Neuropsychiatric involvement in systemic lupus erythematosus: Case report and review of the literature

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Neuropsychiatric (NP) disturbances are a widely recognized complication of systemic lupus erythematosus (SLE). When NP manifestations constitute the initial presentation of the disease, the difficulty of diagnosis of SLE is compounded. The most common clinical features include disorders of mental function or seizures; less often, peripheral neuropathy, cranial nerve disorders, myelopathy and myopathy, stroke, or disorders of movement are manifested. The pathogenetic mechanisms remain unknown, although several theories have been proposed. Diagnostic studies are not specific. Therapy includes treatment with steroids and supportive medication. Evaluation of other therapeutic agents continues. An illustrative case of NP involvement in SLE is reported.

The original description of systemic lupus erythematosus (SLE) in 1872 mentioned "delirium" in 2 of the 11 patients.¹ Focal neurologic abnormalities associated with SLE were first described by Osler² in 1903. The occurrence of neuropsychiatric (NP) disturbances in association with SLE is now well recognized, with their frequency ranging from 14 to 75 percent,³⁻⁶ and many large series showing 50 percent.⁷ These manifestations may constitute the initial presentation of the disease or may occur during the course of the illness; they may be mild and transient, or severe and life threatening.

We report the case of a patient with NP involvement secondary to SLE. Thereafter, we review the pathology, clinical features, diagnostic considerations, management, and prognosis in patients with this aspect of SLE.

Report of case

A 50-year-old Okinawan woman was brought to the emergency department on January 13, 1984, in a hypotensive and comatose condition. A diagnosis of SLE had been made approximately 2 years prior to this admission, and, having had multiple exacerbations of the disease associated with arthritis, nephritis, cerebritis, acute psychosis, depression, and left third cranial nerve palsy, she fulfilled the revised American Rheumatism Association criteria for SLE.⁸ She was started on Imuran 2 weeks prior to admission because of nephritis and cerebritis. The patient had been maintained on a regimen of Prednisone (50 mg. by mouth daily) and, starting 2 weeks prior to admission, Imuran (25 mg. by mouth three times daily). She exhibited symptoms of an upper respiratory tract infection along with slurred speech for 48 hours prior to admission.

The past medical history was otherwise unremarkable except for hypothyroidism, for which she was on replacement therapy, and total abdominal hysterectomy performed many years before. She had smoked one pack of cigarettes per day for 30 years. There was no history of allergies or alcohol abuse.

Physical examination on admission revealed that she was responsive to noxious stimuli only. The blood pressure was 60/40 mm. Hg initially and later rose to 90/60 mm. Hg with pressor agents. The heart rate was 136 beats per minute and regular; respirations were 36 per minute. Temperature was 104.5 F. rectally. Examination of the head, eyes, ears, neck, and throat revealed no evidence of trauma. The pupils were equal, round (4 mm. in diameter), and reactive to light directly and consensually. No papilledema or hemorrhages were noted. A left lateral conjugate gaze palsy was present. The neck was supple. There was a grade 2/6 early systolic murmur heard at the lower left sternal border; the lungs were clear. An abdominal examination yielded unremarkable results. The skin and mucous membranes showed no ecchymoses, petechiae, or purpura. The remainder of the neurologic findings consisted of right central facial weakness, right hemiparesis with the arm affected more than the leg, and a right Babinski sign. Deep tendon reflexes were hyperreflexic on the right side.

The leukocyte count was 15,600/cu. mm. There were 91 percent segmented neutrophils, 5 percent nonsegmented forms, and 4 percent lymphocytes. The platelet count was

324,000/cu. mm. The hematocrit reading was 47.1 ml./dl., and the hemoglobin concentration was 15.1 gm./dl. The peripheral blood smear was essentially normal. The results of coagulation studies were within normal limits. Blood, plasma, and serum chemistry values were as follows: electrolytes and plasma bicarbonate, within normal limits; blood urea nitrogen, 34 mg./dl.; creatinine, 4.2 mg./dl.; serum glucose, 363 mg./dl., and serum calcium, 9.8 mg./dl. A urine drug screen was negative. Urinalysis showed 2+ protein, 8-12 leukocytes/high-power field, trace bacteria, and a specific gravity of 1.015. No red cell casts were noted. The erythrocyte sedimentation rate was 10 mm./hr. Arterial blood gas determination revealed a pH of 7.33, carbon dioxide partial pressure of 223 mm./Hg; bicarbonate level of 17 mEq./L., and oxygen saturation of 99 percent on 100 percent inspired oxygen. The antinuclear antibody test was positive in a homogeneous pattern with a titer of 1:80. Tests for anti-double-strand DNA antibodies were negative by the Farr method. The total hemolytic complement (CH100) was normal at 125 CH100 units, while complement component C3 was 77 mg./dl. (low normal) and the C4 value was 16.8 mg./dl. (also low normal).

A chest radiograph showed no active pulmonary disease. Electrocardiograms demonstrated a supraventricular tachycardia, which dissipated spontaneously shortly after admission.

Cerebrospinal fluid (CSF) values for cells, pressure, and chemical content were normal. Gram's stain and culture of the CSF and blood and urine cultures yielded negative results. The values from thyroid function studies were normal.

Computerized tomography (CT) of the brain without contrast enhancement revealed a left cerebral infarction. A slight mass effect was evident in the distribution of the left middle cerebral artery.

The patient was admitted to the intensive care unit and was aggressively supported with mechanical ventilation, pressor agents, and corticosteroids in stress doses. She gradually became more alert and was removed from the ventilator on the second hospital day. Renal function improved dramatically and the creatinine value returned to 1.8 mg./dl. by discharge. Neurologically, the patient improved, although she had residual weakness on the right side, depression, and expressive aphasia. She was maintained on Imuran (50 mg. by mouth daily), Prednisone (40 mg. by mouth daily), and Synthroid (0.15 mg. by mouth daily). Improvement continued and she was transferred to a rehabilitation center on the twenty-ninth hospital day.

Review of the literature

Pathology and pathogenesis

No single neuropathologic lesion can account for all of the NP manifestations one sees in SLE. Johnson and Richardson⁵ examined 24 SLE patients at autopsy. Although 75 percent of these had clinical evidence of NP abnormalities before death, only 10 patients had specific gross abnormalities at autopsy. These included large intracerebral and pon-

tine hemorrhages, multiple small fresh hemorrhages, areas of old infarction, and, in 1 case, a small subpial hemorrhage. Microinfarcts or increased pericapillary microglia were found in 20 of the 24 cases. They concluded that CNS lupus, in most instances, is a vascular disease affecting mainly the smaller arterioles or capillaries. True necrotizing vasculitis of small and medium vessels was rare.

More recently, Ellis and Verity's⁶ 57 patients, who were followed for up to 11 years, had such gross and microscopic lesions as vasculopathy (65 percent), infarction (44 percent), hemorrhage (42 percent), and infections (28 percent). Of the 57 patients who came to autopsy, 3 were found to have transverse myelopathy, progressive multifocal leukoencephalopathy, or Hodgkin's disease. The common vascular lesions were hyalinization of the meningeal, cortical, and subcortical arterioles (in over 50 percent of cases), perivascular lymphocytosis, and endothelial proliferation; less common were thrombosis and vasculitis indicated by thickening of the capillary wall. The incidence of cerebral infarction was 44 percent. However, microinfarctions were almost three times as common as large infarctions. Most microinfarctions were found in the parietal and temporal pole convexities and also within the pons, but infrequently within the brain stem or pallidus. Larger infarcts were more common in the distribution of the middle cerebral artery. Gross hemorrhage, which occurred in 42 percent of the patients overall, was most commonly subarachnoid. Microhemorrhages occurred in 19 percent of cases, whereas intracerebral hemorrhage was found in 10 percent. Subdural hemorrhage was rare.

Neuropsychiatric features

A large variety of neurologic and/or psychiatric abnormalities can accompany SLE. Often, several abnormalities are present in the same patient.⁴ It is uncommon for NP manifestations to be the initial presentation of SLE (about 3 percent of cases in two large series),^{4,9} but they became apparent either before or within 1 year after diagnosis of SLE in 63 percent of cases.⁴ Diagnosis may be more difficult if any of the following NP manifestations represent the initial presentation of the disease.¹⁰

Psychiatric disorders. One of the most common problems is psychiatric disturbance.¹⁰ Estes and Christian⁹ reported that 42 percent of their 150 SLE patients had psychiatric disorder. The psychiatric manifestations included psychosis, such as organic mental syndromes evidenced by disorientation, hallucination, or deterioration in mental

function, or functional psychoses, such as schizophrenia and affective disorders, or anxiety and depressive neurosis. Of the 24 patients with psychiatric involvement in the series of 52 SLE patients studied by Feinglass and coworkers,⁴ 22 had some organic involvement.

Johnson and Richardson's⁵ series of 24 cases included 5 patients with gross psychoses and 3 with mild affective disorders. In two series in the literature reviewed by Harris and Hughes,⁷ organic brain syndromes were evident in 19 and 18 percent of cases, and functional disorders in 8 and 22 percent of cases.

Identification of NP disorders as directly related to SLE or as secondary to therapy or a consequence of chronic disease is not always straightforward.⁷ Corticosteroids may precipitate psychotic reactions or other NP disturbances in SLE patients under treatment.^{4,10-12}

Seizures. Seizures are reported to be common in SLE. The grand mal type is most frequent,^{4,5,13} but focal epilepsy, psychomotor seizures, and petit mal attacks have also been seen.^{5,13} In addition, status epilepticus can occur and may be very difficult to control.^{5,11} The incidence of seizure during the course of SLE ranges from 7 to 57 percent in one literature review⁶ and from 14 to 20 percent in another.⁷

Seizures may be present in early or later phases of the disease.¹⁰ Johnson and Richardson's⁵ review noted several reports of seizures occurring from 1 to 20 years before other manifestations of SLE. As with psychiatric manifestations, diagnosis of SLE may be difficult to make if seizures are the presenting sign.

Seizures occurring in the course of systemic lupus may also be secondary to uremia and/or hypertension.^{4,7,9,10} Further, in some patients with known idiopathic seizure disorders, an SLE-like syndrome develops during treatment with certain anticonvulsant medications such as phenytoin or trimethadione.^{5,9}

Cranial nerve abnormalities. Disorders of the cranial nerve may accompany SLE. The most commonly affected cranial nerves are II through VII. Of the approximately 11 percent of patients with cranial nerve abnormalities studied by Feinglass and coworkers,⁴ the seventh cranial nerve was the most commonly affected. In the series of Johnson and Richardson,⁵ 42 percent exhibited cranial nerve disorders. They considered extraocular movement and pupillary abnormalities as the most common cranial nerve aberrations. Extraocular movement abnormalities may suggest myasthenia gravis in

the differential diagnosis.⁵ Estes and Christian⁹ found that the oculomotor nerve was more commonly affected than the trochlear or abducent nerves.

Bennett and coworkers¹³ noted the frequency of visual defects such as homonymous hemianopia, blindness, and papilledema. Optic nerve disease resembling optic neuritis was a primary manifestation of SLE in 3 cases reported by Hackett and associates.¹⁴ They stressed the similarity of presentation of these cases to that of patients with demyelinating disorders such as multiple sclerosis.

Other disorders such as ptosis, facial sensory deficits, palatal weakness and dysarthria, tinnitus, and vertigo have also been reported with SLE.^{2,4,5} Of 16 patients who had cranial nerve signs in the Feinglass⁴ series, peripheral neuropathy was present in 8, 7 of whom had both kinds of deficits concurrently.

Movement disorders. In SLE, motor disorders are unusual, occurring in from 4 to 7 percent of the series reviewed by Harris and Hughes.⁷ The most commonly reported motor disorder is chorea.¹¹ In SLE patients, this may initially appear as only slightly exaggerated semipurposeful movement.¹³ A diagnosis of SLE should be considered in women with chorea gravidarum, especially if there has been no history of rheumatic fever.¹⁵

Other movement disorders reported include intention tremors,⁹ cerebellar ataxia⁵ parkinsonian features such as cogwheel rigidity,⁹ and rarely, athetoid movements and ballismus.⁵

Weakness due to cranial or spinal cord involvement. Osler² described an SLE patient who had five or six episodes of hemiplegia within 1 year. The incidence of hemiplegia reported by Johnson and Richardson⁵ was 12 percent, by Ellis and Verity⁶ 21 percent. The latter researchers⁶ found a range of from 0 to 13 percent in other series. Hemiplegia usually occurs at some intermediate stages of the disease, but it can also occur as a terminal event.^{5,13} However, Fox and colleagues¹⁶ described the occurrence of left homonymous hemianopia, hemiparesis, left clonic seizures, and progressive deterioration of consciousness in an SLE patient. In this case cerebral arterial emboli in the branches of the posterior and middle cerebral arteries had originated from the verrucae of Libman-Sacks endocarditis.

Paraparesis or quadriparesis due to spinal cord involvement is a rare manifestation of SLE.⁵ Acute transverse myelopathy is the usual feature. Penn and Rowan¹⁷ cited some cases in the literature in which the classic multisystem symptoms of SLE

antedated the appearance of myelopathy by months or years, and others where myelopathy was the presenting manifestation. A review by Andrianakos and coauthors¹⁸ indicated that the onset is distributed randomly during the course of the disorder. Myelopathy is usually progressive over 24 to 48 hours.¹⁷ The most common presenting motor deficits are numbness and weakness of the lower extremities.¹⁸ Initially, the sensory level of involvement is most often the low to midthoracic region. In some cases, the complaints ascend to the upper thoracic and cervical regions.¹⁷ There is usually paraplegia with loss of both sphincter control and sensation below the level of the lesion. The weakness is characteristically flaccid in nature with areflexia, but some patients demonstrate spasticity with bilateral Babinski signs. The initial presentation may resemble spinal cord compression from a tumor or a demyelinating disease such as multiple sclerosis or Guillain-Barré syndrome.⁴ A spinal fluid analysis and myelogram may be necessary to rule out these other problems.

Peripheral neuropathy. As stated earlier, cranial and peripheral neuropathies may be associated.⁴ Peripheral nerve disorders are seen less frequently than CNS disorders.⁵ The presentation of neuropathy in SLE is variable. Asymmetric involvement, such as wrist or foot drop, may suggest a mononeuropathy or mononeuritis multiplex.⁵ Brachial plexus neuropathy as an initial presentation of SLE, which preceded a polyneuropathy by several weeks, was reported by Bloch and associates.¹⁹ More commonly, sensory features predominate and the patients have subacute sensory or sensory and motor neuropathy.⁴ A neuropathy with CSF characteristics of Guillain-Barré syndrome have been described.^{4,5} Herpes zoster neuritis has been reported in association with SLE, particularly in patients with nephritis who are receiving immunosuppressive agents.²⁰

Myositis. In SLE, myositis associated with pain, tenderness, weakness, and elevated serum muscle enzyme values may occur in from 5 to 30 percent of cases.¹¹ In contrast to the other symptoms of SLE, the myositis is usually mild, with the clinical picture resembling a milder form of polymyositis. Of 228 patients with SLE studied by Tsokos and colleagues,²¹ 18 (8 percent) had prominent muscle disease, the myositis occurring most often at the time of diagnosis of the SLE. Serum aldolase values were a more sensitive indicator of myositis than creatine kinase levels. A muscle biopsy was helpful in differentiating SLE myositis from true polymyositis.

Diagnosis and laboratory tests

No single test or group of tests is specific for diagnosis of NP SLE. The most commonly used diagnostic procedures are discussed here.

Cranial CT. Gonzalez-Scarano and colleagues²² found that 20 of 22 SLE patients had abnormal CT studies while having CNS symptoms. The most common aberration was cerebral atrophy, as shown by sulcal enlargement with or without ventricular enlargement. Whether this finding is specific for cerebral SLE or related to steroid treatment is a matter of controversy.^{10,11}

Brain scanning methods. The use of brain scanning has had variable results. Some have found technetium scanning helpful,^{23,24} but others⁴ have had poorer results with rectilinear scans.

Oxygen-15 brain scanning technique has been used to study cerebral oxygen utilization and cerebral blood flow. Abnormalities were seen in 23 of 24 SLE patients with definite CNS disease, in 14 of 15 with suspected CNS lupus, and in 10 of 12 without clinically apparent CNS lupus.²⁵ The major drawback of this technique is the inaccessibility of a cyclotron, which is needed to produce short-lived O₂.¹⁵ Magnetic resonance imaging of the brain in SLE has recently been reported to be of value in evaluating patients with NP symptoms.

Electroencephalography. Johnson and Richardson⁵ indicated that the electroencephalography (EEG) is generally of little diagnostic or localizing value. The most frequent finding is diffuse slow wave activity suggesting widespread cortical disease.^{4,5} However, even this non-specific finding may help to differentiate between organic and purely functional mental changes in patients with psychiatric manifestations of SLE.

Arteriography. The results of arteriography are usually normal because large vessels are not often involved in SLE. However, there are sporadic reports of major cerebral vessel occlusions.^{4,27}

CSF studies. An examination of the CSF will yield normal results in over half of the cases, but the procedure is helpful mainly in excluding concomitant infection.¹⁰ An abnormal CSF result suggests that there is an organic basis for the NP features being investigated; however, failure to show abnormalities does not preclude an organic lesion. Slight protein elevations are found in up to about 48 percent of cases.^{4,5,7} Values beyond 100

mg./dl. are very unusual,^{5,13} but Feinglass and associates⁴ detected protein elevations in the range of 189 to 300 mg./dl. in 4 of 37 patients tested. A mild lymphocytic pleocytosis as well as low CSF glucose may be seen.^{5,28} The CSF IgG, calculated as a percentage of total protein, exceeds the normal upper limits of 14 percent in some patients.²⁹

Small and associates²⁹ reported that 8 of their 13 patients with CNS SLE had elevated CSF anti-native DNA binding values. In serial CSF studies, the levels returned to normal in 3 of the patients who had improved clinically. Petz and colleagues³⁰ found abnormally low levels of the fourth component of complement (C4) in the CSF of patients with CNS lupus and produced evidence to suggest that this was the result of an immune reaction within the CNS rather than a low serum C4 value. Hadler and coworkers³¹ found no significant difference in CSF C4 levels between patients with CNS SLE and normal controls in single tests but recommended serial determinations, which show low values.

Small and coworkers²⁹ suggested that a battery of tests be used in combination with clinical observations in making the diagnosis of CNS SLE. The tests include measurement of CSF total protein, IgG, and anti-DNA binding, and the performance of brain scan flow.

Management

Corticosteroids remain the standard treatment for NP SLE, on the basis of experience.¹⁰ The literature indicates that high maintenance doses may be no more effective than treatment with smaller doses,²⁸ but that they increase the risk of morbidity or even death from infection and may induce psychotic reactions.¹² The usage of pulse-doses of corticosteroids may offer some benefit.¹⁰

Immunosuppressive agents have been tried in cases of refractory disease or steroid-induced complications.²⁷ However, their use may increase the risk of infection.¹⁰ In certain refractory cases, therapies such as plasmapheresis and total lymphoma irradiation may be utilized.¹⁰

Prognosis and survival

Cerebral involvement is one of the most frequent causes of death in SLE.^{5,7} In the study of 88 patients by Estes and Christian,⁷ the percentage of 5-year survivors with NP manifestations estimated from the time of appearance of those symptoms was approximately 55 percent, compared to 76.9 percent in 150 patients with multisystem disease. The presence of grand mal seizures (in the absence of other CNS manifestations or uremia) or functional psychosis was not a grave prognostic sign. However, the

presence of organic mental syndromes, cranial nerve abnormalities, tremor, or hemiparesis decreased the 5-year survival rate significantly.

Feinglass and associates⁴ found no significant difference in survival rates between SLE patients with and without NP manifestations at 5 and 10 years. A small number of deaths in the NP group were due to neurologic disease; more often, infection was the cause.

Although the prognosis of SLE patients has improved over the last years, the incidence of severe infection with opportunistic organisms, such as *Listeria*, toxoplasmosis, or fungi, is increasing.⁶ Certainly, the frequency of these infections may be related to the treatment of CNS SLE with corticosteroids and immunosuppressive agents. Earlier recognition of CNS SLE will not reduce the occurrence of such complications or opportunistic infection, because treatment is usually long term.

Summary

Because NP disturbances in patients with lupus erythematosus can be serious and often fatal, it is important to recognize them promptly. An illustrative case here has been reported. Recommendations for diagnostic studies to illuminate the etiology of the acute NP manifestations have been reviewed. Current therapeutic regimens were highlighted.

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