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Behçet's disease as a causative factor of cerebral venous sinus thrombosis: subgroup analysis of data from the VENOST study

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Abstract

Objective. This study was performed to determine the rate of cerebral venous sinus thrombosis (CVST) among cases of Behçet's disease (BD) included in a multicentre study of cerebral venous sinus thrombosis (VENOST).

Methods. VENOST was a retrospective and prospective national multicentre observational study that included 1144 patients with CVST. The patients were classified according to aetiologic factors, time of CVST symptom onset, sinus involvement, treatment approach and prognosis.

Results. BD was shown to be a causative factor of CVST in 108 (9.4%) of 1144 patients. The mean age of patients in the BD group was 35.27 years and 68.5% were men, whereas in the non-BD CVST group, the mean age was 40.57 years

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and 28.3% were men ($P < 0.001$). Among the aetiologic factors for patients aged 18–36 years, BD was predominant for men, and puerperium was predominant for women. The onset of symptoms in the BD group was consistent with the subacute form. The transverse sinuses were the most common sites of thrombosis, followed by the superior sagittal sinuses. The most common symptom was headache (96.2%), followed by visual field defects (38%).

Conclusions. BD was found in 9.4% of patients in our VENOST series. Patients with BD were younger and showed a male predominance. The functional outcome of CVST in patients with BD was good; only 12% of patients presenting with cranial nerve involvement and altered consciousness at the beginning had a poor outcome (modified Rankin Score $\geqslant 2$).

Key words: Behçet's disease, cerebral venous sinus thrombosis, outcome, subgroup analysis, VENOST study

Rheumatology key messages

- Behçet's disease affected 9.4% of patients in our cerebral venous sinus thrombosis series.
- Behçet's disease should be considered first as a causative factor for cerebral venous sinus thrombosis among 18- to 36-year-old men.
- Behçet's disease patients with cerebral venous sinus thrombosis were younger and functional outcome after treatment was good.

Introduction

Behçet's disease (BD) is a chronic, multisystemic, inflammatory vascular disease characterized by oral and genital ulcerations, uveitis and skin involvement [1]. It shows a relapsing and remitting pattern, and is most prevalent in Mediterranean countries, the Middle East, East Asia and Japan [2–4]. Epidemiologic studies have indicated that BD is rare, with incidence rates ranging from 20 to 420/100 000 in Turkey, 80/100 000 in Iran and 0.64/100 000 in the UK [5]. The pathogenesis of the disease is related to vasculitis involving arteries and veins of all sizes and types [6], but its aetiology remains unclear [7].

Neurologic involvement (neuro-BD) is relatively rare but shows a high degree of variability, ranging from 5 to 35% across studies [8]. A diagnosis of neuro-BD can be made if the following criteria are met: fulfilment of the International Diagnostic Criteria for BD and its revised form [9, 10], the presence of neurologic symptoms not otherwise explained by any other known systemic or neurologic disease or treatment, objective abnormalities detected in neurologic examination and/or neuroimaging studies, and/or abnormal cerebrospinal fluid findings consistent with neuro-BD [11]. Central and peripheral nervous system involvement may occur in BD, and CNS involvement can be classified as parenchymal or neurovascular pathology. The neurologic manifestations of BD are related to meningoencephalitis, tumour-like lesions, brainstem involvement, arterial occlusions and cerebral venous sinus thrombosis (CVST); this latter manifestation was reported to occur in ~20% of cases of neuro-BD [12] and is more common in paediatric patients with BD, being relatively rare in adults [13].

Geographic, ethnic, cultural and socioeconomic differences among populations may underlie the discrepancies observed in the aetiologies of CVST. CVST is associated with a wide range of aetiologic conditions that are typically multifactorial, and 44% of patients have more than one predisposing factor [14]. The aetiology of CVST can range from thrombophilia to infection. The incidence rates of and aetiologic factors related to CVST have been determined in large European and American series [15], but BD is rare in these countries compared with those in the Mediterranean region and the Middle East. Determination of the incidence of BD as a risk factor for CVST in Arab or Middle Eastern countries is difficult because data have only been reported from small series in these regions [16–19]. Overall, there is insufficient information regarding the concomitant predisposing factors for CVST in patients with BD. Limited data are available regarding the clinical features of CVST in BD compared with other aetiologies.

Here, we report the frequency of BD as an aetiological factor for CVST with the aim of determining concomitant predisposing factors, and describe the main characteristics, treatment approaches, long-term outcomes and factors that affect the prognosis of CVST in patients with BD compared with other aetiologies.

Methods

The methodology for the multicentre study of cerebral venous thrombosis (VENOST), a retrospective and prospective national multicentre observational study that included 1144 patients with CVST diagnosed at 35 centres from June 2000 to June 2015, was described in detail previously [20]. The study was approved by the ethics committee of the coordinating centre (no: 83045809/604/02-12333). No additional approval was required for this study. The present study included all participants in the VENOST cohort. In VENOST, diagnoses of CVST were based on both the clinical presentation of patients and evidence of thrombosis in the cerebral venous sinuses as detected using cranial CT, MRI, magnetic resonance venography and/or digital subtraction angiography (according to established diagnostic criteria) [21]. The patients were classified according to aetiologic factors of CVST and then divided into two groups according to the identified risk factors of CVST: those in whom BD was a risk factor and those with other aetiologies.

Based on the large VENOST cohort, patients with CVST with and without BD were compared according to their clinical presentation on admission, additional concurrent aetiologic factors, imaging findings and prognostic factors. Patients were diagnosed as having BD according to the International Diagnostic Criteria for BD. Among the 1144 patients included in the VENOST study, we identified 108 cases (9.4%) complicated with CVST, as indicated by the clinical and imaging features and confirmed by expert neurologists. The requirement for written informed consent was waived because the study was based on a review of medical records that had been obtained for clinical purposes.

A systematic search for thrombotic conditions was performed in 63.7% of the participating centres. Thrombotic screening included protein S, protein C, antithrombin III, prothrombin mutation (G20210A mutation), factor V Leiden, methylenetetrahydrofolate reductase (*MTHFR*) mutation (C677T polymorphism), LA and aCL. For female patients, a detailed history was taken regarding the puerperium period and oral contraceptive use.

Most authors have used the modified Rankin Score (mRS) to show the rate of dependence for patients with venous infarcts [21–23]. In our study, we also used the mRS to provide information about the severity and outcomes of CVST. We followed up patients for about 1 year, and the mRS was measured at months 1, 3 and 6, and at 1 year.

Results

The VENOST study included 1144 patients with CVST from 35 centres, as confirmed through clinical examinations and detailed imaging; 108 (9.4%) patients were shown to have BD. We compared the demographic characteristics and sex ratio between non-BD patients with CVST (non-BD group, $n = 1036$) and patients with BD who had CVST (BD group, $n = 108$) (Table 1). The mean age of patients in the BD group was 35.27 years and 68.5% were men; both of these values were significantly different from those of the non-BD group (40.57 years and 28.3% men, respectively; $P < 0.001$) (Table 1). Male and female patients in the BD group had mean ages of 33.53 and 39.06 years, respectively ($P = 0.024$), indicating that disease involvement occurred earlier in men than in women (supplementary Table S1, available at *Rheumatology* online).

Symptom onset in the BD group was consistent with the subacute form (43.4%), whereas the acute form (49.4%) was more common among patients in the non-BD group ($P < 0.001$) (Table 1).

In the BD group, the most common symptom was headache (92.6%), followed by visual field defects (38%), nausea and/or vomiting (25.9%), cranial nerve palsy ($n = 14.8\%$), focal neurologic deficits (8.3%), epileptic seizures (7.4%) and altered consciousness (4.6%). However, the most common symptom in the non-BD group was headache (86.6%), followed by nausea and/or vomiting (27.9%). Headache was the only symptom that occurred in isolation (without any other neurologic deficits) in 34 patients (31.5%) in the BD group; this was higher than the rate in the non-BD group, but the difference did not reach statistical significance (Table 1).

Epileptic seizures, focal neurologic deficits and altered consciousness were more common in the non-BD group than in the BD group ($P < 0.001$, $P = 0.005$ and $P < 0.001$, respectively), whereas visual field defects were more common in the BD group than in the non-BD group ($P = 0.005$) (Table 1). In our VENOST series, for patients in the non-BD group, gynaecologic causes of CVST

Table 1 Demographic and clinical characteristics and imaging findings of the patients in both groups

Demographic, clinic and imaging findings	Behçet's (–) $n = 1036$	Behçet's (+) $n = 108$	*P*-value
Age (years)	40.57 (13.89)	35.27 (10.61)	<0.001
Gender			
Female	743 (71.7)	34 (31.5)	<0.001
Male	293 (28.3)	74 (68.5)	
Symstoms onset			
Acute	503 (49.3)	27 (25.5)	<0.001
Subacute	337 (33.0)	46 (43.4)	
Chronic	180 (17.6)	33 (31.1)	
Symptoms			
Isolated headache	253 (24.4)	34 (31.5)	0.107
Headache	897 (86.6)	100 (92.6)	0.076
Nausea and/or vomitting	289 (27.9)	28 (25.9)	0.663
Epileptic seizures	263 (25.4)	8 (7.4)	<0.001
Visual field defect	262 (25.3)	41 (38.0)	0.005
Focal neurological deficit	199 (19.2)	9 (8.3)	0.005
Altered consciousness	199 (19.2)	5 (4.6)	<0.001
Cranial nerve palsies	112 (10.8)	16 (14.8)	0.209
Sinuses involvement			
Isolated transverse sinuses	264 (25.5)	28 (25.9)	0.920
Isolated sagittal sinuses	145 (14.0)	23 (21.3)	0.041
Isolated sigmoid sinuses	34 (3.3)	3 (2.8)	0.778
Isolated cortical veins	23 (2.2)	1 (0.9)	0.372
Isolated jugular sinuses	15 (1.4)	1 (0.9)	0.660
Isolated cavernous sinuses	9 (0.9)	0 (0.0)	0.331
Transverse sinuses	764 (73.7)	76 (70.4)	0.450
Sigmoid sinuses	416 (40.2)	39 (36.1)	0.414
Sagittal sinuses	397 (38.3)	48 (44.4)	0.214
Internal jugular vein	163 (15.7)	15 (13.9)	0.615
Cortical veins	40 (3.9)	2 (1.9)	0.291
Cavernous sinuses	19 (1.8)	0 (0.0)	0.156
Parancyhmal involvement			
No lesion	600 (57.9)	85 (78.7)	<0.001
Infarction	195 (18.8)	23 (21.3)	
Haemorrhagic infarction	198 (19.1)	0 (0.0)	
Intracerebral haemorrhage	43 (4.2)	0 (0.0)	
Gynaecological causes			
Oral contraceptive	108 (14.5)	0 (0.0)	0.017
Pregnancy	73 (9.8)	1 (2.9)	0.181
Puerperium	142 (19.1)	0 (0.0)	0.005
Infections			
Paracranial (focal)	66 (6.4)	4 (3.7)	0.150
Systemic	23 (2.2)	0 (0.0)	
History of VTE			
Cerebral	19 (1.8)	7 (6.5)	<0.001
Deep venous thrombosis	29 (2.8)	12 (11.1)	
Other	8 (0.8)	0 (0.0)	
Malignancy	59 (5.7)	0 (0.0)	0.011
Family history of VTE	11 (1.1)	0 (0.0)	0.282

Values are *n* (%) unless otherwise stated. VTE: venous thromboembolism.

were seen most frequently (43.4%); 142 (19.1%) patients were in puerperium ($P = 0.005$), and 108 (14.5%) patients were using oral contraceptives ($P = 0.017$). Furthermore, in 73 (9.8%) patients, pregnancy was an aetiologic factor. These aetiologies were the most commonly seen among the women. Only one (29%) patient in the BD group had a gynaecologic cause of CVST (supplementary Table S1, available at *Rheumatology* online). On the other hand, BD was the most commonly seen aetiology among men (20.5%).

Patients were subdivided according to age groups (18–36, 37–50 and 51+ years); in the young age group (18–36 years), gynaecologic factors were predominant among women and BD was the most prevalent among men; in the oldest age group, malignancy was predominant (Tables 2 and 3, and supplementary Table S2, available at *Rheumatology* online).

Haematologic parameters were determined in 941 (82.3%) patients, and genetic screening for thrombotic conditions was performed in 729 patients (63.7%). Thrombotic conditions were observed in 321 patients (41.7%) in the non-BD group; 12 patients with BD (18.4%) had thrombotic conditions, but this did not reach statistical significance (supplementary Table S3, available at *Rheumatology* online). A positive previous history of deep vein thrombosis or venous sinus thrombosis was observed in 19 patients in the BD group.

A history of deep vein thrombosis was observed in 12 (11.1%) patients, which was a 4-fold higher number than in the non-BD group ($P < 0.001$); all of these patients were men (Table 1 and supplementary Table S1, available at *Rheumatology* online). A history of malignancy was reported in 5.7% of patients in the non-BD group, but there was no history of malignancy in the BD group ($P < 0.011$) (Table 1).

Neuroimaging features

The most common diagnostic imaging modalities used were cranial MRI and magnetic resonance venography. Radiologic imaging revealed parenchymal lesions in 23 (21.3%) patients (Table 1). The rate of parenchymal lesion involvement was lower in the BD group than in the non-BD group (21.3% *vs* 42.1%; $P < 0.001$). Haemorrhagic infarct and intracerebral haemorrhage were not seen in the BD group, but the incidences of these were 19.1 and 4.2%, respectively, in the non-BD group ($P < 0.001$) (Table 1). The transverse sinuses, either in isolation (25.9%) or with multiple involvement (70.4%), were the most common sites of thrombosis followed by the superior sagittal sinuses (SSS) (isolated SSS, 21.3%; SSS with multiple involvement, 44.4%) in the BD group, but isolated SSS involvement was statistically significant ($P = 0.041$) (Table 1). There were sex differences in terms of involvement of the sinuses; in particular, the SSS was involved more frequently in men ($n = 20$, 27%) than in women ($n = 3$, 8.8%) ($P = 0.032$). Sigmoid sinus involvement was more common among female patients with BD than male patients with BD (50% *vs* 29.7%; $P = 0.042$) (supplementary Table S1, available at *Rheumatology* online).

Treatment and outcome

In our study, within the first month of therapeutic intervention, 71.3% of the patients were first treated with an intravenous pulse steroid for 3–5 days, and the treatment was then alternated by tapering doses of an oral steroid while a therapeutic dose of low-molecular-weight heparin (100 IU/kg $\times 2$) was administered for 1 month. After 1 month, the same intervention group received warfarin treatment for the remaining 5 months. For some of these patients, unfractionated heparin within therapeutic doses was preferred within the first 10 days rather than low-molecular-weight heparin. During this period, the effect of treatment on the patients was assessed by monitoring the activated partial thromboplastin time. Before delivering heparin in unfractionated or low-molecular-weight forms, patients were screened for pulmonary artery aneurism, which is a presenting symptom of BD.

Twenty-three percent of the patients were treated with an oral anticoagulant without a steroid over the 6-month period. Warfarin was the only drug used to continue treatment. We did not use direct oral anticoagulants. Seven (6.4%) patients who could not tolerate warfarin treatment received antiaggregant therapy. In any instances of allergic reactions or intolerance, clopidogrel was used as a substitute for aspirin. CVST can also cause venous infarcts, and this type of infarct results in paresis.

The mRS score at the first visit was available for 98 (90.7%) patients with BD. The distribution of mRS scores was as follows: 0–1, $n = 85$ (86.7%) patients; 2, $n = 7$ (7.1%) patients; and $\geqslant 3$ $n = 6$ (6.1%) patients. Data for the 3-month follow-up were available for 91 (84.3%) patients. The 6-month follow-up data were available for 89 (82.4%) patients, and 1-year follow-up data were available for 87 (80.6%) patients. The outcome of the patients was mRS 0–1 in 86.7, 92.3, 95.5 and 96.6% of patients at months 1, 3, 6 and 12, respectively. These data indicate that the outcomes were good for patients with CVST related to BD (Table 4). Patients presenting with cranial nerve involvement and altered consciousness at the beginning had a poor outcome (mRS $\geqslant 2$) in the first month of follow-up (Table 5).

Discussion

BD is not a common cause of CVST, being implicated in only about 1% of cases according to large, multicentre cohort series from Europe and the USA [14, 21]. Incidence rates of 0.9% have been reported for the Middle East and Saudi Arabia (Table 6) [16–18]. The incidence of BD among patients with CVST ranged from 7 to 10% in studies performed on small numbers of patients recruited from single centres [25, 26]. However, in our previous study, which was the largest single-centre study performed to date [20], BD was present in 9.4% of patients with CVST.

Electronic searches of the MEDLINE database indicated that the rate of occurrence of CVST in patients with BD varied among different regions of the world. Many studies

Table 2 Aetiological factors and outcome according to sex distribution

Aetiological factors and outcomes	Gender		Total	
	Female *n* (%)	Male *n* (%)	*n* (%)	*P*-value
Gynaecological causes				
Oral contraceptive	108 (13.9)		108 (13.9)	
Pregnancy	74 (9.5)		74 (9.5)	
Puerperium	142 (18.3)		142 (18.3)	
Infections				
Paracranial (focal)	33 (4.2)	37 (10.1)	70 (6.1)	<0.001
Systemic	12 (1.5)	11 (3.0)	23 (2.0)	
History of VTE				
Cerebral	13 (1.70)	13 (3.50)	26 (2.30)	<0.001
Deep venous thrombosis	17 (2.20)	24 (6.50)	41 (3.60)	
Other	8 (1.00)	0 (0.00)	8 (0.70)	
Malignancy	33 (4.20)	26 (7.10)	59 (5.20)	0.043
Family history of VTE	6 (0.80)	5 (1.40)	11 (1.00)	0.353
MTHFR mutations heterozygote	28 (5.6)	9 (3.9)	37 (5.1)	0.505
MTHFR mutations homozygote	33 (6.6)	13 (5.6)	46 (6.3)	
Hyperhomosisteinaemia	21 (3.3)	24 (7.7)	45 (4.8)	0.003
Phrothrombin mutation	12 (2.4)	7 (3.0)	19 (2.6)	0.634
Protein C/S deficiency	38 (6.0)	9 (2.9)	47 (5.0)	0.038
Factor V Leiden mutation	22 (4.4)	15 (6.5)	37 (5.1)	0.243
Thrombocytosis	4 (0.6)	6 (1.9)	10 (1.1)	0.080
Polistemia Vera	3 (0.5)	4 (1.3)	7 (0.7)	0.190
Anticardiolipin Ab	3 (0.5)	3 (1.0)	6 (0.6)	0.390
PAI mutation	6 (1.2)	4 (1.7)	10 (1.4)	0.584
Antithrombin III deficiency	4 (0.6)	1 (0.3)	5 (0.5)	0.516
Hyperfibrinogenaemia	2 (0.3)	1 (0.3)	3 (0.3)	0.992
Antiphospholipid Ab	11 (1.7)	0 (0.0)	11 (1.2)	0.003
Activated protein C resistancy	9 (1.4)	5 (1.6)	14 (1.5)	0.832
High ANA titres	17 (2.7)	4 (1.3)	21 (2.2)	0.168
Behçet's disease	34 (4.6)	74 (20.5)	108 (9.4)	<0.001
SLE	13 (1.7)	2 (0.6)	15 (1.4)	<0.001
First month mRS				
0–1	540 (80.0)	247 (75.1)	787 (78.4)	0.097
2	77 (11.4)	40 (12.2)	117 (11.7)	
>3	58 (8.6)	42 (12.8)	100 (10.0)	
Third month mRS				
0–1	514 (89.9)	250 (87.1)	764 (88.9)	0.042
2	38 (6.6)	16 (5.6)	54 (6.3)	
>3	20 (3.5)	21 (7.3)	41 (4.8)	
Sixth month mRS				
0–1	477 (92.4)	235 (89.7)	712 (91.5)	0.429
2	22 (4.3)	15 (5.7)	37 (4.8)	
>3	17 (3.3)	12 (4.6)	29 (3.7)	
12th month mRS				
0–1	424 (93.4)	219 (92.4)	643 (93.1)	0.665
2	15 (3.3)	7 (3.0)	22 (3.2)	
>3	15 (3.3)	11 (4.6)	26 (3.8)	

VTE: venous thromboembolism; MTHFR: methylenetetrahydrofolate reductase; PAI: plasminogen activator inhibitor; mRS: modified Rankin Score.

related to this subject have been published, including both retrospective and prospective studies. The incidence of CVST per 1000 person-years was 3 (95% CI: 1, 8), and it was higher in retrospective studies (3.2, 95% CI: 1, 10) than in prospective studies (2.7, 95% CI: 1, 13). Among patients with neurologic involvement, the incidence rate was 15.1/1000 person-years. The highest frequency rates of 10 and 24/1000 person-years were reported in the series of Wechsler *et al.* [27] and Farah *et al.* [28], respectively.

There have been several reports of CVST in BD. Most of the articles that we found in MEDLINE focused on the prevalence of CVST in patients with BD, with a range of 10–12% [29, 30]. All of these articles focused on the incidence or prevalence of CVST in patients with BD, which

Table 3 Aetiological factors and outcome according to age groups

Aetiological factors and outcomes	Age group (years)			*P*-value
	18–36 *n* (%)	37–50 *n* (%)	51+ *n* (%)	
Gynaecological causes				
Oral contraceptive use	50 (13.8)	49 (17.1)	9 (7.0)	0.022
Pregnancy	55 (15.2)	19 (6.6)	0 (0.0)	<0.001
Puerperium	108 (29.8)	31 (10.8)	3 (2.3)	<0.001
Infections				
Paracranial (focal)	27 (5.1)	23 (6.1)	20 (8.7)	0.407
Systemic	10 (1.9)	9 (2.4)	4 (1.7)	
History of VTE				
Cerebral	10 (1.9)	9 (2.4)	7 (3.0)	0.957
Deep venous thrombosis	20 (3.8)	14 (3.7)	7 (3.0)	
Other	4 (0.8)	3 (0.8)	1 (0.4)	
Malignancy	9 (1.7)	14 (3.7)	36 (15.6)	<0.001
Family history of VTE	5 (0.9)	4 (1.1)	2 (0.9)	0.971
MTHFR mutation heterozygote	22 (6.3)	11 (4.7)	4 (2.8)	0.317
MTHFR mutation homozygote	26 (7.4)	14 (5.9)	6 (4.2)	
Hyperhomosisteinaemia	22 (4.9)	14 (4.5)	9 (4.9)	0.969
Phrothrombin mutation	8 (2.3)	7 (3.0)	4 (2.8)	0.864
Protein C/S deficiency	25 (5.6)	16 (5.2)	6 (3.3)	0.470
Factor V Leiden mutation	12 (3.4)	19 (8.1)	6 (4.2)	0.038
Thrombocytosis	3 (0.7)	5 (1.6)	2 (1.1)	0.463
Polistemia Vera	2 (0.4)	1 (0.3)	4 (2.2)	0.085
Anticardiolipin Ab	3 (0.7)	3 (1.0)	0 (0.0)	0.243
PAI mutation	1 (0.3)	5 (2.1)	4 (2.8)	0.030
Antithrombin III deficiency	1 (0.2)	2 (0.6)	2 (1.1)	0.381
Hyperfibrinogenaemia	2 (0.4)	0 (0.0)	1 (0.5)	0.298
Antiphospholipid Ab	6 (1.3)	3 (1.0)	2 (1.1)	0.891
Activated protein C resistancy	7 (1.6)	6 (1.9)	1 (0.5)	0.389
High ANA titres	6 (1.3)	11 (3.6)	4 (2.2)	0.126
Behçet's disease	68 (13.2)	27 (7.3)	13 (5.9)	0.005
SLE	6 (1.2)	5 (1.4)	4 (1.8)	0.093
First month mRS				
0–1	379 (80.6)	267 (79.9)	141 (70.5)	0.036
2	52 (11.1)	36 (10.8)	29 (14.5)	
>3	39 (8.3)	31 (9.3)	30 (15.0)	
Third month mRS				
0–1	357 (90.6)	262 (89.1)	145 (84.8)	0.004
2	21 (5.3)	24 (8.2)	9 (5.3)	
>3	16 (4.1)	8 (2.7)	17 (9.9)	
Sixth month mRS				
0–1	332 (92.5)	250 (93.6)	130 (85.5)	0.002
2	17 (4.7)	12 (4.5)	8 (5.3)	
>3	10 (2.8)	5 (1.9)	14 (9.2)	
12th month mRS				
0–1	295 (94.6)	225 (93.8)	123 (88.5)	0.003
2	9 (2.9)	10 (4.2)	3 (2.2)	
>3	8 (2.6)	5 (2.1)	13 (9.4)	

VTE: venous thromboembolism; MTHFR: methylenetetrahydrofolate reductase; PAI: plasminogen activator inhibitor; mRS: modified Rankin Score.

was different from the aim of the present study; we aimed to determine the potential causes of BD in patients with CVST, not the rate of CVST among patients with BD. This affected the point of emphasis with respect to the study group. BD remains an important factor to consider in patients with CVST in Mediterranean and Middle Eastern countries. The majority of reports focused on BD in these regions account for about 9–25% of patients with CVST in a small sample size [17, 31, 32]. Among our larger sample size of patients with CVST, we found that 9.4% patients had BD.

BD is not as common in Western countries; however, in Western countries, there are increasing numbers of immigrants, especially from the Middle East. BD has to be

considered among young males from this population who admit with CVST. So, our data could be applicable in patients from immigrant populations.

CVST has a significantly higher incidence among women, but it is generally seen at higher rates among men. In the present study, 68.5% of the patients in the BD group were men. In our VENOST study, like most other studies, we found that gynaecologic factors ($n = 324$) were the main causative factors in CVST, and the other aetiologies were BD ($n = 108$), infectious disease ($n = 99$) and *MTHFR* C677T mutations ($n = 83$) (Table 2). Many articles and multicentre studies reported that the most commonly encountered risk factors were oral contraceptive use, pregnancy and puerperium, which makes the disease more predominant in women. In our study, the patients were subdivided into three groups according to age (18–36, 37–50 and 51+ years), and we found that BD was the first aetiologic factor among men aged 18–36 years with CVST, and for women in puerperium. Thus, if a young man is admitted with CVST, BD should be considered first as a causative factor, especially in countries in which the disease is common. Although gynaecologic factors generally underlie the pathology of CVST, such factors were not common among patients with BD in our series, which may have been related to the high prevalence among men.

In the present study, symptom onset in the BD group was consistent with the subacute form, but it is generally accepted that the mode of onset is acute in nature but shows a progressive course in clinical follow-up. The most frequent signs of CVST in patients with BD are usually headache, papilledema, fever, nausea/vomiting, focal neurologic deficits, seizures and confusion. The SSS and transverse sinuses are the most commonly affected sinuses, with no bias for the left or right sinuses. In our study, headache was also the most frequent sign of CVST, and the transverse sinuses were the most common sites of thrombosis.

Saadoun *et al.* [33] reported thrombotic factors in 31% (16/51) of CVST patients with BD. However, as mentioned previously, their study included 64 consecutive patients with CVST who fulfilled the internationally recognized criteria for BD. It is known that BD has concurrent thrombotic risk factors. In the present study, 12 (11%) of 108 patients showed thrombotic conditions, which is lower than in previous studies. We found no statistical relationship between the relapse course or worsening condition and concomitant thrombotic risk factors in patients with BD.

In our study, we used the mRS to provide information about the severity and outcomes of CVST. The outcome of patients was commonly mRS 0–1. In the literature, most authors found good outcomes, with 89.1% of patients achieving complete recovery [23]. The proportion of patients with recurrent CVST was low [34, 35].

The current study had several limitations, including a lack of information regarding prognostic factors in the 1-year period and the relapse rate of BD. We also had no information regarding recanalization of the venous sinuses, or on the effect of the treatment strategy on prognosis.

In conclusion, BD was found in 9.4% of the patients with CVST in our VENOST series. Patients with BD were younger and showed a male predominance compared

Table 4 Outcome according to the mRS between the patient groups

Outcomes	Behçet's (−) $n = 1036$	Behçet's (+) $n = 108$	*P*-value
First month ($n = 1004$)			
0–1	702 (77.5)	85 (86.7)	0.107
2	110 (12.1)	7 (7.1)	
⩾3	94 (10.4)	6 (6.1)	
Third month ($n = 859$)			
0–1	680 (88.5)	84 (92.3)	0.556
2	50 (6.5)	4 (4.4)	
⩾3	38 (4.9)	3 (3.3)	
Sixth month ($n = 778$)			
0–1	627 (91.0)	85 (95.5)	0.129
2	36 (5.2)	1 (1.1)	
⩾3	26 (3.8)	3 (3.4)	
12th month ($n = 691$)			
0–1	559 (92.5)	84 (96.6)	0.190
2	22 (3.6)	0 (0.0)	
⩾3	23 (3.8)	3 (3.4)	

Values are *n* (%). mRS, modified Rankin Score.

Table 5 Risk factors according to a higher mRS (⩾2, first month) among patients with Behçet's disease

Risk factors	Univariate OR (95% CI)	*P*-value	Multivariate OR (95% CI)	*P*-value
Headache, yes/no	0.208 (0.043, 1.007)	0.051	1.086 (0.096, 12.309)	0.947
Focal neurological deficit, yes/no	9.000 (1.915, 42.300)	0.005	5.401 (0.597, 48.846)	0.133
Altered consciousness, yes/no	12.45 (1.852, 83.714)	0.009	13.237 (1.312, 133.519)	0.028
Cranial nerve palsies, yes/no	8.250 (2.223, 30.611)	0.002	7.788 (1.777, 34.133)	0.006
Parencyhmal involvement isolated venous infarction/no lesion	3.696 (1.093, 12.502)	0.035	1.192 (0.197, 7.212)	0.848

mRS: modified Rankin Score.

Table 6 Aetiological comparisons among published clinical studies

References	Study design	Number of patients	Mean age, years	Gynaecologic, %	Prothorombotic, %	Infectious, %	Malignancy, %	Behçet's disease, %
Ferro *et al.* [14]	Multi-centre European	640	39.1	74.4 Pregnancy: 6.3 Puerperium: 13.8 OC: 54.3	34.1	12.3	7.4	1
Wasay *et al.* [24]	Multi-centre USA	182	38	12 Pregnancy + puerperium: 7 OC: 5	21	0.5	7	1
Khealani *et al.* [16]	Pakistan and Middle East	109	35	20	5	18	4.6	0.9
Algahtani *et al.* [18]	Saudi Arabia	111	29.5	32.6 Pregnancy + puerperium: 20 OC: 12.6	19.8	9.9	9.9	0.9
Souirti *et al.* [25]	Moroccan	30	27.9	Post partum: 33	15	26	7	7
Duman *et al.* [20]	Turkey	1144	40.7	41.7 Pregnancy: 9.5 Puerperium: 18.3 OC: 13.9	26.4	8.1	5.2	9.4

OC: oral contraceptives.

with other aetiologic factors related to CVST; therefore, BD should be considered first as a causative factor among men, especially in countries in which the disease is common. As a result, in our series, the functional outcome of CVST in patients with BD was good; only 12% of patients presenting with cranial nerve involvement and altered consciousness at the beginning had a poor outcome (mRS $\geqslant 2$).

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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