

Cerebral Venous Thrombosis in Systemic Lupus Erythematosus

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We describe six cases of cerebral venous thrombosis in patients with systemic lupus erythematosus. In one patient, cerebral venous thrombosis was the initial manifestation of lupus; in the five others, it occurred 1–33 years after the diagnosis of lupus. The main clinical features of cerebral venous thrombosis were persistent headache in all six patients, focal symptoms in four, and seizures in three; papilledema was present in only one patient. Cerebral venous thrombosis was diagnosed based on angiography or magnetic resonance imaging. Both the transverse (in five patients) and the superior sagittal (in three) sinuses were involved. Extracranial arterial and/or venous thrombosis were present in three patients, abortion in two, thrombocytopenia in four, and lupus anticoagulant in three. The neurologic symptoms resolved rapidly in five patients treated with steroids and heparin. Cerebral venous thrombosis should be suspected in patients with lupus who complain of persistent headache, especially in the presence of neurologic symptoms. (*Stroke* 1990;21:1226–1231)

Among the numerous causes¹ of cerebral venous thrombosis, systemic lupus erythematosus (SLE) has been rarely mentioned, with only five cases published^{2–5}; lupus anticoagulant was present in two of these cases.⁵ We retrospectively studied six patients fulfilling the classical criteria for SLE⁶ who developed cerebral venous thrombosis documented angiographically or anatomically.

Case Reports

Between 1973 and 1987, cerebral venous thrombosis was diagnosed in six of 400 patients with SLE. The main features of the two disorders are summarized in Tables 1 and 2, respectively. Case 4 has been reported.⁷ All six patients fulfilled the classical criteria for SLE.⁶ There were five women and one man, the usual sex ratio of SLE. The age at onset of SLE ranged from 10 to 30 (mean 20) years. The age at diagnosis of cerebral venous thrombosis ranged from 24 to 52 (mean 35) years. In one patient it was the initial manifestation of SLE, but in the other five the interval between the diagnoses of SLE and cerebral venous thrombosis ranged from 1 to 33 years.

Table 1 shows the manifestations of SLE. Five patients had arthritis, and five had cutaneous manifestations (malar rash, discoid rash, or photosensitivity). Five had lupus nephritis, but the nephrotic syndrome was present in only one patient. Five had neurologic manifestations unrelated to cerebral venous thrombosis (seizures in three patients and psychiatric symptoms in two). Thrombocytopenia occurred in four. Antinuclear and anti-deoxyribonucleic acid (DNA) antibodies were present in four patients; both antibodies were lacking in the other two (cases 1 and 4) despite follow-ups of 9 and 29 years, respectively. The presence of lupus anticoagulant diagnosed on the basis of a partial thromboplastin time (PTT) ≥ 6 seconds longer than the upper normal limit and failure of the prolonged PTT to correct upon 1:1 dilution of the patient's plasma with control plasma was present in three patients. Other assays such as the Russell's viper venom time were not routinely performed. Anticardiolipin antibodies were looked for in two patients and were found in one (case 6). A false-positive test for syphilis (VDRL) was not found in any patient. Three patients had other vascular events (upper- or lower-limb thrombophlebitis and middle cerebral, renal, or tibial artery thrombosis). Two patients had histories of spontaneous abortions, and two developed vascular complications while pregnant (one developed cerebral venous thrombosis and the other developed middle cerebral artery occlusion). Of the four patients with vascular events and/or abortion three

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TABLE 1. Main Features of SLE in Six Patients With Cerebral Venous Thrombosis

Feature	Patient					
	1	2	3	4	5	6
Sex	F	F	F	F	M	F
Age at onset of SLE (yr)	29	14	30	23	10	12
Criteria for diagnosing SLE						
Malar rash	-	-	+	-	+	+
Discoid rash	+	-	-	-	+	+
Photosensitivity	+	-	-	+	-	+
Oral ulcers	-	-	-	-	+	-
Arthritis	+	+	+	-	+	+
Serositis	-	-	-	-	-	-
Renal disorder	+	+	+	+	+	-
Neurologic disorder (not cerebral venous thrombosis)	+	+	+	+	+	-
Hematologic disorder						
Hemolytic anemia	-	+	-	-	-	-
Leukopenia	-	+	-	-	-	-
Lymphopenia	-	+	-	-	-	-
Thrombocytopenia	+	+	-	+	-	+
Immunologic disorder						
Lupus erythematosus cell	-	+	...	-	-	-
Anti-DNA antibody	-	+	+	-	+	+
Anti-Sm antibody	-	-	-	-	+	-
False-positive VDRL	-	-	-	-	-	-
Antinuclear antibody	-	+	+	-	+	+
Other features of SLE						
Lupus anticoagulant	-	-	+	+	-	+
Spontaneous abortion	-	-	-	+	-	+
Thrombosis						
Arterial	Renal, limb		-	-	Middle cerebral	-
Venous (extracranial)	Limb		-	Limb	-	-

SLE, systemic lupus erythematosus; DNA, deoxyribonucleic acid; VDRL, test for syphilis; F, female; M, male.

TABLE 2. Main Features of Cerebral Venous Thrombosis in Six Patients With Systemic Lupus Erythematosus

Feature	Patient					
	1	2	3	4	5	6
Age at first symptom of thrombosis (yr)	29	47	31	52	26	24
Headache	+	+	+	+	+	+
Focal symptoms	-	Alternate hemiparesis	Aphasia, agraphia	-	Left monoplegia	Left hemiplegia
Seizures	-	-	+	+	-	+
Papilledema	+	-	-	-	-	-
Diagnostic tests						
Computed tomography	...*	...	Frontal hypodensity	Old arterial cerebral infarction	Normal	Parietal hypodensity and hyperdensity
Angiography	...*	SSS, TS	SSS, TS	TS, JV	TS	SSS
Treatment	None	S+A	S+A	S+A	S+A	S+A
Course	Optic atrophy	Resolved	Resolved	Resolved	Resolved	Resolved

L, left; SSS, superior sagittal sinus; TS, transverse sinus; JV, jugular vein; S+A, steroids and anticoagulants.

*Diagnosis was made during surgical decompression in 1973.

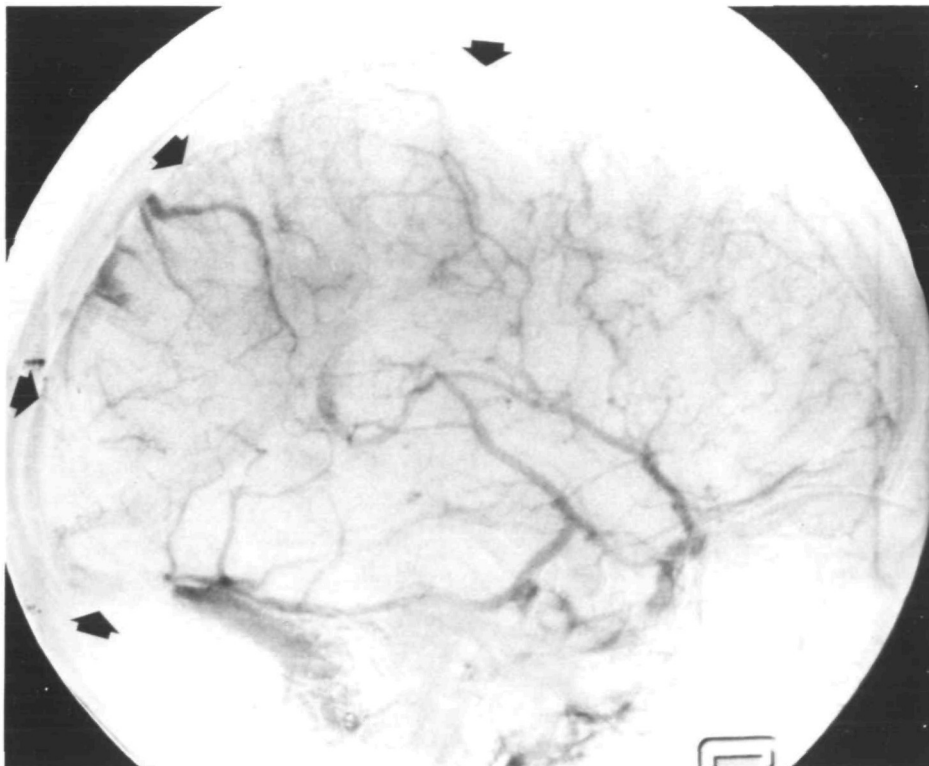


FIGURE 1. Right carotid angiogram of 24-year-old woman with systemic lupus erythematosus and cerebral venous thrombosis. Note absence of filling of superior sagittal sinus and of parietal cortical veins (arrows).

had thrombocytopenia and lupus anticoagulant was present in two.

The neurologic manifestations of cerebral venous thrombosis are listed in Table 2. The mode of onset was acute (<48 hours) in five patients and progressive (a few weeks) in the other. Focal deficits (left hemiparesis and hypesthesia, alternate hemiplegia, aphasia and agraphia, and left lower limb paresis) were present in four patients. Three had seizures (grand mal seizures in one and partial motor seizures in two). No patient had an altered level of consciousness. Persistent headache was a constant feature; however, isolated intracranial hypertension with headache and papilledema was the initial presentation of cerebral venous thrombosis in one patient. Lumbar puncture was performed in four patients, and the cerebrospinal fluid composition was found to be abnormal (55 mg protein/dl and 55 lymphocytes/mm³) in one. Unenhanced cerebral computed tomography (CT scan), performed in four patients, was normal in one and abnormal (hypodensity of the left frontal lobe, hyperdensity surrounded by hypodensity of the right parietal lobe suggestive of a hemorrhagic infarction of venous origin, and hypodensity as sequelae of a past left middle cerebral artery occlusion) in three. Cerebral angiography was performed in five patients and showed a partial or total lack of filling of one or several sinuses (the superior sagittal sinus and/or the transverse sinus) on at least two projections. Cortical vein involvement associated with sinus occlusion was seen in one case. In the earliest patient (case 1, 1973), left transverse sinus occlusion was diagnosed during surgery for intracra-

nia hypertension. Magnetic resonance imaging (MRI) was performed in only one patient (case 6).

Due to delayed diagnosis, one patient (case 1) was not treated and developed optic atrophy secondary to papilledema. The other five patients received heparin associated with steroids (1 mg/kg prednisone daily); neurologic improvement occurred within 1 week and recovery within 1 month. Heparin was given without any complications, even when a hemorrhagic infarct was present (case 6). Oral anticoagulant therapy was started after 4 weeks of heparin and has not been discontinued until the time of the study in two patients (3 and 12 months). The other two patients received oral anticoagulant therapy during at least 3 months and were subsequently lost to follow-up. Warfarin was given to one patient during 5 months until she died of an extraneurologic lupus flare. After initial tapering, corticosteroids had been maintained in all patients.

Case 6

This 24-year-old white woman had been treated with hydroxychloroquine from the age of 12 years to the age of 22 years for discoid lupus. At age 23 years she had a spontaneous abortion after 30 weeks of pregnancy. Pathologic examination of the placenta revealed multiple infarcts.

One year later, she was admitted to the hospital at 28 weeks of her second pregnancy. Laboratory investigations showed a platelet count of 60,000/mm³, an erythrocyte sedimentation rate of 27 mm/hr, a PTT of 60 seconds, a prothrombin time of 10 seconds, a positive anticardiolipin antibody assay, and a nega-

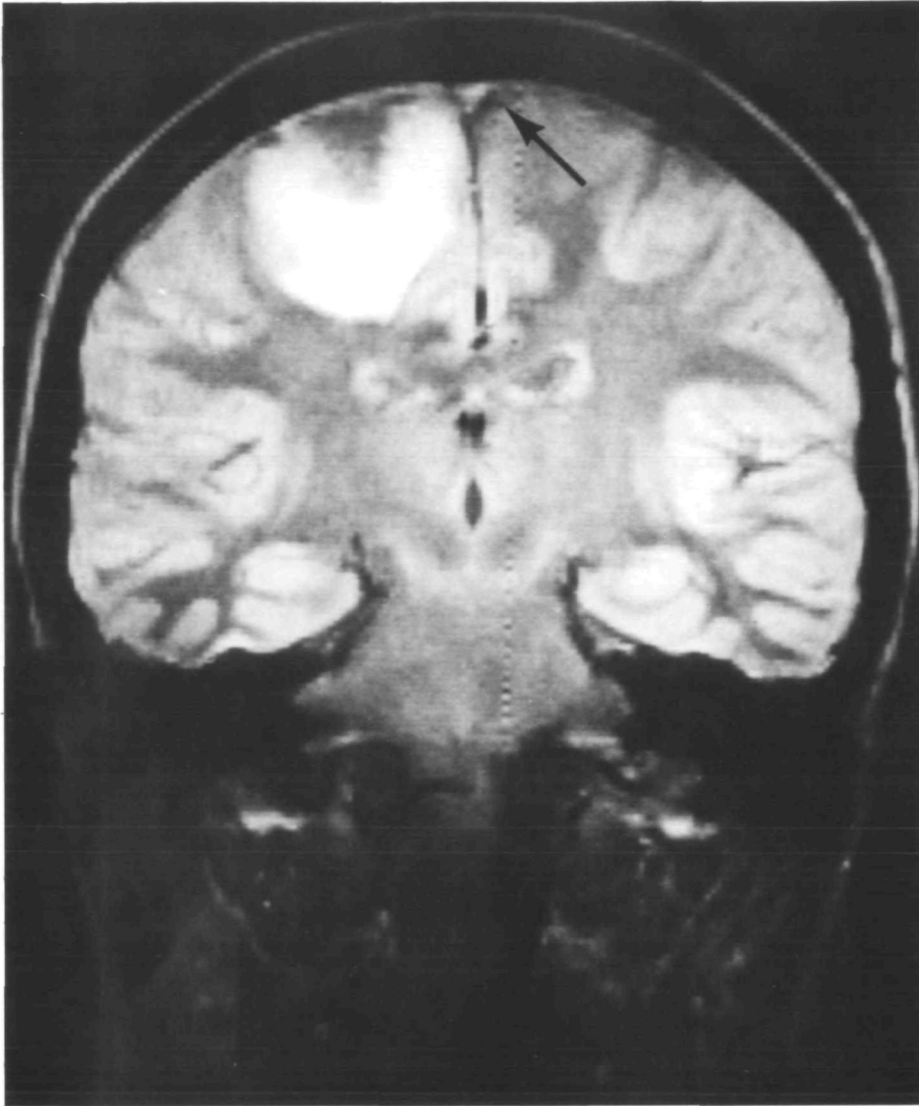


FIGURE 2. Magnetic resonance image taken 1 day after angiogram in Figure 1. T2-weighted image. Note superior sagittal sinus (arrow); parietal hemorrhagic infarction.

tive VDRL. Her antinuclear antibody titer was 1/20, and an anti-DNA radioimmunoassay was positive. At 30 weeks she had placental abruption with disseminated intravascular coagulation, and a cesarian section was performed. The baby was hypotrophic. The woman's disseminated intravascular coagulation improved in 48 hours with symptomatic management. Steroid therapy was started (55 mg prednisone daily), and the patient was discharged. During the postpartum period she complained of increasing headaches. She denied any photophobia, nausea, or diplopia.

Fifteen days after delivery, she was readmitted for left partial motor seizures, with secondary generalization and subsequent left hemiplegia. Examination on admission revealed a nonconfused woman with moderate left hemiplegia and sensory disturbance. Funduscopy was normal. General examination was normal. Laboratory investigations showed a platelet count of $135,000/\text{mm}^3$, an erythrocyte sedimentation rate of 44 mm/hr, a PTT of 35 (normal 22–36) seconds, and a thrombin time of 10 (normal 9.5–11.5)

seconds. Lupus anticoagulant was absent. Her antinuclear antibody titer was 1/1,000, and an anti-DNA antibody assay was slightly positive; an anticardiolipin antibody assay was positive. Urinalyses were normal. Unenhanced CT scan showed a right parietal hyperdensity surrounded by hypodensity, suggestive of hemorrhagic infarction. Angiography revealed the absence of filling of the superior sagittal sinus and of the parietal cortical veins (Figure 1).

On MRI (1.5 T) the next day, the occluded sinus appeared isointense on T1-weighted images (resonance time [TR] 400 msec and echo time [TE] 12 msec) and hyperintense on T2-weighted images (TR 1,800 msec and TE 60 msec). The hemorrhagic infarct was visible (Figure 2). The patient was treated with continuous heparin infusion (20,000 units/day) for 3 weeks and later with warfarin. The steroid dosage remained unchanged. The day after heparin was started she improved dramatically, and she recovered completely within 3 weeks.

TABLE 3. Previously Reported Cases of Cerebral Venous Thrombosis in Patients With SLE

Feature	Reference				
	Kaplan et al ²	Shiozawa et al ³	Parnass et al ⁴	Levine et al ⁵	Levine et al ⁵
Sex	F	F	F	F	M
Age at first symptom of Thrombosis (yr)	11	41	27	21	32
Headache	+	+	+	+	+
Focal symptoms	-	-	Right hemiplegia	-	-
Seizures	-	-	-	-	-
Papilledema	+	+	+	-	+
Diagnostic tests					
Computed tomography	Jugular vein thrombosis	Normal	Parietal hypodensity	Normal	Hyperdensity sinus rectus
Angiography	...	SSS	SSS, TS	TS	SSS
Features of SLE					
Antinuclear antibodies	+	+	+	-	?
Anti-DNA antibodies	+	+	-	-	?
Lupus anticoagulant	-	...	-	+	+
Treatment	S	S	S	S+H	S+H
Course	Resolved	Resolved	Resolved	Resolved	Resolved

SLE, systemic lupus erythematosus; DNA, deoxyribonucleic acid; F, female; M, male; SSS, superior sagittal sinus; TS, transverse sinus; S, steroids; H, heparin.

One month after this patient's second admission, MRI demonstrated vascular recanalization with resumption of blood flow in the superior sagittal sinus and regression of the infarct. She was maintained on steroids, and heparin was changed to warfarin (international normalized ratio=3). One year later, the patient's condition remains satisfactory.

Discussion

Cerebral venous thrombosis is a rare complication of SLE. Only five such patients have been reported previously (Table 3). Three of the five²⁻⁴ fulfilled four or more criteria for SLE. Among the patients of Levine et al,⁵ one fulfilled three criteria (arthritis, nephritis, and thrombocytopenia) and can be considered as having probable SLE; the other patient had a history of spontaneous abortions, deep venous thrombosis, pulmonary embolism, and thrombocytopenia with lupus anticoagulant. Cerebral venous thrombosis was the presenting symptom of SLE in the patient of Shiozawa et al³ and in our case 1. Cerebral venous thrombosis occurred during pregnancy in the first patient of Levine et al⁵ and in our case 6. Assays for antinuclear and anti-DNA antibodies were negative in the patients of Levine et al⁵ and in our cases 1 and 4.

Clinical and neuroimaging features of cerebral venous thrombosis in SLE patients were similar to those of patients with cerebral venous thrombosis of other origin.^{1,8,9} Focal signs were present in four of our six patients, whereas isolated intracranial hypertension was present in one. In the literature, signs of intracranial hypertension of progressive onset were isolated in four cases^{2,3,5} and were associated with a right hemiparesis in the patient reported by Parnass et al.⁴

Isolated intracranial hypertension has been described in association with SLE in other patients,¹⁰⁻¹² and the pathogenesis is regarded as unknown. Since angiography was not systematically performed, cerebral venous thrombosis might have been overlooked in some of these cases. Diagnosis is based only rarely on CT alone, usually on angiography^{1,8} and more recently on MRI, which is now the study of choice if available.⁹

Manifestations of SLE are similar in our patients and in the five cases reported previously. There is an increased tendency to arterial and venous thrombosis, especially when lupus anticoagulant is present. Recent studies have clearly demonstrated the strong association between the presence of lupus anticoagulant and the occurrence of cerebral arterial, cerebral venous, and/or systemic arterial thrombosis,¹³⁻¹⁶ spontaneous abortions,^{17,18} and thrombocytopenia.¹⁹ Lupus anticoagulant often coexists with other antiphospholipid antibodies (anticardiolipin antibodies and/or a false-positive VDRL),^{19,20} The mechanisms responsible for in vivo thrombosis involve complex interactions between endothelial cells and lupus anticoagulant, leading to an inhibition of the functions of protein C and protein S.²¹⁻²³ However, other factors such as defective fibrinolysis, altered antithrombin III function,²⁴ hyperfibrinemia, or coagulation changes observed during pregnancy or nephritis, especially during nephrotic syndrome, may play a role. In this respect, the high frequency of renal involvement in patients with cerebral venous thrombosis (References 2-5, Table 1) should be emphasized.

The use of anticoagulants in the treatment of cerebral venous thrombosis remains controversial. A recent controlled study comparing heparin and placebo suggested that heparin was both effective and

safe, even in patients with hemorrhagic infarcts.²⁵ Our results favor the use of combined therapy with heparin and steroids in patients with cerebral venous thrombosis complicating SLE. Levine et al⁵ obtained similar good results with this therapy. Three patients reported in the literature received steroids without anticoagulation; two improved, but the third required lumboperitoneal shunt for persistent intracranial hypertension.² Long-term treatment for cerebral venous thrombosis is not standardized. Lupus anticoagulant may persist despite treatment with corticosteroids, and recurrent cerebral arterial ischemic events are not uncommon, even with anticoagulant and antiplatelet therapy.¹⁴

Our report demonstrates that cerebral venous thrombosis is one possible mechanism of central nervous system involvement in patients with SLE.²⁶ Since cerebral venous thrombosis can occasionally be the presenting symptom of the disease, SLE and lupus anticoagulant should be systematically looked for in women with cerebral venous thrombosis. On the other hand, despite the high prevalence of migraine in patients with documented SLE,²⁷ cerebral venous thrombosis should be suspected in patients with persistent headache, especially those with neurologic symptoms. Patients with lupus anticoagulant, thrombocytopenia, and/or previous vascular events are notably prone to develop such a complication. In such patients, angiographic or MRI demonstration of cerebral venous thrombosis prompts combined therapy with steroids and heparin.

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