A Multicenter Study of 1144 Patients with Cerebral Venous Thrombosis: The VENOST Study

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Background: Based on a number of small observational studies, cerebral venous sinus thrombosis has diverse clinical and imaging features, risk factors, and variable outcome. In a large, multicenter cerebral venous thrombosis (VENOST) study, we sought to more precisely characterize the clinical characteristics of Caucasian patients. *Methods:* All data for the VENOST study were collected between the years 2000 and 2015 from the clinical follow-up files. Clinical and radiological characteristics, risk factors, and outcomes were compared in terms of age and sex distribution. *Results:* Among 1144 patients 68% were women, and in older age group (>50 years) male patients were more prevalent (16.6% versus 27.8%). The most frequent symptoms were headache (89.4%) and visual field defects (28.9%) in men, and headache (86.1%) and epileptic seizures (26.8%) in women. Gynecological factors comprised the largest group in women, in particular puerperium (18.3%). Prothrombotic conditions (26.4%), mainly methylenetetrahydrofolate reductase mutation (6.3%) and Factor V Leiden mutation (5.1%), were the most common etiologies in both genders. 8.1% of patients had infection-associated and 5.2% had malignancy-related etiology that was significantly higher in men and older age group. Parenchymal involvement constitutively hemorrhagic infarcts, malignancy, and older age was associated with higher Rankin score. Epileptic seizures had no effect on prognosis. *Conclusions:* Clinical and radiological findings were consistent with previous larger studies but predisposing factors were different with a higher incidence of puerperium. Oral contraceptive use was not a prevalent risk factor in our cohort. Malignancy, older age, and hemorrhagic infarcts had worse outcome. **Key Words:** Cerebrovascular disease—cerebral venous sinus thrombosis—clinic—imaging.

Introduction

Cerebral venous and sinus thrombosis (CVST) results from thrombosis of the cerebral venous system, including dural venous sinuses, and deep and superficial cerebral veins.[1] CVST is presumed to be less frequent than ischemic infarct and intracerebral hemorrhage (ICH) with an estimated incidence range of 1-12 cases per million per year, and it accounts for .5%-3% of all stroke types.[2-5]

CVST is associated with a wide range of etiological conditions. The main risk factors for CVST are thrombophilia, oral contraceptive use, pregnancy, puerperium, infections, and malignancy.[5,6] Both genetic and acquired prothrombotic disorders may also give rise to CVST.[6] Geographic, ethnic, cultural, and socioeconomic factors in different populations have been reported to explain epidemiological, etiological, and clinical discrepancies of CVST.[7,8] The clinical characteristics of CVST may be expressed in a broad spectrum from headache to coma that mimicked numerous other disorders which poses a diagnostic and therapeutic challenge.[9,10]

The largest study for CVST was a prospective and multicenter study comprised of 624 patients leading to determine reliable evidence on clinical presentation, risk factors, outcome, and prognostic factors.[7] Cerebral venous sinuses thrombosis (VENOST) is a national, multicenter retrospective and prospective study including 1144 patients with CVST. Based on Ferro et al,[7] we aimed to reveal geographical and ethnic discrepancies on the clinical and etiological parameters comparing previous studies.

Materials and Methods

VENOST is a retrospective and prospective multicenter, hospital-based observational study of CVST patients aged more than 18 years. Thirty-five comprehensive national stroke centers agreed to participate in the study. Medical records of 1193 patients with CVST were obtained from follow-up files. All data for the VENOST study were collected between the years 2000 and 2015 from the clinical follow-up files. Patients followed by the years between 2000 and 2013 were retrospectively evaluated whereas patients were included prospectively after 2013. CVST patients were identified by neurologists, mostly vascular neurologists, working in the subspecialty clinics at their respective institutions. The study was approved by ethical committee of the coordinating center (No. 83045809/604/02-12333). A standardized case report form was used to collect the clinical data. The diagnosis of CVST was documented based on both the clinical presentation of patients and of thrombosis in cerebral venous sinuses on cranial computed tomography (CT) scan, magnetic resonance imaging (MRI), magnetic resonance venography (MRV), and digital cerebral angiography (DSA) according to established diagnostic criteria.[11] All data were

reviewed for logic and consistency by the 2 coordinators and a statistician.

The following data were retrieved: demographics, clinical symptoms and neurological signs at the initial hospital admission, radiological evaluations, etiological factors, acute and maintenance treatment, and follow-up results. Type of onset was considered to be acute if duration of symptoms was less than 48 hours on admission, subacute if duration was between 48 hours and 1 month, and chronic if symptom duration was longer than 1 month. A list of associated illnesses or conditions that might predispose to CVST was recorded. Putative etiological and risk factors included the following: infections (systemic or paracranial infection—otitis media, mastoiditis, or sinusitis); gynecological etiologies (such as puerperium/pregnancy or oral contraceptive use); systemic inflammatory diseases; rheumatologic or connective tissue disease; malignancy (including hematologic malignancies); hematologic diseases; and other specified causes. Behçet's disease was also investigated. Information on patient and family history of CVST, deep venous thrombosis, or pulmonary embolism was noted. Clinical symptoms and signs were recorded as progressive headache, nausea and vomiting, seizures, altered consciousness, visual field disturbances, focal neurological deficit (such as hemiparesis/plegia), and cranial nerve involvement. The number of involved sinuses or veins, localizations of thrombus, and lesions at admission on CT and MRI scans (presence of parenchymal involvement, ischemic infarction, hemorrhagic infarction, ICH) was obtained. Information on acquired or congenital thrombophilic abnormalities, including antithrombin III, protein C/S deficiency, homocysteine, anticardiolipin and antiphospholipid antibodies, mutations in the methylenetetrahydrofolate reductase gene (MTHFR), prothrombin gene, Factor V Leiden or plasminogen activator inhibitor (PAI) gene, and antinuclear antibodies, was collected if available. All treatment modalities based on physician preference were recorded.

As the frequency and etiology of CVST may vary according to sex and age, patients were compared by sex and age groups for the clinical symptoms, etiological factors, vascular involvement, and frequency of parenchymal involvement. Regarding the median age of our patients which is 37 years, the patients were divided into 3 categories: less than 37 years of age, 37-50 years, and more than 50 years (postmenopausal period). Outcome in the follow-up was categorized with the modified Rankin Scale (mRS). Patients with mRS scores of 0-1 were classified as independent (favorable outcome), mRS score of 2 as minimal disability, and mRS scores of 3-6 as dependent or dead (poor outcome). Follow-up visits were recorded after 1, 3, 6, and 12 months of the initial diagnosis of CVST, if available, for patients who were followed up directly through interviews and observations by the investigators to determine the periodic results of patient's functional outcome.

Statistical Methods

Continuous data were summarized as mean ± standard deviation or median with interquartile range, and categorical data were presented as frequency and percent. Independent sample t-test was used to compare groups for continuous variables. Categorical data were analyzed by using Pearson chi-square or likelihood ratio test statistics. Odds ratios (OR) were calculated for the possible prognostic factors using the multivariate logistic regression analysis. Statistical analyses were conducted with SPSS v.22 statistical package (SPSS Inc Released 2009. Version 22, Armonk, NY, USA).

Results

Among the 1193 patients diagnosed with CVST, a total of 1144 with confirmed CVST were recruited. Forty-nine patients were excluded as their data were inconclusive. Table 1 presents key demographic data. The female rate was 67.9% in general whereas the percentage of male patients was higher in the older age group (16.6% versus 27.8%) ($P < .001$). Acute mode of onset is overall the most frequent (50.1%) in women ($P = .003$), with subacute mode of onset more common in men (41.5%) ($P < .001$).

Acute mode of onset is more common in younger ages (49.6% in young patients and 42.2% in patients >50 years) ($P = .046$), whereas chronic mode of onset is more prevalent in older age (15.7% versus 25.9%) ($P < .001$).

Clinical and Neuroimaging Features

The most common symptom was headache (n = 997 cases; 87.2%), followed by nausea and vomiting (n = 317, 27.7%), visual field defects (n = 303, 26.5%), epileptic seizures (n = 271, 23.7%), focal neurological deficits (n = 208, 18.2%), altered consciousness (n = 204, 17.8%), and cranial nerve palsies (n = 128, 11.2%) (Table 1). Other minor symptoms were aphasia/dysarthria (1.2%) and hypoesthesia (2.0%). In 287 (25.1%) patients, headache was the only symptom without any other neurological deficit. A total of 271 (23.7%) patients experienced presenting seizures before the diagnosis of CVST, and seizure was observed early within 24 hours of onset in 164 patients. Epileptic seizures were found to be significantly more frequent in women (26.8% versus 17.2%; $P < .001$). Epileptic seizures were not impacted by age ($P = .585$). Focal neurological deficit was also more frequent in women (19.7% versus 15.0%, $P = .054$). Epileptic seizures did not have a negative impact on mRS scores of the patients, and most patients with epileptic seizures had favorable outcome. The most frequent symptoms and findings in men were headache (89.4%) and visual field defect (28.9%) whereas it was headache (86.1%) and epileptic seizures (26.8%) in women. Visual field defects were frequently observed in younger age groups ($P = .036$), but altered consciousness and cranial nerve palsies were

Table 1. *Demographic and clinical characteristics of VENOST patients according to gender distribution*

		Gender				Total		
		Female		Male				
		n	%	n	%	n	%	*P*
Age group	18-36	362	46.6	171	46.6	533	46.6	.999
	37-50	286	36.8	94	25.6	380	33.2	<.001
	51+	129	16.6	102	27.8	231	20.2	<.001
Mode of onset	Acute	382	50.1	148	40.7	530	47.1	.003
	Subacute	232	30.4	151	41.5	383	34.0	<.001
	Chronic	148	19.4	65	17.9	213	18.9	.526
Clinical symptoms and signs	Isolated headache	185	23.8	102	27.8	287	25.1	.147
	Headache	669	86.1	328	89.4	997	87.2	.123
	Nausea and vomiting	223	28.7	94	25.6	317	27.7	.276
	Epileptic seizures	208	26.8	63	17.2	271	23.7	<.001
	Visual field defect	197	25.4	106	28.9	303	26.5	.207
	Focal neurological deficit	153	19.7	55	15.0	208	18.2	.054
	Altered consciousness	145	18.7	59	16.1	204	17.8	.286
	Cranial nerve palsies	83	10.7	45	12.3	128	11.2	.429
Radiological workup	Cranial MRI	46	6.0	14	3.8	60	5.3	.263
	Cranial MRV	31	4.0	10	2.7	41	3.6	
	Cranial MRI + MRV	682	88.2	333	91.0	1015	89.1	
	Cerebral angiography	14	1.8	9	2.5	23	2.0	
Number of sinuses involved	1 sinus	373	48.0	178	48.5	551	48.2	.159
	2 sinuses	274	35.3	113	30.8	387	33.8	
	More than 2 sinuses	130	16.7	76	20.7	206	18.0	
Involved sinuses	Isolated transverse sinuses	200	25.7	92	25.1	292	25.5	.808
	Isolated sagittal sinuses	110	14.2	58	15.8	168	14.7	.463
	Isolated sigmoid sinuses	25	3.2	12	3.3	37	3.2	.963
	Isolated cortical veins	19	2.4	5	1.4	24	2.1	.233
	Isolated jugular sinuses	10	1.3	6	1.6	16	1.4	.640
	Isolated cavernous sinuses	6	.8	3	.8	9	.8	.936
	Transverse sinuses	572	73.6	268	73.0	840	73.4	.832
	Sigmoid sinuses	310	39.9	145	39.5	455	39.8	.901
	Sagittal sinuses	291	37.5	154	42.0	445	38.9	.144
	Internal jugular vein	118	15.2	60	16.3	178	15.6	.613
	Cortical veins	29	3.7	13	3.5	42	3.7	.873
	Cavernous sinuses	15	1.9	4	1.1	19	1.7	.299
Parenchymal involvement	No lesion	444	57.1	241	65.7	685	59.9	.005
	Infarction	153	19.7	65	17.7	218	19.1	.419
	Hemorrhagic infarction	148	19.0	50	13.6	198	17.3	.017
	Intracerebral hemorrhage	32	4.1	11	3.0	43	3.8	.326

Abbreviations: MRI, magnetic resonance imaging; MRV, magnetic resonance venography.

nonsignificantly more frequent in ages more than 50 years (P = .312 and .326, respectively).

CVST was diagnosed with cranial MRI and MRV in 1015 patients, with cranial CT and/or CT venography in 35 patients, and with cranial CT, MRI, and MRV in 6 patients. The most common modality used was both MRI and MRV imaging (89.1%). The diagnosis of CVST was established in DSA in suspicious 23 (2.0%) patients. Radiological imaging revealed parenchymal lesions in 459 (40.1%) patients and the remaining patients had normal imaging (including patients with isolated edema). A total of 416 (36.4%) patients had infarction at diagnosis, in which 198 were with hemorrhagic transformation (17.3%) and 43 had hemorrhagic stroke (3.8%). Parenchymal lesion involvement was observed least frequently in younger age, and as the age increased, so did the rate of the parenchymal infarction, and it was most commonly observed in patients aged more than 50 years.

Venous involvement was found in 1 sinus in 551 (48.2%) patients, in 2 sinuses in 387 (33.8%) patients, and in more than 2 sinuses in 206 (18.0%) patients. More than half of the patients had involvement of multiple sinuses. The

transverse sinus either in isolated or multiple involvement was the most common site thrombosis (73.4%, n = 840), followed by the sigmoid sinus (39.8%, n = 455) and superior sagittal sinus (SSS) (38.9%, n = 445). By location, 292 (25.5%) patients had a thrombosis in isolated transverse sinus (in which 64.0% had right transverse sinus involvement), 168 (14.7%) in isolated SSS, 37 (3.2%) in isolated sigmoid sinus, and 24 (2.1%) in isolated cortical venous thrombosis (Table 1). There were no sex differences in terms of involvement of the sinuses ($P = .159$). The involvement of isolated jugular vein and isolated cavernous sinus, and involvement of more than 2 sinuses were observed more frequently in older age ($P = .027$, $P = .007$).

Etiology and Risk Factors

Gynecological causes comprised the largest group (41.7%), including 142 (18.3%) patients in puerperium, 108 (13.9%) patients using oral contraceptives, and 74 (9.5%) patients in pregnancy. A total of 108 patients had Behçet's disease (9.4%), and 15 patients had systemic lupus erythematosus (1.4%). A positive previous history of venous thromboembolism was observed in 67 cases (5.9%) and family history was observed in 11 (1.0%) patients (Table 2). Hematological parameters were completed in 941 (82.3%) patients and genetic screening for thrombophilia was recorded in 729 (63.7%) patients. In 248 (26.4%) patients, prothrombotic conditions were found; some patients had 2 or more prothrombotic conditions together increasing the number to 297 patients. These causes included MTHFR homozygote mutation in 46 (6.3%) patients and heterozygote mutation in 37 (5.1%) patients, Factor V Leiden homozygote mutation in 37 (5.1%), prothrombin gene mutation in 19 (2.6%) and PAI mutation in 10 (1.4%), protein S or protein C deficiency in 47 (5.0%), hyperhomocysteinemia in 45 (4.8%), iron deficiency anemia in 30 (3.2%), activated protein C resistance in 14 (1.5%), thrombocytosis in 10 (1.1%), polycythemia vera in 7 (.7%), anticardiolipin Ab in 6 (.6%), hyperfibrinogenemia in 3 (.3%), antithrombin III deficiency in 5 (.5%), iron deficiency anemia in 30 (3,2%), and sickle cell anemia in 2 (.2%) (Table 2).

Fifty-nine patients (5.2%) were malignancy related. The most frequent malignancies consisted of breast cancer in 8 patients, hematological malignancies in 7 patients, colon cancer in 4 patients, central nervous system malignancy in 4 patients, and lung cancer in 3 patients. History of malignancy was found to be significantly higher in cases involving 50 years of age ($P < .001$) (Table 2). Ninety-three (8.1%) patients had infection-associated CVST; 70 (6.1%) patients had paracranial infection including sinusitis, otitis media, and mastoiditis; and 23 (2.0%) patients had systemic infections. The frequency of the paracranial infections was increased by age (Table 2) and infection etiology is more common in men ($P < .001$). A total of 269 (23.5%) patients had more than 1 known risk factor. Fourteen patients were categorized in miscellaneous causes (spinal anesthesia [n = 4], head trauma [n = 2], thyroid disease [n = 3], dehydration [n = 3], ulcerative colitis [n = 2]). Underlying causes were not identified in 281 (24.6%) patients.

Treatment and Outcome

In the early period, most patients were anticoagulated (83.9%) with intravenous heparin (796 cases; 69.6%) or subcutaneous low-molecular weight heparin (LMWH) (164 patients; 14.3%) in effective dosages. A total of 763 (66.7%) patients received warfarin, 48 (4.2%) patients received antiplatelet drugs, and 46 (4.0%) patients continued LMWH in prophylactic dosage. The severity and outcome of CVST were evaluated with mRS and outcome was evaluated by clinicians. mRS score in the first month visit was available for 1004 (87.8%) patients. The distribution of the scores was as follows: mRS 0-1 in 787 (78.4%) patients, mRS 2 in 117 (11.7%) patients, mRS 3-5 in 100 (10.0%) patients, and none of the patients had mRS 6 due to CVST. Follow-up visits were evaluated through face-to-face interviews by clinicians. Data for the 3-month follow-up were available for 859 (75.0%) patients. The 6-month follow-up was obtained in 778 (68.0%) patients and 1-year follow-up was obtained in 691 (60.4%) patients. In the third month evaluation, cases with mRS higher than or equal to 3 were found to be significantly higher in men (7.3% versus 3.5%, $P = .042$) and higher age group ($P = .001$). The 12th month outcome was favorable in younger age ($P = .057$) whereas it is poor in older age group ($P = .001$) (Table 2).

The outcome of the patients was determined according to mRS scores. There were no differences according to sex related to disease course at the end of the first year. Patients presenting with focal neurological deficit and impaired consciousness had a worse outcome. On the other hand, the progress of the illness was better in patients with visual field defect, isolated headache, and cranial nerve palsies. Concerning radiological findings according to mRS scores, univariate analysis revealed that the outcome was favorable in patients with no parenchymal lesions and worst in patients with hemorrhagic infarcts (Table 3). A 1-year prognosis was favorable for the patients with the transverse sinus involvement ($P = .026$), the follow-up was unfavorable for the SSS ($P = .001$). CVST was caused by gynecological etiology such as puerperium and oral contraceptive use; the cause of the disease was favorable whereas there was no difference for the course of the disease at puerperium period. The course of the disease showed positive results in infectious-related CVST cases. But malignancy, which was the underlying cause, showed unfavorable results ($P = .003$). We did not find different clinical course results according to etiology related to MTHFR mutation, Factor V Leiden mutation, Behçet's disease, protein C/S deficiency,

Table 2. *Etiological factors and outcome according to age groups*

	Age group						
	18-36		37-50		51+		
	n	%	n	%	n	%	*P*
Gynecological causes							
Oral contraceptive use	50	13.8	49	17.1	9	7.0	.022
Pregnancy	55	15.2	19	6.6	0	.0	<.001
Puerperium	108	29.8	31	10.8	3	2.3	<.001
Infections							
Paracranial (focal)	27	5.1	23	6.1	20	8.7	.830
Systemic	10	1.9	9	2.4	4	1.7	.165
History of VTE							
Cerebral	10	1.9	9	2.4	7	3.0	.622
Deep venous thrombosis	20	3.8	14	3.7	7	3.0	.886
Other	4	.8	3	.8	1	.4	.847
Malignancy	9	1.7	14	3.7	36	15.6	<.001
Family history of VTE	5	.9	4	1.1	2	.9	.971
MTHFR mutation heterozygote	22	6.3	11	4.7	4	2.8	.237
MTHFR mutation homozygote	26	7.4	14	5.9	6	4.2	.354
Hyperhomocysteinemia	22	4.9	14	4.5	9	4.9	.969
Prothrombin mutation	8	2.3	7	3.0	4	2.8	.864
Protein C/ S deficiency	25	5.6	16	5.2	6	3.3	.470
Factor V Leiden mutation	12	3.4	19	8.1	6	4.2	.038
Thrombocytosis	3	.7	5	1.6	2	1.1	.463
Polisitemia vera	2	.4	1	.3	4	2.2	.085
Anticardiolipin Ab	3	.7	3	1.0	0	.0	.243
PAI mutation	1	.3	5	2.1	4	2.8	.030
Antithrombin III deficiency	1	.2	2	.6	2	1.1	.381
Hyperfibrinogenemia	2	.4	0	.0	1	.5	.298
Antiphospholipid Ab	6	1.3	3	1.0	2	1.1	.891
Activated protein C resistance	7	1.6	6	1.9	1	.5	.389
High ANA titers	6	1.3	11	3.6	4	2.2	.126
Behçet's disease	68	13.2	27	7.3	13	5.9	.005
SLE	6	1.2	5	1.4	4	1.8	.093
First month Rankin							
0-1	379	80.6	267	79.9	141	70.5	.010
2	52	11.1	36	10.8	29	14.5	.371
>3	39	8.3	31	9.3	30	15.0	.026
Third month Rankin							
0-1	357	90.6	262	89.1	145	84.8	.128
2	21	5.3	24	8.2	9	5.3	.263
>3	16	4.1	8	2.7	17	9.9	.001
Sixth month Rankin							
0-1	332	92.5	250	93.6	130	85.5	.011
2	17	4.7	12	4.5	8	5.3	.938
>3	10	2.8	5	1.9	14	9.2	<.001
12th month Rankin							
0-1	295	94.6	225	93.8	123	88.5	.057
2	9	2.9	10	4.2	3	2.2	.518
>3	8	2.6	5	2.1	13	9.4	.001

Abbreviations: ANA, anti nuclear anticor; MTHFR, methylenetetrahydrofolate reductase; PAI, plasminogen activator inhibitor; SLE, systemic lupus erythematosus; VTE, venous thromboembolism.

Table 3. *Univariate analysis between radiological findings and mRS scores*

	Univariate		
Radiological finding	OR	95% CI	*P*
Isolated venous infarction/No lesion	4.270	1.457-12.513	.008
Hemorrhagic venous infarction/No lesion	7.753	2.889-20.801	<.001
Hemorrhagic lesion /No lesion	7.633	1.449-40.217	.017

Abbreviations: CI, confidence interval; mRS, modified Rankin Scale; OR, odds ratio.

activated protein C resistance cases, and the patients who had high levels for anti nuclear anticor tests.

The prognostic factors such as aged 50 years or younger, sinuses involvement more than 2, parenchymal involvement, and malignancy were evaluated in patients whose mRS results were higher than or equal to 3. ORs were calculated for those factors using the multivariate logistic regression analysis (Table 4). There is no statistical association between sinus involvement more than 2 ($P = .845$), but the other 3 factors were statistically significant ($P < .001$). In the multivariate analysis, older age (>50 years) (OR = 3.550, 95% CI = 1.492-8.448, $P = .004$), parenchymal involvement (OR = 6.498, 95% CI = 2.386-17.697, $P < .001$), and malignancy (OR = 3.239, 95% CI = 1.077-9.739, $P = .034$) were significantly associated with higher mRS scores (mRS ≥ 3). Regarding the relation between prognosis and venous involvement in patients with mRS higher than or equal to 3, we found that involvement of SSS was also (OR: 4.228; 95% Cl: 1.753-10.198) associated with poor outcome. Epileptic seizures had no affect on prognosis. Patients with focal neurological deficit (OR: 3.264, 95% CI: 1.463-7.282) and altered consciousness (OR: 5.856, 95% CI: 2.635-13.011) had unfavorable prognosis. On the other hand, 91 (13.2%) patients did not present headache, and outcome was favorable in patients with headache compared to those without headache (8.8% versus 3.0%, $P = .014$).

Discussion

In VENOST study, we collected data from 1144 Caucasian CVST patients identified in 35 hospitals, and evaluated clinical presentations, risk factors, treatment, and neuroimaging findings. The prior largest data of CVST patients are the ICVST study analyzed in 624 patients in 21 countries.[7] Excluding this study, CVST cohorts mostly comprised a much smaller number of patients from single centers.[4,11-14]

As opposed to arterial strokes, CVST has a significantly higher incidence in women. The majority of patients in VENOST study were female (67.9%), with a female-to-male ratio of 2.11 in whole cohort consistent with all, except 1, previous studies which reported a 58%-79% woman preponderance.[12,15,16] This imbalance is prominent during the female reproductive years. The mean age in our study was 40.7 years which was quite similar to larger studies,[7,11,17,18] and 46.6% of the patients were less than 37 years of age. The mean age of CVST patients was younger in Saudi Arabia and Mexico whereas it is older in Italy and Korea compared to our cohort.[4,19-21]

The onset type is variable among the studies. Many studies report acute onset to be more common, but Sidhom et al and Wang et al's studies demonstrate less often acute onset.[17,22,23] VENOST study of younger age was more frequent in patients with acute onset, and subacute onset was more common in men.

Headache is the most common presenting symptom of CVST patients (70%-90%) in many studies.[7,8,15,17,23] It may be the sole complaint in a large number of patients. Of the 1144 patients, 87.2% experienced headaches, and it was the only symptom in 287 (25.1%) patients consisted in previous studies.[24] Seizures are more frequent in CVST than in other stroke types, but the proportion among studies varies from 1.4% to 50.4%.[18,25] In the ISCVT study, seizure occurred in 39% of patients, higher than our results.[26] Seizures were less often reported in Wang et al (1.4%) and Terni et al's studies

Table 4. *Univariate and multivariate analyses for risk factors according to higher mRS (≥3)*

	Univariate			Multivariate		
	OR	95% CI	*P*	OR	95% CI	*P*
51+/≤50	4.278	1.936-9.543	<.001	3.535	1.484-8.422	.004
More than 2 sinuses involvement	.947	.551-1.630	.845	.848	.481-1.495	.568
Parenchymal involvement: Yes/No	6.584	2.452-17.677	<.001	6.622	2.426-18.077	<.001
Malignancy: Yes/No	6.579	2.456-17.623	<.001	3.307	1.095-9.985	.034

Abbreviations: CI, confidence interval; mRS, modified Rankin Scale; OR, odds ratio.

Table 5. *Etiological comparisons among studies*

	VENOST study	Dentali et al[14]	Ferro et al[7]	Wasay et al[11]	Algahtani et al[19]	Khealani et al[8]	English et al[27]	Terazzi et al[20]	Sidhom et al[17]	Souirti et al[15]
Number of cases	1144	706	624	182	111	109	78	48	41.0	30
Gynecological causes							68			
Oral contraceptive	13.9	39.4	54.3	NA	20	12	45	47.4	11.0	NA
Pregnancy	9.5	7.8	6.3	7	12.6	NA	NA	NA	9.0	NA
Puerperium	18.3		13.8		NA	31	23	5.3	29.0	33
Infections	8.1	8.3	12.3	NA	9.9	18	16	6.3	34.0	26
History of VTE	5.9	7.6	NA	NA	NA	NA	5	16.7	NA	NA
Malignancy	5.2	7.4	7.4	7	9.9	4.6	13	6.3	7.0	NA
Prothrombotic conditions	26.4	41.1	34.1	21	19.8	5	29	38.5	56.0	NA
Behçet's disease	9.4	NA	1	1	.9	.9	NA	NA	5.0	7
Iron deficiency	3.2	NA	9.2	NA	NA	NA	NA	NA	10.0	NA
Idiopathic	24.6	44.2	12.5	43	NA	NA	16	17	NA	23
SLE	1.4	NA	1	4	NA	NA	NA	NA	5.0	NA

Abbreviations: NA, not available; SLE, systemic lupus erythematosus; VTE, venous thromboembolism.

(6.9%).[22,23] In VENOST study, altered consciousness and cranial nerve palsies were more frequent in patients aged more than 50 years whereas younger patients frequently presented with visual field deficit and isolated headache symptoms. Altered consciousness was the presenting feature in 17.8% of the patients. Clinical presentation of our cohort is almost identical to what has been reported in many previous studies, with the exception of visual field deficits, which was more common in men, and cranial nerve palsy was more common in elderly patients. Focal neurological deficit was noted in 18.2% which was quite less often than previous results reporting a rate of 37.8%-72%.[20,25,27]

Although CT is the mainstay of initial assessment and triage, MRI in combination with magnetic MRV has been shown to have the highest sensitivity and specificity in CVST diagnosis. In our study, the most common modality used was both MRI and MRV imaging (89.1%). As reported by others, we found MRI and MRV combination to be the most effective noninvasive technique to confirm the diagnosis.[28] DSA was used for only 23 (2.0%) patients to confirm the diagnosis in this study which is the gold standard for establishing the diagnosis of CVST.[29] The most frequently affected sinuses in VENOST study were the transverse (particularly right side) and sigmoid sinuses (mainly among multiple sinuses involvement), followed by the SSS. In the ICVST study, SSS was identified as the most commonly affected sinus (62%), followed by the transverse sinuses (41.2%-44.7%) consistent with some other studies.[7] On the other hand, similar to our results, other studies revealed that the 2 most common localizations of thrombosis were the transverse sinus with the sigmoid sinus (66.4 %) and the SSS (47.6%).[18] Studies showed multiple sinuses involvement in 78.9% of cases, in which the transverse sinus plus sigmoid sinus was the most commonly involved combination.[30] In VENOST study, 51.8% of patients had involvement of multiple sinuses but there was no sex difference.

Studies demonstrated that ICH may be observed in 12%-44% of the patients and nonparenchymal involvement in 45% of the patients.[27,30,31] Of the 624 patients recruited in ICVST study, 245 (39%) had ICH.[7] In the present study, 416 (36.4%) patients had infarction at diagnosis, in which 198 were with hemorrhagic lesion (hemorrhagic transformation in 17.3% and 3.8% of patients with ICH). Parenchymal lesion involvement was most commonly observed in patients aged more than 50 years. Patients without parenchymal involvement had a better outcome and 62.2% of those patients had mRS score of 0-1. CVST patients with hemorrhage had severe clinical features although their prognosis was better than that of patients with hemorrhagic infarcts, but worse than that of patients without parenchymal involvement or with ischemic lesions. Frequency of baseline ICHs and infarcts was higher in patients aged more than 50 years.

As the female-to-male ratio in VENOST study was 2.11 at young and middle ages, this might be explained by sex-specific risk factors. For young and middle-aged women, oral contraceptive use, pregnancy, and puerperium were the most common risk factors. Clinical studies revealed important differences among CVST-associated risk factors and predisposing conditions. The main risk factors for CVST were found to be thrombophilia, oral contraceptive use, pregnancy, puerperium, infections, and malignancy.[1-3] Based on these studies, infections and puerperium are still believed to be the main causes of CVST particularly in developing countries (Table 5).[4,5] In VENOST study, the most common etiological factors in women were related to gynecological factors, and in men related to prothrombotic conditions followed by infection etiology.

The underlying cause why gynecological factors, particularly puerperium and pregnancy, were high may be explained by the higher birth rates in our country, and the use of oral contraceptive is not in general use. The second causative risk factor was (26.4%) prothrombotic conditions in our study, and prothrombotic causes were commonly seen in patients younger than 37 years of age. MTHFR mutation was the most commonly seen mutation, followed by Factor V Leiden mutation, and the third one was protein S/C deficiency. Infection etiology, mainly focal infections, is quite common in our male patients compared to Terazzi, Dentali, and Ferro studies.[7,14,20]

Behçet's disease is a rare cause of CVST.[7,11] In the Middle East, the majority of the studies focused on Behçet's disease.[32-34] In our series, the underlying etiology related to Behçet's disease maintains 9.4% of total, which was much more higher compared with other Western countries.[7,11] Although iron deficiency anemia is a rare cause of cerebral sinus thrombosis, and the relation between iron deficiency anemia and venous thromboembolism remains unclear, there are some controversies about this subject. Hung et al[35] concluded that there was an association between iron deficiency anemia and venous thromboembolism. Fe deficiency anemia as a cause of CVST in our study was about 3.2% of total patients. The most frequent malignancies in VENOST study consisted of breast cancer followed by hematological malignancies. History of malignancy was found to be significantly higher in cases involving 50 years of age ($P < .001$).

This study had some limitations, including the observational nature and, hence, lack of uniform evaluation for etiology, treatment options, and high dropout rates from long-term follow-up. But the strength of our study is its large sample size involving patients from only 1 country. It does not represent the entire CVST patients nor is this a random sample, but given the rarity of CVST, our multicenter collaboration with a larger number of the patients allows us to better understand the clinical and etiological features and outcome of the disease. This study provides a motivation for a multicenter and multinational retrospective and prospective standardized follow-up.

In summary, CVST patients were most common in young women with headaches and focal neurological deficits or seizures. The diagnosis of CVST should be considered in all young patients presenting with unexplained headache, with or without focal neurological deficits and seizures. Multifocal sinus involvement was common. Gynecological factors, particularly puerperium and pregnancy, were high. Risk factors can be confirmed including high incidence of gynecological causes, potential thrombophilia, and focal infections in male patients, and need to be evaluated in the setting of CVST. International collaborative studies are mandatory to better characterize the ethnic and regional differences, and enable new advances in diagnostic and treatment strategies.

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