Cerebral Venous Sinus Thrombosis as a Rare Complication of Systemic Lupus Erythematosus: Subgroup Analysis of the VENOST Study

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Aim: Systemic lupus erythematosus (SLE) is an unusual risk factor for cerebral venous sinus thrombosis (CVST). As few CVST patients with SLE have been reported, little is known regarding its frequency as an underlying etiology, clinical characteristics, or long-term outcome. We evaluated a large cohort of CVST patients with SLE in a multicenter study of cerebral venous thrombosis, the VENOST study, and their clinical characteristics. *Material and Method:* Among the 1144 CVST patients in the VENOST cohort, patients diagnosed with SLE were studied. Their demographic and clinical characteristics, etiological risk factors, venous involvement status, and outcomes were recorded. *Results:* In total, 15 (1.31%) of 1144 CVST patients had SLE. The mean age of these patients was 39.9 ± 12.1 years and 13 (86.7%) were female. Presenting symptoms included headache (73.3%), visual field defects (40.0%), and altered consciousness (26.7%). The main sinuses involved were the transverse (60.0%), sagittal (40.0%), and sigmoid (20.0%) sinuses. Parenchymal involvement was not seen in 73.3% of the patients. On the modified Rankin scale, 92.9% of the patients scored 0-1 at the 1-month follow-up and 90.9% scored 0-1 at the 1-year follow-up. *Conclusions:* SLE was found in 1.31% of the CVST patients, most frequently in young women. Headache was the most common symptom and the CVST onset was chronic in the majority of cases. The patient outcomes were favorable. CVST should be suspected in SLE patients, even in those with isolated chronic headache symptoms with or without other neurological findings.

Key Words: Systemic lupus erythematosus—cerebral venous sinus thrombosis—headache—neurological symptoms

Introduction

Cerebral venous sinus thrombosis (CVST) is a major cause of stroke in young patients.[1] The incidence of CVST ranges between 1 and 12 cases per 1,000,000 adults per year.[2] It is higher in developing countries due to gender-specific risk factors, such as pregnancy, and puerperium, and infectious diseases.[2] CVST has many other risk factors, such as oral contraceptive use, genetic and acquired prothrombotic states, malignancy, and autoimmune, and inflammatory diseases.[3]

Systemic lupus erythematosus (SLE) is a chronic, heterogeneous, autoimmune inflammatory disease involving multiple systems that is more frequent in women. Neuropsychiatric involvement is variable, occurring in 12%-95% of SLE patients.[4] Central nervous system involvement is associated with high morbidity and mortality.[5] Many clinical findings have been reported in SLE patients with neurological involvement, including headache, seizures, aseptic meningitis, cognitive dysfunction, cerebrovascular disease, psychosis, demyelinating syndrome, and myelopathy. The incidence of cerebrovascular involvement in SLE ranges from 3% to 20%.[6] CVST is a rare complication of SLE.[7] In such patients, the thrombotic risk is strongly related to the presence of antiphospholipid antibodies (aPL) and lupus anticoagulant.[1,8] Because SLE is rarely mentioned as a risk factor for CVST, little is known about its frequency as an underlying etiology, clinical characteristics, response to treatment, or long-term outcome.[5,7,9] In this study, we evaluated the demographic and clinical characteristics of CVST patients with SLE in a large multicenter cerebral venous thrombosis cohort, the VENOST study.[10]

Methods

VENOST is a published, hospital-based retrospective and prospective study of 1144 patients with CVST who were admitted to national stroke centers and consented to participate.[10] In VENOST, patients with CVST were diagnosed by neurologists experienced in cerebrovascular diseases, and

confirmed based on the patients' clinical features and radiological investigations according to diagnostic criteria.[11] Patients aged below 18 years, or with inconclusive data, were excluded from the study.

Among the 1144 CVST patients, those diagnosed with SLE according to the revised criteria of the American College of Rheumatology[12] were studied. Patients who showed, had abnormal findings in examinations for etiological risk factors were sent to rheumatology departments for SLE diagnosis; the demographic and clinical characteristics of all such patients were recorded. Symptom onset was categorized as acute (<48 hours from symptom onset to admission), subacute (48 hours to 1 month from symptom onset to admission), or chronic (more than 1 month from symptom onset to admission). Concomitant predisposing factors for CVST were noted, including oral contraceptive use, pregnancy, puerperium, infections, medical and family history of thrombosis, and malignancy. Additional prothrombotic conditions were screened for, such as deficiencies in antithrombin III, protein C, and protein S, mutations in the methylenetetrahydrofolate reductase gene, prothrombin gene, plasminogen activator inhibitor (PAI), and factor V Leiden gene, and homocysteine. The number and locations of involved sinuses or veins, and radiological parenchymal involvement (ischemic or hemorrhagic infarction, intracerebral hemorrhage) at admission were also recorded. Follow-up visits involved face-to-face interviews conducted by clinicians. The modified Rankin scale (mRS) was scored as follows: 0-1, independent (good outcome); 2, minimal disability; and more than or equal to 3, dependent or dead (poor outcome). Treatment and follow-up outcomes, evaluated using the mRS, were recorded at 1, 3, 6, and 12 months after the initial diagnosis of CVST.

The statistical package SPSS (ver. 22.0; SPSS Inc., Chicago, IL) was used for the statistical analyses. Categorical variables are shown as frequencies and percentages. Continuous variables are presented as the mean ± standard deviation. $P < .05$ was accepted as statistically significant

Results

Of the 1144 CVST patients from the VENOST cohort, 15 (1.31%) had SLE and 13 (86.7%) were female. The mean age of the patients was 39.9 ± 12.1 years. Table 1 presents the demographic and clinical features of the CVST patients with SLE. The symptom onset was acute in 4 (28.6%), subacute in 4 (28.6%), and chronic in 6 (42.9%) patients. The presenting symptoms and signs included isolated headache in 20.0% of patients, headache in 73.3%, visual field defects in 40.0%, altered consciousness in 26.7%, nausea or vomiting in 20.0%, seizures in 20.0%, cranial nerve palsy in 13.3%, and a focal neurological deficit in 6.7%.

In all patients, CVST was diagnosed by both magnetic resonance imaging and magnetic resonance venography. One sinus was involved in 11 (73.3%) patients, and more than 1 sinus in 4 (26.7%) patients. The most commonly involved sinuses were the transverse sinus in 9 (60.0%) patients, sagittal sinus in 6 (40.0%), and sigmoid sinus in 3 (20.0%). There was no parenchymal involvement in 73.3% of the patients; 1 (6.7%) patient had infarction with an ischemic lesion, and 3 (20.0%) had intracerebral hemorrhage. Table 2 shows the predisposing factors: 1 patient each used oral contraceptives, was puerperal, or had a paracranial (focal) infection, aPL, protein C/S deficiency, or history of deep venous thrombosis.

Regarding follow-up, 13 (86.6%) patients attended the 3-month visit, 12 (80%) the 6-month visit, and 11 (73.3%) the 1-year visit. All 13 (92.9%) patients had mRS scores of

Table 1. *Demographic and clinical features of CSVT patients with SLE*

		Frequency (%)
Age		39.93 ± 12.18
Gender	Female	13/15 (86.7%)
	Male	2/15 (13.3%)
Symptoms onset	Acute	4/14 (28.6%)
	Subacute	4/14 (28.6%)
	Chronic	6/14 (42.9%)
Symptoms and signs	Isolated Headache	3/15 (20.0%)
	Headache	11/15 (73.3%)
	Nausea and/or Vomitting	3/15 (20.0%)
	Epileptic seizures	3/15 (20.0%)
	Visual field defect	6/15 (40.0%)
	Focal neurological deficit	1/15 (6.7%)
	Altered consciousness	4/15 (26.7%)
	Cranial nerve palsies	2/15 (13.3%)
Number of sinuses involved	1 sinus	11 (73.3%)
	More than 1 sinuse	4 (26.7%)
Involved sinuses	Isolated transverse sinuses	5 (33.3%)
	Isolated sagittal sinuses	3 (20.0%)
	Isolated sigmoid sinuses	2 (13.3%)
	Isolated cortical veins	0 (0.0%)
	Isolated jugular sinuses	1 (6.7%)
	Isolated cavernous sinuses	0 (0.0%)
	Transvers sinuses	9 (60.0%)
	Sigmoid sinuses	3 (20.0%)
	Sagittal sinuses	6 (40.0%)
	Internal jugular vein	1 (6.7%)
	Cortical veins	0 (0.0%)
	Cavernous sinuses	0 (0.0%)
Parencyhmal involvement	No lesion	11/15 (73.3%)
	Infarction	1/15 (6.7%)
	Hemorrhagic infarction	0/15 (0.0%)
	Intracerebral Hemorrhage	3/15 (20.0%)

Abbreviations: CSVT, cerebral venous sinus thrombosis; SLE, systemic lupus erythematosus.

Table 2. *Risk factors of CSVT patients with SLE*

	Tested	Abnormal	%
Gynecological causes			
Oral contraceptive use	13	1	7.7
Pregnancy	13	0	0.0
Puerperium	13	1	7.7
Infections			
Paracranial (focal)	15	1	6.7
Systemic	15	0	0.0
History of VTE			
Cerebral	15	0	0.0
Deep venous thrombosis	15	1	6.7
Other	15	1	6.7
Malignancy	15	0	0.0
Family history of VTE	15	0	0.0
MTHFR homozygosity	11	0	0.0
MTHFR heterozygosity	11	0	0.0
Phrothrombin mutation	11	0	0.0
PAI-Mutation	11	0	0.0
Factor V Leiden Mutation	11	0	0.0
Antiphospholipid Ab	13	1	7.7
Hyperhomosisteinemia	13	0	0.0
Hyperfibrinogenemia	13	0	0.0
Protein C/ S deficiency	13	1	7.7
Activated Protein C resistancy	13	0	0.0
Antithrombin III deficiency	13	0	0.0
High ANA titers	13	0	0.0
Thrombocytosis	13	0	0.0
Anticardiolipin Ab	13	0	0.0
Polistemia Vera	13	0	0.0

Abbreviations: MTHFR, methylenetetrahydrofolate reductase gene

0-1 at the 1-month visit, while at the 1-year visit, 10 (90.9%) had scores of 0-1 and 1 (9.1%) had a score of 2.

Discussion

Although cerebrovascular events are relatively common, CVST represents an unusual type of vascular involvement in SLE.[6] The small number of reported CVST patients with SLE makes it difficult to determine the clinical characteristics of these patients.[7–9] We presented the clinical characteristics, radiological findings, and outcomes of 15 CVST patients meeting the diagnostic criteria of SLE.

Since the first report, in 1975, of CVST in a patient with SLE based on autopsy findings,[13] an association between CVST and SLE has been demonstrated.[1,7-9,14-18] The exact prevalence of SLE as a cause of CVST is still not known.[6] Two multicenter studies including CVST cohorts reported that SLE was an underlying etiology.[11,19] The International Study on Cerebral Vein and Dural Sinus Thrombosis from Europe investigated 624 adult patients with CVST, drawn from 21 countries, and noted the presence of SLE in 7 (1%) patients.[19] A multicenter cohort from the United States found that 7 (4%) of 182 CVST patients had SLE as a causative factor.[11] In VENOST10, SLE was found in 1.31% of 1144 CVST patients, which is consistent with International Study on Cerebral Vein and Dural Sinus Thrombosis,[19] confirming the rarity of CVST due to SLE. Another 2 studies showed the rate of CVST in SLE patients as .36%[7] and 7.9%.[20] The different proportions in these studies may be attributed to differences in the number of patients, patient selection bias, methodology, and ethnic, and regional variation.

We found that CVST related to SLE has a typical clinical picture; the patients were frequently young to middle aged females (86.7%). The female predominance in our results is explained by the fact that both CVST and SLE affect females more frequently. The mean age of our patients was 39 years, which is similar to previously reported CVST cases with other etiologies.[11,19]

The onset mode of CVST may be acute, subacute, or chronic. Although less than 10% of CVST patients have the chronic-onset form,[21] the onset was chronic in 42.9% of our patients.

Headache is the most widespread presenting symptom, seen in 70%-90% of cases,[10,11,19,22-24] and it can be the sole symptom.[18] In comparison, 28%-57% of SLE patients suffer from headache, mostly tension-type headache and migraine.[25] Headache was the most common presenting symptom in previous reports on CVST and SLE patients[1,14,15,18] similar to our findings. Associated symptoms or signs included visual field defects in 40.0%, altered consciousness in 26.7%, seizures in 20%, nausea or vomiting in 20.0%, cranial nerve palsies in 13.3%, and focal neurological deficits in 6.7% of our patients. Our findings concurred with many studies in the literature.[1,14,15,18] Regarding the location of thrombosis, the transverse (60%) and sagittal (40%) sinuses were involved most frequently in our patients, which is consistent with previous studies.[1,8,14,15,17,18,26,27] Wang et al. reported that the transverse sinus was the main site of occlusion in patients with SLE and CVST (82.4%), followed by the sigmoid sinus.[7] In the same study, cerebral ischemia or infarction was present in 11.8% of cases, and subarachnoid hemorrhage in 23.5%. In our series, 26.7% of the patients had more than one involved sinus; this percentage was higher in other reports,[1,7,28,29] which may be associated with the timing and type of imaging. There was no parenchymal involvement in 73.3% of the patients, while 6.7% of patients had infarction with an ischemic lesion and 20.0% had intracerebral hemorrhage. Similar to our findings, non-parenchymal involvement was reported to be more prevalent in other studies.[9,14,18]

Various mechanisms may contribute to the development of CVST in SLE patients. Our data identified additional risk factors in a few patients, and provide information about the concomitant predisposing factors for CVST in SLE. Oral contraceptive use was found in one patient, and paracranial (focal) infection in another. CVST developed in the puerperium in one patient. Furthermore, the existence of aPL and

protein C/S deficiency were documented one patient. One patient had a history of deep venous thrombosis. More than one risk factor is present in approximately 40% of patients with CVST.[19] The presence of concomitant risk factors in these patients might increase the potential for CVST. In some 0cases, concomitant aPL or lupus anticoagulant was negative,[8,9,15,16,26,28,30] while it was positive in others.[14,29,31]

Although patients with CVST have better functional outcomes than patients with arterial strokes, CVST can lead to serious neurological outcomes, and even death. The neurological outcome was good in most reported CVST and SLE cases.[1,8,9,15,7,14,29] Similarly, in our series, a good prognosis was obtained with appropriate treatment in the majority of the patients.

In conclusion, SLE was found in 1.31% of CVST patients, and occurred more frequently in relatively young women. Headache was the most frequent symptom and the onset mode was chronic in the majority of the patients. The transverse sinus was the most frequent location of thrombus, followed by the sagittal sinus. The patient outcomes were favorable overall. The clinical features of our patients were similar to those of patients with CVST of other etiologies, except for a higher tendency toward chronic onset and single sinus occlusion.[7,32] CVST, an uncommon complication, should be suspected in SLE patients with a chronic headache, with or without other neurological symptoms.

Conflicts of interest

None

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