Current Concepts of Cerebrovascular Disease — Stroke

Neurological Manifestations of Systemic Lupus Erythematosus and Thrombotic Thrombocytopenic Purpura

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NEUROPSYCHIATRIC SYMPTOMS and signs are a prominent part of systemic lupus erythematosus (SLE) and thrombotic thrombocytopenic purpura (TTP). These disorders are similar also in that they frequently share such clinical manifestations as hemolytic anemia, thrombocytopenia, renal disease, and fever. Adding to the complexity of diagnosis is the fact that patients may occasionally have clinical and laboratory evidence of both disorders. This article will review these disorders with emphasis on neurological manifestations.

Systemic Lupus Erythematosus

Neuropsychiatric Manifestations

The manifestations of neuropsychiatric illness in lupus erythematosus in order of decreasing frequency are (1) alterations of mental function including organic brain syndromes, affective illnesses, and schizophrenia-like disorders; (2) transient or recurrent seizures, usually generalized, although a variety of forms has been described; (3) paresis resulting from ischemia or hemorrhage; (4) tremor, choreoathetosis, or ataxia; (5) nuclear and infranuclear cranial neuropathies; and (6) peripheral neuropathies, usually of a mixed sensory-motor variety.

Feinglass et al. surveyed the relationships of nervous system involvement to other manifestations of the disease. Neuropsychiatric manifestations attributed to central nervous system SLE occurred in 37% of 140 patients, and five of these presented with neuropsychiatric signs and symptoms. The most frequent manifestations were psychiatric dysfunction, seizures, long tract signs, cranial neuropathy, and peripheral neuropathy. Psychiatric abnormalities secondary to SLE were characterized by organic features and by associated neurological findings, often diffuse or multifocal. The spinal fluid was abnormal in only 32%, usually a modest elevation of protein (70 to 92 mg/dl) and/or pleocytosis. The EEG was abnormal in 71%, particularly in association with seizures or focal neurological signs. Frequent, central nervous system abnormalities were an early feature, and in 63% neuropsychiatric involvement either preceded or occurred within the first year of diagnosis. A large majority (82%) of neuropsychiatric episodes occurred while patients were on no steroids or on low dose therapy, and only two patients were felt to have steroid-induced psychoses. The immediate prognosis for improvement in neuropsychiatric function was good, and corticosteroids appeared to be of benefit in a substantial number of patients, although their precise role was difficult to quantitate.

Estes and Christian reported that neuropsychiatric manifestations occurred in 59% of 150 patients studied prospectively. Disorders of mental function were observed in 42% and grand mal seizures in 26% (17% without renal disease). Cranial nerve involvement occurred in seven patients, six of whom had oculomotor signs and three of whom developed optic atrophy and blindness. Intention tremor was observed in eight and was associated with cogwheel rigidity in two. Hemiparesis occurred in eight, six of whom had chronic renal disease with hypertension and/or uremia. Ten developed peripheral neuropathy, primarily sensory.

Johnson and Richardson carried out a clinicopathological study of 24 cases of documented SLE. Neurological and psychiatric manifestations were found in 18 (75%). This high percentage is typically seen when the patients are followed to termination. In nine, neurological involvement occurred during the last six weeks of life. Death was attributable to central nervous system disease in four who died of intracerebral hemorrhage and two who died with status epilepticus. Seizures were present in 13, cranial nerve disorders in 10, hemiparesis in 3, paresis in 1, peripheral neuropathy in 2, and mental disorders in 8.

Penn and Rowan reported four cases of myelopathy in SLE and reviewed five earlier case reports. Two patients presented with myelopathy alone; the others had classic multisystem SLE antedating the appearance of myelopathy by months to years. The clinical neurological involvement was confined to the spinal cord. The onset was often rapid, occurring in 24 to 48 hours. The patients complained of numbness and weakness of one or both legs, ascending rapidly to involve the trunk. The spinal level on initial examination was most frequently low to midthoracic, and in four cases it ascended to the upper thoracic or cervical areas. There were flaccid paraplegia, loss of sensation below the level of the lesion, and loss of sphincter control in all patients. Four patients survived long enough to develop spasticity with bilateral extensor plantar responses. Spinal fluid usually showed increased protein and pleocytosis. Improvement occurred in two of the nine cases.


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Brandt and coworkers described involvement of visual pathways posterior to the optic chiasm. Their patients developed visual hallucinations, scotomas, homonymous field defects, and cortical blindness. These features indicated disease in the posterior cerebral artery distribution, a localization often supported by other neurological findings, such as vocal cord paralysis and diminished gag reflex.

The marked variability in nervous system involvement is further emphasized by reports of Sydenham’s chorea associated with SLE. Donaldson and Espiner reviewed the occurrence of chorea in 22 cases. The mean age of onset was 18 years, older than expected in rheumatic fever. Chorea was the initial manifestation in 8 cases and followed other clinical signs in 11; in 3 chorea and the other systemic features presented simultaneously. Chorea developed from seven years before to ten years after other systemic manifestations. The mean duration was eight weeks, similar to that found in rheumatic fever. The incidence of additional central nervous system involvement was high.

Fulford et al. observed six patients whose clinical picture resembled multiple sclerosis; however, the laboratory findings were suggestive of SLE. The most common neurological change was spastic paraplegia. The writers concluded that these patients represented a distinct variant or subgroup for which they coined the term “lipoid sclerosis.”

In essence, central nervous system involvement in SLE has no characteristic clinical course or pattern. The diagnosis depends on proving the presence of SLE and being certain to rule out the occurrence of other factors which may produce similar changes, such as cerebral arteriosclerosis, neoplasms, subdural hematomas, multiple sclerosis, etc.

Pathogenesis and Clinical Significance

The pathogenesis of neurological findings in SLE is still ill defined. Observed neuropathological changes often fall short of fully explaining the clinical manifestations, especially the “astonishing abnormalities of mental function.” A growing body of evidence suggests that immune processes occur within the central nervous system in SLE. Lowering of the fourth component of complement in cerebrospinal fluid has been reported in association with the development of acute neurological illness. Immunofluorescence studies have shown diffuse deposits of gamma globulin in the choroid plexus, and antibody to DNA as well as DNA: anti-DNA complexes have been identified in the cerebrospinal fluid of such patients.

Estes and Christian analyzed the prognosis of SLE when specific organ systems are involved by the disease. Neuro-psychiatric manifestations are second only to renal disease as a cause of death, with both organic mental syndromes and central neurological involvement (excluding seizures) having the most unfavorable prognosis. When five-year survival rates were estimated, it was observed that seizures in the absence of other central nervous system manifestations or uremia were not a grave prognostic sign. Similarly, functional psychoses without evidence of other central nervous system involvement did not adversely affect survival. However, the presence of organic mental syndromes plus evidence of such other central nervous system involvement as cranial nerve signs, tremor, or hemiparesis sharply lowered the five-year survival rate. The presence of renal disease in each of these categories was roughly the same and thus was not a major factor.

Diagnosis of SLE

The diagnosis of SLE remains imprecise. In general, three elements should be required to establish a diagnosis: (1) multisystem disease, (2) positive serological tests, and (3) absence of a better diagnosis. Multisystem disease may be defined as involvement of more than one of the skin and mucous membranes, joints, kidneys, serous membranes, blood, lungs, or nervous system.

Serological tests should include the fluorescent antinuclear antibody (FANA) test which is positive in almost all untreated patients with active SLE. However, the FANA test is not specific, and when positive, evidence of autoantibodies having greater specificity for SLE should be sought. The LE cell test continues to be important since it is positive in approximately 75% of patients. Antibodies against native DNA are highly specific for SLE and can be detected by a variety of methods, particularly hemagglutination or radioimmunoassay. Also, serum complement is very frequently depressed during the active phases of SLE, helping to exclude other connective tissue disorders in which it is normal.

Exclusion of other diseases which may result in multisystem involvement and antinuclear antibodies is particularly important. These diseases include rheumatoid arthritis, systemic sclerosis (scleroderma), drug-induced SLE-like syndromes, chronic active hepatitis, and polyarteritis.

The American Rheumatism Association has proposed criteria for classifying patients for clinical trials, population surveys, and other studies. A patient is said to have SLE if any four or more of the following are observed serially or simultaneously: (1) facial erythema, (2) discoid lupus, (3) Raynaud’s phenomenon, (4) alopecia, (5) photosensitivity, (6) oral or nasopharyngeal ulceration, (7) arthritis without deformity, (8) LE cells, (9) chronic false positive serological tests for syphilis, (10) proteinuria (3.5 g/day), (11) cellular casts, (12) pleuritis or pericarditis, (13) psychosis or convulsions, and (14) hemolytic anemia, leukopenia, or thrombocytopenia. Although a high percentage of SLE patients ultimately fulfill these criteria, at the time of initial examination when therapeutic decisions are needed, perhaps one-third of patients will not. Furthermore, the considerable value of many useful laboratory tests is ignored.

Therapy of Central Nervous System SLE

The optimal management of patients with central nervous system manifestations of SLE is not established. Recent experience indicates a diversity of clinical manifestations, a high immediate mortality, and long-range neurological morbidity only partly dependent on other system involvement. Several groups have reported good therapeutic results with high doses of corticosteroids (from 500 to 3,000 mg hydrocortisone per day) for central nervous system disease crisis. Some investigators have attributed a decrease in death from central nervous system disease in SLE to high dose corticosteroid regimens. However, others report unimpressive results and a high incidence of fatal
NEUROLOGICAL SIGNS OF LUPUS/Petz

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) is an unusual disorder which is manifested as a pentad of clinical findings: thrombocytopenic purpura, hemolytic anemia, neurological abnormalities, fever, and evidence of renal disease. The most frequently recorded chief complaints are those of neurological abnormalities and hemorrhagic phenomena (table 1). The symptoms and physical findings in reported cases of TTP (table 2) include neurological manifestations in 90% of patients (table 3). Cranial nerve palsies, paresthesias, and vertigo have also been reported. An important characteristic of the disease is that on subsequent examination about one-third of such patients will be intact neurologically. Thus, neurological abnormalities may be remittent and subject to frequent, rapid change so that, for example, hemiplegia or aphasia may clear completely a few hours after appearance. In some patients neurological manifestations may precede by many months or years the recognition of TTP.

Initially, seizures or coma are present in a minority of patients, but eventually one or both of these develop in about 50% of patients. Recurrent seizures accompanied by high fever and progression into coma are common terminal events.

The frequency of neurological manifestations is attributed to the striking involvement of small vessels of the gray matter of the hemispheres and the brain stem on pathological examination. Despite widespread vascular occlusions, however, there is little cerebral infarction which may account for the transientness of the neurological abnormalities.

Other components of the characteristic pentad of clinical findings are present in 88 to 98% of patients (table 2). The most common hemorrhagic manifestations are purpura and retinal hemorrhages, but major gastrointestinal or genitourinary hemorrhages may be seen. Thrombocytopenia is an almost constant finding, and examination of bone marrow aspirations usually reveals a normal or increased number of megakaryocytes. Evidence of disseminated intravascular coagulation is present in only a minority of patients, and even when present, it does not appear to be a primary factor in pathogenesis. Hemolysis is the major cause of anemia. It is characterized by the presence of numerous irregularly contracted red cells (burr cells, helmet cells, fragmented cells, schistocytes) in the peripheral blood and is considered an example of a microangiopathic hemolytic anemia. Hyperbilirubinemia, a common manifestation of TTP, is caused by an elevation of the indirect fraction in almost all cases. Renal involvement is manifested by proteinuria, hematuria, pyuria, casts, and azotemia.

The pathological diagnosis has been made during life by biopsy of skin, muscle, lymph node, bone marrow, and surgically removed spleen. At autopsy characteristic vascular occlusions may be found in any organ but are seen most frequently in the heart, brain, kidneys, pancreas, and adrenals. The characteristic pathological lesion consists of widespread hyaline occlusions in terminal arterioles and capillaries. There is a striking absence of inflammatory change in the involved vessels, and areas of infarction are limited considering the number of vessels involved.

The differential diagnosis of TTP includes idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, Evans syndrome (coexistence of immune hemolytic anemia and thrombocytopenia), SLE, metastatic malignancy with disseminated intravascular coagulation, and other causes of microangiopathic hemolytic anemia.

A number of theories have been proposed to explain the nature and cause of this complex disorder. Among the mechanisms which have been implicated are toxins, drug sensitivity, bacterial infection, autoimmune reactions, collagen disease, and intravascular coagulation. However, the evidence in support of any of these is minimal, and the etiology or etiologies of TTP, as well as its pathogenesis, remain unknown.

TTP usually runs a rapidly progressive and fatal course, and the majority of patients die within three months of onset. No consistently effective therapy has been found.
although many forms of treatment have been used, including exchange transfusions, heparin, splenectomy, corticosteroids, hemodialysis, and, lately, antiplatelet drugs. A frequent combination of therapeutic modalities used in the few reported survivors of TTP consists of large doses of steroids (more than 100 to 150 mg of prednisone daily) with splenectomy. The additional use of antiplatelet drugs (aspirin and dipyridamole) is recommended because they are benign and apparently effective in some patients.12

Association of TTP and SLE

Some have attempted to draw a parallel between TTP and SLE. However, the two diseases differ significantly in sex incidence, duration, course, complications, prognosis, response to therapy, and pathology. LE cell tests are only rarely positive in patients with TTP. If the histological changes of “wire loop” kidney lesions, “onion-skin” splenic arterioles, or Libman-Sachs endocarditis are used as criteria for the diagnosis of SLE, only 13 of 237 autopsied cases of TTP in one series9 could also be diagnosed as SLE. Nevertheless, even though unusual, the two syndromes may coexist in some patients, and in particular, the findings of TTP may develop as a late manifestation of SLE.

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