Cerebral Venous Thrombosis with Lupus Anticoagulants
Report of Two Cases

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Lupus anticoagulants are circulating autoantibodies, primarily directed against phospholipids, that prolong the partial thromboplastin time. They have been previously associated with systemic arterial and venous thrombosis and arterial stroke, but not with cerebral venous thrombosis. We describe 2 young patients with cerebral venous thrombosis documented by intravenous digital subtraction angiography in whom a lupus anticoagulant was demonstrated. Both patients improved with corticosteroid and anticoagulant therapy. (Stroke 1987;18:801-804)

Cerebral venous thrombosis (CVT) may result from a variety of pathologic processes including hypercoagulable states. Lupus anticoagulants (LAs) are circulating autoantibodies primarily directed against phospholipids. LAs prolong all phospholipid-dependent coagulation tests and appear to act by at least several mechanisms. LAs have been associated with an increased incidence of systemic arterial and venous thrombotic events in patients with and without systemic lupus erythematosus (SLE). Ischemic cerebral arterial disease, both transient ischemic attacks (TIAs) and stroke, have been recently documented in association with LAs. Venous occlusions of the retinal, pulmonary, renal, hepatic, and lower extremity circulations have also been described in patients with LAs. To our knowledge, we present the first 2 cases of LA-associated CVT.

Case 1
A 21-year-old white woman was admitted in November 1985 with a 2-week history of headaches. The pain was worse on awakening, bitemporal-retroauricular in location, and waxed and waned. Coughing or sneezing increased the headache and brought on transient episodes of blurry vision — "like looking through a curtain." She then developed diplopia and photophobia. At this time she was 2 months pregnant. Laboratory values included a prolonged partial thromboplastin time (PTT) of 65 seconds, prothrombin time (PT) of 12.5 seconds, Westergren erythrocyte sedimentation rate (ESR) of 18 mm/hr, platelet count of 121,000/mm³, and normal serum complement studies. Antinuclear antibody titer was < 1:40, and an IFA anti-DNA was < 10. Neurologic consultation diagnosed vascular headache with a normal neurologic examination, including funduscopy. Naproxen was prescribed. She was discharged and readmitted the following week, having just completed a spontaneous abortion at 9 weeks.

The headaches and diplopia persisted and were now constant. She began having gait difficulty. There was no history of diabetes, hypertension, or heart disease. She had used oral contraceptives from 1978 through 1983. There was also a history of recurrent lower extremity deep venous and pulmonary thromboses, thrombocytopenia, and recurrent herpes labialis. There had been a previous history of monthly migraines preceded by "wavy vision." In December 1984 she had a spontaneous abortion at 18 weeks. Pathologic examination of the fetal placenta revealed maceration, fibrosis, focal necrosis, placentitis, and chorioamnionitis. The umbilical cord revealed acute inflammation in the walls of the arteries and vein.

Examination on the second admission revealed normal optic disks, a left sixth nerve palsy, moderate generalized hyperreflexia, and mild dysmetria of the upper extremities bilaterally. Laboratory investigation included an ESR of 3 mm/hr, platelet count of 116,000/mm³, and a PTT of 54 (normal, 22-36) seconds. Her PTT was 52 seconds with 1:1 dilution with normal plasma (mixing studies). Platelet neutralization procedures and tissue thromboplastin inhibition confirmed the presence of the LA. PT was 12 (normal, 9.5-11.5) seconds. Antithrombin III level was 99% (normal, 80-120%). Assays of coagulation factors revealed markedly reduced activity of Factors IX (37%),
XI (19%), and XII (28%) with normal activity of Factors II and VIII. Head computed tomography (CT) scan after contrast infusion revealed a partial obstruction to filling of the torcular herophili (partial delta sign) and was otherwise unremarkable. Cerebrospinal fluid (CSF) examination revealed sterile, clear fluid at an opening pressure of 420 mm H2O, which contained 1 white blood cell/mm3, 2 red blood cells/mm3, 17 mg protein/dl, 64 mg glucose/dl, and a nonreactive VDRL. There was no oligoclonal banding. The IgG index was 0.8 (normal, 0.4–0.7). She was started on 60 mg/day prednisone and 20 mg/day furosemide. The following day, intravenous digital subtraction cerebral angiography (IV-DSA) revealed total obstruction to filling of the transverse sinus and increased collateral venous drainage around the obstruction (Figure 1). A diagnosis of cerebral venous sinus thrombosis was made. She was placed on subcutaneous heparin, warfarin, and dipyridamole in addition to prednisone and furosemide. Her sixth nerve palsy and headache gradually improved, and she has been without further thrombotic episodes during a 1-year follow-up. Her PTT remains slightly prolonged despite therapy.

Case 2

A 32-year-old white man complained of the insidious onset of increasing left periauricular headache, neck pain, lightheadedness, nausea, vomiting, and unsteady gait. Several days later, he noted diplopia and left ear fullness. One week prior to his headache, he was evaluated for ankle edema, proteinuria, reduced creatine clearance, elevated immune complexes, and thrombocytopenia. Renal biopsy revealed mesangial-proliferative glomerulonephritis. His mother had a history of idiopathic thrombocytopenic purpura (ITP). Examination revealed no orthostasis, a supple neck, and mild lid edema. Ophthalmology consultation found mild optic disk edema with retinal veins slightly congested and easily collapsed with pressure. A left fourth nerve palsy was also noted. The neurologic examination was otherwise unremarkable. PTT was prolonged on 2 occasions, to 39 and 42 (normal, 22–36) seconds and failed to correct (41 seconds) with a 1:1 dilution of the patient’s serum with normal plasma, consistent with the presence of a lupus-like circulating anticoagulant. The LA was confirmed with platelet neutralization procedures and tissue thromboplastin inhibition. PT, thrombin clot time, bleeding time, Factor VIII, Antithrombin III, fibrin degradation products, antinuclear antibody, VDRL, and complement studies were normal. Platelet count was 74,000/mm3. The noncontrast head CT 6 days after admission demonstrated focal areas of increased density along the straight sinus and in the region of the torcular and posterior sagittal sinus, consistent with intraluminal thrombi within the dural venous sinus. IV-DSA revealed poor filling of the anterior and posterior portions of the superior sagittal sinus. He was treated with 50 mg/day prednisone and i.v. heparin, and his PTT decreased to 25 seconds after 5 days. His platelets rose to 340,000/mm3, and his headache and fourth nerve palsy gradually resolved. He was maintained on warfarin and prednisone. One week later, high-resolution head CT of the posterior fossa revealed no residual evidence of CVT.

Discussion

Our first patient was pregnant when she developed her neurologic symptoms, and she subsequently had a spontaneous abortion. Pregnancy alone may increase the risk of cortical vein thrombosis, but usually in association with hyperemesis gravidarum and the resulting dehydration, which were not noted in our patient. There was also a history of spontaneous abortions, deep venous thromboses, and a pulmonary embolus, all documented associations with LAs. The placental pathologic findings from our patient’s miscarriage were characteristic of those seen in association with LAs. The history of migraine has not been previously associated with CVT but has occasionally been noted in association with LAs. Increased intracranial pressure or pseudotumor cerebri are well-documented presentations of CVT. Her CT and IV-DSA findings, although not specific for CVT, did not support a diagnosis of idiopathic pseudotumor cerebri.

Our second patient suffered a sagittal sinus thrombosis as well as transverse sinus thromboses in association with an LA. He had a mild nephrotic syndrome secondary to a mesangial-proliferative glomerulonephritis. Although nephrotic syndrome may be associated with a “hypercoagulable state,” CVT associated with the nephrotic syndrome is distinctly rare. Lau et al described a child less than 3 years old with nephrotic syndrome and multiple thromboembolic phenomena, including a superior sagittal sinus thrombosis. Review of their patient’s coagulation data revealed a...
prolonged PTT prior to heparin therapy, suggesting the possibility of an LA.

One other case in the literature may have had an LA in association with CVT. Averback's Case 2, a 29-year-old woman, had a CVT immediately postpartum with prolonged PTTs, thrombocytopenia, normal PT, and "visceral autolysis" of the stillbirth. She completely recovered after treatment with heparin, hydrocortisone, and ampicillin. Estanol et al reported 20 women between the ages of 15 and 45 years with intracranial venous thrombosis; 14 of the 20 studied were without evidence of circulating anticoagulant.

LA has been associated with venous occlusions of the retinal, pulmonary, renal, hepatic, and lower extremity circulations. We therefore infer a possible role of LA in our 2 cases of CVT.

C VT has previously been associated with traumatic, systemic, and other coagulopathic disorders and is thoroughly reviewed elsewhere. LA are a heterogeneous group of acquired circulating immunoglobulins (IgG, IgM, or mixed-class) first described in patients with SLE. Major criteria for diagnosing a circulating LA have been precisely delineated. LAs prolong PTT partly through inhibition of the phospholipids used in the coagulation assays; thus, they appear to act as anticoagulants in vitro. However, recognition of LA has gained new clinical importance because of a growing number of associated neurologic conditions, in particular, thrombotic stroke and TIA.

Patients with LA appear to have an increased tendency for systemic and cerebral arterial thrombotic events. LA has been associated with SLE, phenothiazine use, autoimmune diseases, thrombotic arterial stroke during pregnancy, peripheral venous thrombotic occlusions, thrombocytopenia, false-positive VDRL, spontaneous abortions, neoplasia, acquired immunodeficiency syndrome, and otherwise healthy children and adults.

The mechanism(s) of an LA-induced thrombotic tendency is not clear. Inhibition of vascular tissue prostacyclin production, antiphospholipid (including anticardiolipin) activity, prekallikrein inhibition, changes in Antithrombin III function, platelet activity and aggregation, and inhibition of Protein C activation have all been demonstrated. Direct injury to the vessel wall through an antibody-antigen complex has also been hypothesized as a mechanism promoting thrombosis. Phosphatidylserine appears to be the specific phospholipid against which the LA anticoagulant activity is directed.

Recurrent cerebral ischemic events in patients receiving antiplatelet, anticoagulant, and steroid therapy are not uncommon when associated with LAs. LAs have been anecdotally reported to disappear with corticosteroid, splenectomy, plasmapheresis, pulse immunosuppressive therapy, or spontaneously. Both our patients received corticosteroids and anticoagulants and improved clinically, and their PTTs were less prolonged.

Our report expands the cerebrovascular manifestations associated with LAs to include CVT and should be considered in the differential diagnosis of cerebral venous thrombosis.

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References

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