a subacute chronic mode of onset is more common in the RHRF (-) group. The most common symptoms were headache, visual field defects, and cranial neuropathies in the RHRF (-) group and headache and epileptic seizure in the RHRF (+) group. The comparison of these two groups according to clinical symptoms and signs: epileptic seizures (34%), nausea and vomiting (33%), and focal neurologic deficit (25%), was more common in the RHRF (+) group and visual field defect (29%) and cranial nerve palsies (13%) were more common in the RHRF (-) group.

In the total female group investigations, CVST was diagnosed with cranial MRI and MRV in 682 patients, with cranial MRI in 46 patients, with only cranial MRV in 31 patients, and with cranial CT and MRV in 14 patients. Parenchymal lesions were detected in 333 (42.8%) female patients including 160 (49.3%) in the RHRF (+) group and 173 (38.1%) in the RHRF (-) group (p = 0.003). Parenchymal lesion involvement, especially hemorrhagic transformation (n = 80, 25%), was more common in the RHRF (+) group. Venous involvement was found in 1 sinus in 373 (48%) female patients, in 2 sinuses in 274 (35%) patients, and in more than 2 sinuses in 130 (17%) patients. In the comparison of these two groups, there was no difference in intravenous involvement. Transverse sinus involvement was the most common site thrombosis within the total female group (n = 572, 73%), within the RHRF (+) group (n = 243, 75%), and within the RHRF (-) group (n = 329, 73%). The sigmoid sinus and sagittal sinus involvements were followed by transverse sinus in two groups.

Demographic aspects and comparative data of cases with RHRF (+) and RHRF (-) are displayed in Table 1.

A positive previous history of venous thromboembolism and malignancy was detected in 6% and 7% in the RHRF (-) group. Hematologic parameters were completed in 206 (26.5%) patients, and no differences were detected between the two groups. When the RHRF (+) group was investigated, it was found to be the largest group in the puerperium period (43.8%) but the smallest group in the pregnancy period (22.8%). Rankin scores, which suggested neurological disability after 12 months, were found significantly high in the RHRF (-) group. Etiological factors and outcome according to groups are presented in Table 2.

The mean age of OC users was higher than other groups. The mode of acute clinical onset was high in all subgroups of RHRF (+) cases. In addition, chronic onset and intracerebral hemorrhage ratio were found more frequently in the OC user group than in the other subgroups. Epileptic seizures were found to be significantly higher in the puerperium group. Demographic and clinical characteristics of subgroup analyses are shown in Table 3.

A history of deep venous thrombosis ratio was found high in the pregnancy group. Hematologic and genetic tests and Ranking scales were similar among the groups. A comparison of etiological factors and outcomes of subgroups is seen in Table 4.

4. Discussion

Pregnancy, puerperium, and hormone replacement treatment increase the tendency to cerebral venous sinus thrombosis (CVST) in women. CVST is much more frequently seen in women than in men -a ratio of 3/1 [6]. In the study of Coutinho et al., female ratio was found to be 75% and female gender-specific risk factors at 65% [4]. In the International Study on Cerebral Venous and Dural Sinus Thrombosis (ISCVST), the female ratio was found to be 75% of patients. Gender-specific risk factors such as OCs, pregnancy, puerperium, and hormone replacement therapy were responsible [7]. The results of meta-analyses showed that
gender-specific risk factors were only not effective in children and the elderly female groups and that the use of OCs increased venous thrombosis development in reproductive age females [8]. In our study, the female ratio was found to be 68% and gender-specific risks which were grouped as RHRF (+) by us were found in 41% of women. Our findings are similar to the results of previous studies.

In our study, the mean age of women with reproductive health-related risk factors (RHRF) was lower than that of the RHRF (-) group. In subgroup analyses of RHRF (+) cases,
the mean age of OC users was higher than that of the other groups. This difference may be related to planning of the age of pregnancy [3].

Previous venous thrombosis history, thrombophilia, certain medical comorbidities, obesity, smoking, and postpartum hemorrhage increase the risk of CVST [9, 10]. In our study, the highest part of the RHRF (+) group consisted of cases of puerperium. Puerperium often occurs in the sixth to eighth week after delivery. In different population-based case-control studies on venous thrombosis, it was explained that risk increased 5-fold in the pregnancy period and a 60-fold in the puerperium [11]. Also, it has been reported that it occurs more commonly after a cesarean birth than a vaginal birth [12]. Infection, high maternal age and excessive vomiting during pregnancy increase the development of venous sinuses. On the other hand, isolated cavernous sinus involvement is high in the presence of septicemia [13]. All of the hormone levels, cardiovascular system, and pregnancy-related hematologic changes return to the baseline state within the slow process of puerperium. Human chorionic gonadotropin (hCG) and sex steroids are at low levels for the first 2-3 weeks. These changes may cause the tendency to thrombosis [14–16].

In our study, headache was the most frequent symptom for all subgroups. However, epileptic seizures were higher in the puerperium group. In the study of Kashkoush et al., the highest frequencies of symptom were found to be headache (74%), seizure (50%), and an altered consciousness (45%) in puerperium [17].

The inherited mutations in anticoagulant or thrombolytic factors genes (the Factor V Leiden, the prothrombin Factor II) and mutations in genes coding for proteins C and S may increase the risk of developing venous thrombosis [18]. We did not find any relationship between inherited risk factors and CVST.

Venous thrombosis risk increases with OC use. Combined OCs containing estrogen and progesterone have higher risk [19]. When the patient has a history of previous CVST, the recurrence risk is increased by OC use [20, 21]. We did not determine the content of the OCs. In the RHRF (-) group, a previous history of CVST was high. In the subgroup analysis, a previous history of CVST was high in the “pregnancy group.” Very little is known about the relapse rate during pregnancy and puerperium in women with a history of CVST [22]. The results of our study suggest that physicians must keep in mind the possible recurrence of CVST in pregnancy.

In our study, malignancy was more frequent in the RHRF (-) group. It has been reported that cancer patients have an increased risk of tendency of venous thrombosis [23].

In the study by Lee et al., it has been reported that the transverse sinus is involved in the majority of cases (75.6%). Sigmoid sinus and superior sagittal sinus involvement followed it at ratios of 58.5% and 29.3%, respectively [24]. In our study, the “transverse sinus” was affected more than other venous sinuses. On the other hand, isolated cavernous sinus involvement was significantly high in RHRF (-) group. Cavernous sinus involvement is high in the presence of septicemia and malignancy [25]. Therefore, in our study, this result was expected to be more in the RHRF (-) group.

It has been reported that the prognosis in pregnant patients is better than in nonpregnant patients with CVST if they receive timely treatment [26]. In the VENOST main study, the prognosis of CVST was found to be better in women than men [1]. In our subgroup analysis, the prognosis was found to be worse in the RHRF (-) group.

5. Conclusions

Our results indicate that when CVST was detected in women with RHRF (-), the existence of malignancy should be investigated. The previous history of CVST may be related to recurrence in pregnancy. Clinical onset may present with chronic headache in CSVT cases related to OC use. Epileptic seizures may be a more frequent symptom in puerperal CSVT cases. Physicians must keep these situations in mind.

Data Availability

All data will be available on request.

Conflicts of Interest

The authors declared that they have no conflicts of interest for this article.

Authors’ Contributions

Sevki Sahin and Taskin Duman have contributed equally.

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