NEUROLOGICAL ASPECT OF SYSTEMIC LUPUS ERYTHEMATOSUS

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(Received for publication September 7, 1966)

After Kaposi1) designated the condition characterized by fever, toxic manifestations and cutaneous lesions resembling those of erysipelas disseminatus as lupus erythematosus disseminatus 94 years ago and Osler2) first emphasized the significance of the systemic manifestations of the disease 71 years ago, Daly3) was first to make a systematic review of cerebral involvements and referred to the now well-known neurological signs of this disease—toxic psychosis, convulsion and scattered neurological findings. Peripheral neuritis was first described in this disease by Hepteinstall and Sowry4) in 1952 and Malamud and Saver5) in 1954 summarized neuropathological findings. Harvey et al.6) in a review of literature and analysis of their cases, and Clark7)-9) in a series of papers mentioned a variety of neurological signs and symptoms. Numerous case reports of SLE (systemic lupus erythematosus) with neurological signs and symptoms have also been made over the past ten years.

METHOD OF STUDY

The charts of the patients diagnosed as having systemic lupus erythematosus at The Johns Hopkins Hospital between 1951 and 1964 were screened and those of the patients having positive L-E preparation and at least one of the three major symptoms of the disease—polyarthritis, butterfly skin lesion, renal involvement in the background of general symptomatology most compatible with SLE were carefully reviewed in regard to the presence of any neuromusculo-retinal abnormalities. Thus 46 patients were selected. The charts of these patients were studied to investigate the nature of their neuro-musculo-retinal abnormalities, the ways of their development and their course and prognosis. Also the effects of steroid treatment on these abnormalities were studied.

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In the present study, no attempt was made to reveal the incidence of neurological abnormalities of SLE because of the three reasons. The first is that very rigid criteria were used for diagnosis of SLE to avoid confusing the issue by including those possibly with diseases other than SLE. The second is that not all the charts of the patients seen in the above-mentioned period were available. The third is that the attempt has been made by others. Each symptom is dealt with in the following sections with illustrative cases.

Table 1

<table>
<thead>
<tr>
<th>Neurological Signs and Symptoms seen in the Patients in the Present Series</th>
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<tbody>
<tr>
<td>Signs and symptoms</td>
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<td>Convulsion</td>
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<tr>
<td>Psychosis</td>
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<tr>
<td>Stroke</td>
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<tr>
<td>Subarachnoid hemorrhage</td>
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<tr>
<td>Meningeal involvement</td>
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<td>Chorea minor</td>
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<tr>
<td>Neuroophthalmological involvement</td>
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<tr>
<td>Peripheral neuropathy</td>
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<tr>
<td>Myasthenic syndrome</td>
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<tr>
<td>Myopathy</td>
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<td>Herpes zoster</td>
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Most of the patients had more than 1 sign or symptom.

RESULTS

Convulsive Seizures

It is now well known that convulsive seizures occur not infrequently in the course of SLE. Benett et al. found incidence ranging from 7 to 31% in 6 large series of patients with SLE. Russell et al. reported that among 144 patients with the disease reported in literature up to 1951, 22 had convulsions. Fifteen had convulsions during the terminal stage of the disease. Four had isolated grand mal seizures during the active, preterminal phase. Information is not available in the other three. The same authors reported in their own series, 7 patients with seizures out of 28 with SLE. Two had recurrent attacks of convulsions, preceding by 2 years in 1 case and by several years in the other, the onset of other signs of SLE. In 3 patients, convulsive seizures occurred during the active phases of the disease. They did not recur when SLE was controlled. Two other patients had recurrent convulsions only terminally, one
of them in association with oliguria and uremia. Clark and Bailey[7] in their
review of 100 patients with SLE mentioned 14 patients with seizures, 3 having
them terminally.

Fifteen patients in the present series had convulsions and among them only
one terminally. One patient had repeated febrile seizures between age 2 and 10,
this being the only one having convulsions before the development of SLE
symptoms. All patients but one developed convulsions during active stages of
the disease. Ten had no recurrence after the initial episodes although not on
anticonvulsants. In 2 others they recurred only during relapses of the disease.
In others this point is not clear. Ten patients were receiving adrenocorticosteroid
treatment at the time of the initial convulsion. In 1 patient, 16 attacks of con-
vulsions occurred over 48 hours when ACTH and cortisone were suddenly with-
drawn. In contrast, 2 patients had seizures 4 and 5 days respectively after they
were started on steroid treatment while other symptoms were subsiding. Hyper-
tension and azotemia in 3 patients and hyponatremia in 1 might have precipitated
the convulsions. Thirteen had generalized convulsions while 1 had focal and
generalized seizures. Electroencephalogram taken immediately following con-
vulsions in 4 patients showed no lateralized abnormality or seizure discharge.
Ten lumbar punctures were done (twice in 1 patient) and on 3 occasions elevated
protein up to 128 mg% was found. On 6 occasions red blood cells up to 86/mm³,
white blood cells up to 10/mm³ were noted. No evidence of meningitis or peri-
pheral neuropathy was present at that time.

It is interesting to note that 18 patients[12-18] have been reported, who devel-
oped SLE while receiving hydantoin, trimethadione paradione or primidone for
seizures. Sixteen patients were under age 20 and in 2 others age is not men-
tioned. The medications were taken from 1 month to 3 years before the first
sign of SLE developed. Benton et al.[14] felt that these medications produce SLE
rather than unmask the latent disease. Supporting this is the age distribution
of these patients, different from that of usual SLE. Regression in most cases
occurred when anticonvulsants were discontinued. One wonders if most, if not

<table>
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<td><strong>Convulsions in the Course of SLE</strong></td>
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</table>

| 1. Incidence in the literature 7-31%. |
| 2. Generally in active stages of the disease. |
| 3. Occasionally within several days after steroid treatment is begun. |
| 4. Occasionally associated with uremia, electrolytes imbalance and
  other SLE complications. |
all, of the cases reported, in which the initial symptom was seizure, belong to this category. They too developed SLE symptoms after taking the same anticonvulsants incriminated in other cases. Their age distribution is also similar.

Case (1): This female was in good health until March 1955 when at the age of 17, she developed swelling and pain of the ankles and was found to have positive L-E preparations. She was treated with prednisone and noted symptomatic relief. That summer she had frequent episodes of purpura, especially on lowering doses of steroid. In September, she developed pain, swelling and heat in elbows, fingers, knees and ankles. Also severe epistaxis was noted. This was followed by generalized convulsions with tongue biting. Prednisone was continued and she felt better. She continued to have bleeding tendency and splenectomy had to be done 6 months later. However no more convulsion was noted although no anticonvulsants were given to the patient.

Psychoses

Psychoses are common neurological symptoms of SLE. Their incidence varies from 9% reported by Jesser et al.,21) to 52% by O'Connor.22) In the latter's series of 40 patients, 11 developed acute brain syndrome, 7 schizophrenia, 3 psychotic depression. Eighteen of the 21 patients were receiving steroid at the time of the episode. As a rule, psychoses occurred when steroid dosage was increased to control medical symptoms. Of eleven previously psychotic patients who subsequently received steroids, 3 had recurrence of psychoses. The remaining 8 received essentially the same level of cortisone as they had had at the time of their psychoses. The length of the psychotic episodes ranged from hours to months. None remained grossly psychotic for more than 4 months. Comparable series was reported by Stern and Robbins23) who found that of 53 patients, 15 had organic mental syndrome, 6 schizophrenia, 2 psychotic depression and 3 steroid induced psychosis. Patients previously psychotic while treated with steroids tolerated subsequent courses of therapy with no ill effects. Those with purely organic mental syndrome responded readily to steroid. In schizophrenic patients psychosis frequently continued, even after all evidence of SLE activity had ceased.

Ten patients with psychoses associated with SLE, have been reported in detail. In 1 patient psychosis preceded physical signs, but the diagnosis of SLE is questionable. In 7, psychoses developed while SLE was active and in 1, while SLE was under control with a constant dose of steroid. Four patients were receiving steroid at the time of the onset and change in steroid dosage had no effect on the symptoms. Among four patients, who were not receiving the
treatment at onset and were subsequently started on it, 2 improved and 2 neither improved nor became worse. In 5 patients, psychoses cleared or improved within 4 months, resulting in discharge from mental institutions. One had recurrence which also cleared rapidly. The other 5 patients remained permanently psychotic.

In this study, 9 patients developed overt psychoses, 6 showing organic mental syndrome characterized mainly by confusion, disorientation, agitation, outbursts of rage, unsystematized delusions or illusions. In 1, psychosis was a mixture of organic mental syndrome and schizophrenia. Catatonia was the main feature in another.

Five patients developed psychoses during active stages of the disease. Institution or increase of steroid treatment relieved them in 2 of these patients. One recovered without steroid treatment. In 2 others increase of steroid dosage did not relieve the symptom and subsequent reduction improved it in 1. The other 4 became psychotic within several days after institution or increase of steroid treatment at the time when physical signs were improving. All of them improved when steroid dosage was reduced. Three of them, however, had recurrence when it was again increased. Institution of steroid treatment caused recurrence of psychoses in 2 others who had initial episodes of psychosis when not on steroid and had improved.

Of the seven patients, whose follow-ups are available, initial psychoses cleared in a few days to a few weeks in 6 and the seventh had to stay in a mental institution for 6 months before it cleared. Recurrence occurred in 5 and in 3 they were permanent.

Table 3

<table>
<thead>
<tr>
<th>Psychoses in the Course of SLE</th>
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<tbody>
<tr>
<td>1. Incidence in the literature 9-52%</td>
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<tr>
<td>2. Organic mental syndrome is most common.</td>
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<tr>
<td>3. Generally either during active stages of the disease or within several days after steroid treatment is begun or increased.</td>
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<td>4. Initial episodes are usually transient, relapses often permanent.</td>
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Case (2): This female was admitted to The because of Raynaud's syndrome in March 1952 at age 40. She complained of multiple joint pains and hives. On the 4th postoperative day following dorsal sympathectomy, she started saying that she was dying of an incurable disease. She appeared to have auditory hallucinations. In the evening she became unmanageable and run out of her ward. Then she became catatonic and stopped respond-
ing to questions. Neurological examination was unrevealing. She was transferred to a mental hospital where she stayed for 6 months, gradually improving. In June 1954, she was readmitted to the hospital because of facial butterfly skin rash and found to have positive L-E preparations, hyperglobulinemia and albuminuria. She was started on cortisone 200 mg daily and acutely became psychotic with hallucination, agitation and catatonia. She was noted to be confused and disoriented. Two weeks later, she developed left focal seizures and became hemiplegic. She was transferred again to a mental hospital where she remained psychotic and hemiparetic and died of pyelonephritis 1.5 years later. The examination of the brain revealed areas of softening in the right cerebral hemisphere. Microscopically neither arteritis nor arteriosclerosis was noted.

Stroke

Relatively sudden development of hemiparesis, paraparesis or other lateralizing signs, most probably secondary to vascular accidents is not uncommon in the course of SLE. Twenty-two case reports are found in literature. These include 16 cases of hemiparesis, 5 paraparesis and 1 brain stem signs. The onset of these signs was associated with other signs of active SLE in 11 patients. Of 16 cases with hemiparesis, 11 developed it over several hours to a few days. In two the onset was preceded by convulsive seizures. Paraparesis in 4 cases developed over 3 to 17 days and in 1 case this point is not clear. Six hemiparetics and 3 paraparetics had lumbar punctures and in all of them except 3, cerebrospinal fluid protein was found elevated up to 216 mg%. Other abnormalities such as pleocytosis, elevated pressure, abnormal colloidal gold curve were noted in 3 patients. Eight patients died soon after onset of stroke.

In this series, 10 patients developed stroke. Hemiparesis was noted in 6 (2 had 2 separate episodes of hemiparesis), paraparesis in 1, monoparesis in 1 and hemianopsia in 1. In the 10th patient brain stem signs consisting of severe vertigo, ataxia, intentional tremor of the arm and dysarthria were noted. The age at the onset of initial episodes ranges from 20 to 67. Four were in their thirties, three in their fourties, the other three were 20, 55 and 67 years old respectively. In 6 patients (including 2 with 2 episodes), these signs developed over a few minutes to a few days. In 2 others, the onset was preceded by convulsive seizures. Five had active SLE and 7 including 2 with 2 episodes were receiving steroid at the onset. Three patients had mild to moderate hypertension along with migraine, arteriosclerosis and syphilis respectively. Another patient had positive STS of low titre, possibly a biological false positive. The
fifth patient had an episode of dehydration and hypotension preceding the onset of paraparesis. No patient had overt signs of hemorrhagic tendency. Two patients had signs of arterial insufficiency in the extremities, one having Raynaud's syndrome 6 years before and another gangrene of the toes 1 year before the development of hemiparesis. Lumbar puncture was done at the time of onset of these signs in 6 patients (1 with 2 episodes had 2 lumbar punctures) and except on 1 occasion in which the onset was associated with subarachnoid hemorrhage, cerebrospinal fluid was normal in pressure, protein and number of cells. Two died within 1 month after the onset of stroke and the neurological involvement was the major cause of death. Seven were followed for 5 months to 9 years and no further episodes of lateralizing signs were noted during this period, those present remaining unchanged or regressed.

Table 4

*Stroke in the Course of SLE*

<table>
<thead>
<tr>
<th></th>
<th>literature</th>
<th>present series</th>
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<tbody>
<tr>
<td>No. of the patients</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>Onset in active stage</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Onset preceded by seizure</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>CSF protein elevated</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Death soon after onset</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Steroid treatment at onset</td>
<td>1</td>
<td>1</td>
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*Case (3)*: In 1953, at age 30, this female was diagnosed as having SLE on the basis of fever, arthritis, lymphadenopathy, leucopenia and hyperglobulinemia. Subsequently she was repeatedly noted to have positive L-E preparations. In 1958, she had muscular weakness and a muscle biopsy showed hyaline degeneration. Over 2 years prior to her demise, she noted episodes of diminished vision of the left eye associated with dizziness, tinnitus and headache. In 1962, she was noted to have gangrene of the toes. Femoral arteriogram showed minimal intimal changes in the superficial femoral and popliteal arteries but no major vessel obstruction. In June 1963, she suddenly developed weakness of her right arm and aphasia, but these neurological abnormalities rapidly disappeared over the next 4 days in hospital. For 7 days prior to her last admission on September 2, 1963, she complained of intermittent weakness of the right extremities and also of intermittent blindness. Subsequently her right extremities became completely paralysed and sagging of the right side of her face was noted. She
became unable to swallow. On admission BP was 124/80, P. 132 reg., T. 101.2, and R. 30. She did not speak but occasionally made grunting sounds. Horizontal movement of the eyes was minimal with retention of vertical movement. Right extremities were completely paralysed and left partially paralysed. Lungs, heart and abdomen were unremarkable. No joint or skin lesion was noted. Abnormal laboratory studies were sedimentation rate of 36 and serum albumin, globulin ratio of 3.5 to 4.6 g%. Cerebrospinal fluid was normal. She became completely unresponsive over the next 3 days and expired on the 6th hospital day. She was on steroid continuously for 5.5 years before death. Autopsy revealed that left internal carotid artery, middle cerebral artery and anterior cerebral artery were all occupied by a continuous, firm thrombus. The right vertebral artery and basilar artery were also thrombosed. Extensive ischemic infarction was noted in left cerebral hemisphere, brain stem and cerebellum. No evidence of arteriosclerosis was noted. Microscopic examination failed to reveal any additional change. Specifically no vascular lesion was noted beyond the thromboses.

Case (4): This 26 year old female, typist, developed arthritis, fever, chest pain and pericardial friction rub in 1955. In 1956, she was admitted to The Johns Hopkins Hospital because of arthritis of the fingers and diffuse abdominal pain, and positive L-E preparation was found. While in hospital, she complained of numbness in her right foot and was noted to have an absent right ankle jerk. She was treated with cortisone and discharged from hospital on a maintenance dose. She continued to have occasional attacks of fever and arthralgia. On March 12, 1957, she felt “light-headed,” started to drag her left leg and noted that her left hand was weak. She had no headache and did not feel ill. She was seen in The Johns Hopkins Hospital on the following day and mild left hemiparesis was noted. The dose of cortisone was unchanged. She was again seen 5 days later. At that time although fine movements with her left hand were still clumsy, left hemiparesis was improved. Lumbar puncture revealed no abnormality. She has had recurrent attacks of arthralgia with fever but no further neurological disturbances.

Subarachnoid Hemorrhage

Seven cases of subarachnoid hemorrhage occurring in the course of SLE have been reported with autopsy findings in 2 cases. Among them, 3 had thrombocytopenia and one prolonged coagulation and prothrombin time. Signs of active SLE were present at the onset of the hemorrhage in 3 patients. In others this information is not available. No source of the hemorrhage was
noted in the autopsy cases.

In this study, 3 patients had subarachnoid hemorrhage. All patients were negro female and the age ranged from 29 to 44. No patient had overt signs of hemorrhagic tendency. One patient was hypertensive and the other uremic. SLE was under control in 2 patients with steroid treatment at the time of the hemorrhage and in the third it was active. Two died of the hemorrhage and no recurrence was noted in the following two years in the surviving case.

Case (5): In 1958 at age 25, this female developed chest pain and arthralgia. In January 1959, she was admitted to The Johns Hopkins Hospital with pericarditis, pleural effusion, anemia and positive L-E preparations. She was started on prednisone. On May 30 1962, while answering telephone in the morning, she felt dizzy and collapsed. On recovering consciousness, severe frontal headache and pain in the neck were present. She was brought to hospital and lethargy, marked nuchal rigidity were noted. Blood pressure and temperature were normal. Lumbar puncture revealed bloody, xanthochromic fluid with 50,000 red blood cells per cubic millimeter. Platelets were adequate on smear. Prednisone was continued and she showed gradual improvement over the next 25 days in hospital. Since then she has been closely followed and no further neurological difficulty has occurred.

Meningeal Involvement

Dubois reported a patient with SLE with 128 mononuclear cells in cerebrospinal fluid in association with lethargy. He also stated that spinal fluid pleocytosis was observed in 3 others associated with meningismus in his series of patients with SLE. No detailed account was given on these patients. Pierce and Logothetis reported another case in which cerebrospinal fluid pleocytosis occurred in the course of SLE together with fever and headache. In this case and Dubois' first case, the symptoms suggestive of meningeal involvement developed insidiously in the active stages of the disease. Both patients responded well to steroid treatment and pleocytosis and the associated symptoms disappeared rapidly. In 1 patient bacterial and fungal meningitis were excluded by spinal fluid smear examination, culture and skin tests. Stool examination for virus was nonrevealing.

In the present series, spinal fluid pleocytosis of unknown etiology ranging from 10 to 1470 was noted in 3 patients. In all, meningeal signs such as headache, vomiting, lethargy and fever were noted at the same time. Mononuclears predominated over polymorphnuclear cells in all 3, although in 1 patient polymorphnuclears were more numerous at the peak. The other signs of active SLE and
an increase in cerebrospinal fluid protein up to 93 mg% accompanied pleocytosis in all these patients. Pleocytosis invariably disappeared within a month although in 1 case it recurred in 3 months. Two patients received no specific treatment and another ACTH.

Case (6) : In 1951, this 24 year old male was admitted to The Johns Hopkins Hospital because of arthralgia, generalized lymphadenopathy and history of Raynaud's syndrome and was started on ACTH which relieved his symptoms. In May 1952, he was rehospitalized because of frontal headache, fever of 104, nausea, vomiting, diarrhea, chest pain. On examination, he had mildly stiff neck, dry red blotchy skin lesions over the arms and hands and typical rheumatoid joint changes. Lumbar puncture revealed 28 monocytes and protein of 93 mg%. He gradually showed symptomatic improvement and repeated lumbar puncture 6 days later revealed only 1 white blood cell and protein of 28 mg%. He was hospitalized for the third time in December 1952 because of pleurisy, anemia, protenuria, hematuria, and positive L-E preparation was noted. He died 6 months later and autopsy did not reveal any gross change in the brain.

Reports of bacterial or fungal meningitis complicating SLE have been numerous. Of 4 cases of cryptococcal meningitis,6(43-47) 2 cases of listeria monocytogenes meningitis,48(49) and 1 case of tuberculous meningitis in literature, 2 cryptococcal and 1 listerial cases were not receiving steroid nor debilitated at the onset of meningitis. One of the 4 cases of cryptococcal meningitis, reported by Harvey et al. is included in the present series. The frequency of the combination of these 2 diseases warrants repeating its case summary.

Case (7) : This 39 year old male was admitted to The Johns Hopkins Hospital in October 1950 because of swelling and redness of his hands and arms, generalized lymphadenopathy and history of polyarthritis and pleurisy. Examination revealed positive L-E preparation and inverted A-G ratio. He responded to ACTH treatment. After discharge from hospital, he continued to have recurrent attacks of the similar symptoms. In June 1952, he was rehospitalized because of aggravation of skin lesions of his extremities. He was given increasing doses of intravenous ACTH, but no response was obtained. Four days later he began to have severe headache and temperature rose to 101.5. He vomitted several times. Lumbar puncture revealed 68 white blood cells, ten red blood cells, 86 mg% of protein, 72 mg% of sugar. He became confused and started screaming. Temperature rose further to 104° and on repeated lumbar puncture cryptococci were found in the cerebrospinal fluid. He became stuporous, developed cranial nerve palsies, generalized tonic, clonic convulsions and expired 1 month after the onset of meningitis. Autopsy revealed, in addition to typical changes of SLE in the spleen and kidneys, an extensive meningitis with a col-
lection of exudates containing cryptococci in the major sulci of the cerebral hemispheres and a number of small abscesses in the cortex.

Another case in this series had nocardia abscesses in the brain although no meningeal involvement was present.

Chorea Minor

Eight patients\(^{51-55,78}\) have been reported in literature with Sydenham's chorea in the course of SLE. All patients except 1 are teenagers and only 1 adult patient has been reported. The diagnosis of SLE seems well established in most of these cases. No case of chorea minor complicating SLE was found in this series.

Peripheral Neuropathy

Dubois and Tuffanelli\(^{50}\) found incidence of peripheral neuropathy to be 11.7% among 520 patients with SLE. Heptinstall and Sowry\(^{41}\) are the first to report a well described case of peripheral neuropathy associated with SLE. Since then 8 similar cases\(^{57-60}\) have been reported with autopsy study in 4 cases. Except for one of the five cases reported by Bailey et al. all were examples of symmetrical polyneuropathy with main weakness and sensory changes in the distal portions of the extremities. The severity of involvement was not marked in these cases and except for 2, the patients were not incapacitated by the weakness or sensory disturbances. In 7 of 9 patients, the cerebrospinal fluid protein was abnormally high, ranging from 90 to 460 mg%, while the cell count was from 0 to 12 per cubic millimeter. The course of the neuropathy is well described in 3 cases. In the first case it gradually improved over a year, but other signs of SLE became worse over the same period and the patient died 14 months after the onset of neuropathy. In the second case, the patient had three episodes of exacerbation of neuropathy over 14 months. Each episode lasted 2-3 months and responded to prednisone. In the third case, neuropathy gradually improved over 6 months. In other cases, the neuropathy lasted several months to a few years and never completely remitted. Dubois stated that of his 5 cases with severe neuropathy, there was complete improvement in 3 and only partial benefit in the other 2 after months to years of adequate corticosteroid treatment. The autopsy study in 5 cases revealed various degree of degeneration of axis cylinders with loss of myelin sheath. In 2 cases, degeneration of ganglion cells in the spinal ganglia and of the posterior column of the spinal cord was present. Blood vessel changes consisting of necrosis, cellular infiltration, thickening of the intima and
thrombotic occlusions were present in 3 cases. It may be pointed out, however, that these reports indicate the vascular changes not as widespread as one would expect from the changes of the nerve fibers. The case reported by Scheinberg is unique in that amorphous material stained faintly blue with hematoxylin was noted between the individual nerve fibers. The author believed that this material had none of the features of collagen degeneration and was related to the hematoxylin bodies which were noted in the other organs. This and another case reported by Bailey et al. did not show any vascular changes.

In this series, 5 of 6 patients with peripheral neuropathy had symmetrical involvement of the distal portions of the extremities. The sixth patient had mononeuropathy. In 5 patients, the main disturbance was sensory changes associated with diminished deep tendon reflexes. Peripheral neuropathy was never the first sign of SLE and in all patients it developed a few months to several years after the initial sign of the disease. No parallel relation in activity was seen between neuropathy and other signs of SLE. The degree of involvement was mild in all and no patient was incapacitated. In only 1 patient, was lumbar puncture done and this revealed normal protein and 5 mononuclear cells. Signs of neuropathy were repeatedly noted over 7 years in 1 patient and in another an episode of numbness and burning sensation of the extremities lasted only a few days. In other patients, no follow-up is available.

According to Dubois and Tuffanelli, herpes zoster is seen in 3.2% of the patients with SLE. Four patients in this series developed herpes zoster in the course of SLE. None of the patients were debilitated at the time of development of herpes. One patient had meningeal signs at the same time and lumbar puncture revealed 80 mononuclear cells per cubic millimeter with normal chemistries.

Case (8) : In September 1953, this 41 year old female was admitted to The Johns Hopkins Hospital because of pleural effusion, history of arthritis and hematuria both in the remote and recent past. Physical examination revealed fever, arthralgia, hepatomegaly and congestive failure. Positive laboratory studies included albuminuria and positive L-E preparations. She complained of numbness, and distal blunting to light touch and pin prick in all 4 extremities was found. There was no weakness or reflex change. Lumbar puncture revealed 5 monocytes per cubic millimeter, protein of 18 mg%. Three years later she died of subarachnoid hemorrhage. No postmortem examination was done.

Myasthenic Syndrome

Sixteen cases have been reported in which myasthenic symptoms
were seen in association with SLE. In these cases the myasthenic symptoms consisted of weakness of the external ocular muscles, bulbar muscles and muscles of the extremities. In 12 cases, unequivocal response of the weakness to cholinergics was noted. In 1, it was only fair and in another equivocal. In 2 others, this point is not clear. In 3 patients, typical fluctuation in strength of the muscles is reported. Again in 3 patients electromyogram was compatible with myasthenia. In 1, it showed increasing voltage in response to repetitive stimuli. In all except 2 cases the myasthenic symptoms antedated the onset of SLE symptoms and in 2 the myasthenic symptoms had disappeared before the latter started.

Harvey et al. have reported the case with myasthenia, included in this series. A brief summary of the case is given below.

Case (9): In 1935, at age 30, this female developed diplopia and ptosis of the left lid. She was diagnosed as having myasthenia gravis and treated with neostigmin with equivocal improvement. These symptoms disappeared in a few months. In 1936, a typical SLE skin lesion was noted on her face and 4 years later she began to have polyarthritis. In 1952 a positive L-E preparation was noted.

Myopathy

Muscular involvement by SLE produces myopathy of 2 clinically different types. From observation on 520 patients with SLE, Dubois and Tuffanelli concluded "myalgia was often so disabling that frequently the patients were admitted with a tentative diagnosis of dermatomyositis. True muscle weakness, however, was rare." This is in agreement with Erbslo-Baedeker's observation. They noted "The chief muscular symptom is muscular pain—. Marked weakness is not common, but—." According to the first group of authors, incidence of myalgia is 48.2%. The pain is usually symmetrical, involves multiple muscle groups in the upper as well as lower extremities and tends to be proximal in location. Overlap and combination with articular pain are frequent.

Histological studies of the involved muscles have revealed the fact that all the changes seen in myositis of different etiologies are seen in lupus myopathy. Perivascular nodular accumulation of inflammatory cells, foci of necrosis and degeneration of muscle fibers have all been described. Since Pearson and Yamazaki reported the first case, vacuolar myopathy associated with SLE has repeatedly been reported and in 1 of the cases there was an indication that prolonged chloroquine treatment was responsible for the myopathy. These patients developed weakness of the proximal muscles of the extremities and
bulbar muscles in the course of SLE and histological examination of the muscles showed marked vacuolation of the sarcoplasm. Some muscle fibers were almost completely replaced by vacuoles. Finely granular, eosinophilic precipitates were seen in some of the vacuoles.

In this series, there were 9 patients with muscle pain and 4 patients with muscle weakness. Five patients had myalgia in active stages of the disease and in the remaining four in chronic stages. The pain was noted in the larger proximal muscles of the extremities in all 5 patients in whom the site of the pain was clearly recorded. Five of the 9 patients were noted to have muscle tenderness on examination. One had a muscle biopsy while having muscle pain and tenderness and this revealed perivascular infiltration of lymphocytes and plasma cells. Although in most patients, muscle pain and tenderness disappeared in days to weeks, in 1 patient muscle pain persisted over 4 years. Five patients had muscle biopsy and interstitial myositis in 3, hyaline necrosis of fibers in 1 and foci of muscular atrophy and fibrosis with associated lymphocytic infiltration in 1 were noted.\text{\textsuperscript{4}} Case (3) previously described also had myopathy. It is now described in more detail.

Sixteen years after onset of the first SLE symptoms at age 35, she noted gradually progressive weakness of the extremities and became unable to walk more than 25 feet. On examination there were nasal voice with slurred speech, intermittent drooping of the left lid, marked and generalized weakness and wasting of all 4 extremities which were more pronounced in the proximal than in the distal muscles. Deep tendon reflexes were all depressed. Lumbar puncture revealed only 1 mononuclear cell and protein of 25 mg%. Prostigmin test was negative and muscle biopsy showed widespread, well localized, focal areas of hyaline degeneration of the muscle fibers. There were very few inflammatory cells present at the site of this degeneration and there were rare foci of round cell infiltration throughout the specimen. No vascular or neural lesion was noted. When she developed the symptoms, the patient had not taken a steroid preparation for 3 years. The weakness gradually improved over the next several months. Postmortem examination five years later revealed almost complete replacement of psoas muscles by adipose tissue, degenerative changes of various degrees and perivascular round cell infiltrations in quadriceps femoris, pectoralis and diaphragm.

Neuroophthalmological Manifestations

Ocular changes in SLE have been reported.\textsuperscript{74}–\textsuperscript{76} Maumenee\textsuperscript{75} reported 5 cases and noted cytoid bodies, small superficial retinal hemorrhages and slight
papilledema. The cytoid bodies were interpreted as manifestations of a generalized toxemia as they appeared only after the patients developed rather marked systemic manifestations. Geertruyden et al.\textsuperscript{76} reported a case of SLE in which they followed the retinal changes carefully over a year. They noted a parallelism between the retinal spots and systemic symptoms as well as a cyclic evolution of the cytoid bodies—appearance of a soft spot, sharpening of the ophthalmoscopic appearance and period of stabilization, regression and eventual disappearance without leaving a trace. The duration of the cycle and size of the lesion were variable for different elements, but they never attained size bigger than one-sixth the disc diameter. Dubois et al.\textsuperscript{56} found incidence of cytoid bodies and retinal hemorrhages to be 9.6 and 10.5% respectively among 520 cases of SLE.

In this series, cytoid bodies were noted in 9 patients, among whom three had, in addition, other retinal changes including hemorrhages, exudates, occlusion of the retinal vessels and aneurysms with absence of hypertension and diabetes mellitus. Two other patients had the similar retinal changes without cytoid bodies, but both were hypertensive. The cytoid bodies were seen in the active and chronic stages. In 1 patient, numerous cytoid bodies were noted in an active stage but none was seen when the patient returned to hospital 9 years later with another illness. Other findings are listed in Table 5.

\textbf{Table 5}

\textit{Neuroophthalmological Findings in the Present Series}

<table>
<thead>
<tr>
<th>Finding</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytoid body</td>
<td>9</td>
</tr>
<tr>
<td>Retinal hemorrhage</td>
<td>4</td>
</tr>
<tr>
<td>Ptosis</td>
<td>3</td>
</tr>
<tr>
<td>Occlusion of an artery or vein</td>
<td>2</td>
</tr>
<tr>
<td>Aneurysm</td>
<td>2</td>
</tr>
<tr>
<td>Retinal exudate</td>
<td>2</td>
</tr>
<tr>
<td>Argyll-Robertson pupil</td>
<td>2</td>
</tr>
<tr>
<td>Hemianopsia, cortical blindness</td>
<td>2</td>
</tr>
<tr>
<td>Diplopia</td>
<td>2</td>
</tr>
<tr>
<td>Papilledema</td>
<td>1</td>
</tr>
</tbody>
</table>

Ptosis was noted in 1 patient with Horner's sign, another with myopathy and the third with myasthenic symptoms. The latter patient also complained of diplopia. Argyll-Robertson pupils were noted in 2 patients in whom STS was
positive.

The following patient is of interest because of unusually prominent papilledema which regressed together with other signs of SLE when prednisone treatment was started.

Case (10): This 18 year old female was admitted to The Johns Hopkins Hospital in September 1961 because of fever, cough, anorexia, weight loss and severe throbbing headache of 3 months duration. Examination revealed fever of 102.6, markedly swollen optic discs, pustules over her face, generalized lymphadenopathy, rales at both lung bases. No hemorrhage or exudate was noted in fundi. Laboratory studies revealed many typical L-E cells in the peripheral blood, anemia with hematocrit of 27, elevation of sedimentation rate to 34, inverted serum albumin globulin ratio, marked albuminuria and microscopic hematuria. Serum urea nitrogen was normal. Lumbar puncture was done and the opening pressure was 410 mm. Fluid was clear and contained 3 white blood cells and 2 red blood cells per cubic millimeter. Protein was 10 mg%. Electroencephalography and cerebral scintiscan failed to reveal any evidence of intracranial mass lesion. She was started on prednisone and papilledema gradually regressed. On the 18th hospital day lumbar puncture revealed normal pressure. By the 26th hospital day, the disc margin was only slightly blurred, at which time she was discharged on prednisone. In hospital, albuminuria and anemia also responded to the treatment. In the following 1.5 years no further evidence of papilledema, increased intracranial pressure or other neurological abnormality was noted.

Neuropathological Findings

Forty-eight cases of SLE in literature have been subjected to neuropathological study. Of these cases, 29 were found to have various degree of vascular changes consisting of intimal thickening, fibrinoid degeneration, thrombosis, cellular infiltration. These changes were seen in the small arteries, arterioles, veins of the brain, spinal cord, peripheral nerves and of the meninges. Only in 1 case, was involvement of the trunk of a major cerebral artery noted. Generally these vascular changes were scattered and sporadic. Of these 28 cases with the vascular changes, 17 cases were found to have scattered foci of softening. In 5 cases, the softening and the vascular changes were limited to 1 area. Six of 19 cases without vascular changes showed various kinds of intracranial hemorrhage. These included 2 cases of subarachnoid hemorrhage, 2 cases of subdural hemorrhage (one associated with intracerebral hemorrhage) and 2 cases of diffuse petechial hemorrhages. The
source of the hemorrhages was not clear. Four cases had meningitis and intracerebral abscesses. In 6 other cases, nonspecific changes such as edema, microscopic foci of spongy degeneration, perivascular degeneration and infiltration were seen. In 2 cases, macroscopic and microscopic examination failed to reveal any lesion.

Larson\(^5^4\) reported the following neuropathological findings in 41 patients with SLE. Among 22 patients in whom no neurological or psychiatric deficit was clinically evident, 9 had focal areas of encephalomalacia with varying degrees of arteritis. Of 19 patients with neurologic signs and symptoms, 8 had no pathological abnormalities. Seven patients had multiple focal areas of encephalomalacia with varying degrees of arteritis, three infection and one peripheral neuritis.

Table 6

<table>
<thead>
<tr>
<th>Findings</th>
<th>Pts. without CNS manifest</th>
<th>Pts. with CNS manifest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Focal encephalomalacia</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Infection</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Peripheral neuritis</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>10</td>
</tr>
</tbody>
</table>

Harada's pathological study\(^7^7\) of 12 cases with SLE did not reveal any difference between those with clinical neurological signs and those without them. Neither did he find any pathological difference between cases given corticosteroid and others without the treatment.

In this series, 5 of 9 cases autopsied had no neuropathological abnormality. Two cases had extensive infarction in the central nervous system with one having thromboses of the major cerebral arteries. In the second case, no vascular lesion was noted. Autopsy findings in these 2 cases have been given. In the remaining 2 cases cryptococcal meningitis and abscesses in 1 and nocardia abscesses in the other were noted.

DISCUSSION

A wide variety of neurological signs and symptoms have been seen in the
course of systemic lupus erythematosus. They represent involvement at all levels of neuraxis and range from encephalopathy to myopathy and retinopathy. Several attempts have been made to reveal true incidence of these signs and symptoms and the present study was undertaken with an intention to delineate the neurological aspect of the disease more clearly.

The most controversial subject in regard to the neurological aspect has been the question if these signs and symptoms are mainly products of the neurological involvement by the disease or rather side effects of the adrenocorticosteroid treatment. The present review indicates that generally neurological involvements are directly related to SLE, developing together with systemic signs of the disease or responding to the treatments for SLE. However, in a significant number of cases with convulsions, psychoses and myopathy characterized by weakness, the symptoms seem to be more closely related to steroid treatment, convulsions and psychoses occurring within days and myopathy within weeks to months after institution or increase of steroid treatment and improving when the treatment is withdrawn. This was most obvious in cases with psychoses in this study, as 4 out of 9 patients with the symptom developed it within several days after institution or increase of steroid treatment and all of them improved when steroid dosage was reduced. Another patient became psychotic when on a constant dose of steroid, did not respond to increase in steroid dosage and improved when it was reduced. O'Connor's study of 21 psychotic patients is in agreement with the present study in this point.

Then, how can one tell if one of these symptoms in a particular instance is related to the disease or to the treatment? Probably the most helpful guide is a relationship of their onset to other signs of active SLE and to steroid treatment. If the symptom develops at the same time as the systemic symptoms of the disease, it is more probably due to the nervous involvement of the disease itself and will respond to increase in steroid treatment, while those developing while the systemic symptoms are subsiding in response to institution or increase of steroid treatment, will respond to reduction in steroid dosage. If still in doubt, it is wiser to increase steroid first and observe the response. If the sign or symptom does not respond to this, then steroid dosage can be reduced.

The exact mechanism by which SLE produces neurological signs is not clear, but vascular involvement has been postulated. More recent pathological studies, however, revealed the fact that incidence of vascular changes is almost same between those with neurological signs and those without them. Also it is difficult to explain some of the clinical features of the signs and symptoms on the basis of the vascular theory. These features include higher incidence of convolution and psychoses than that of hemiparesis and other focal signs, higher
incidence of generalized convulsion than that of focal convulsion, occurrence of meningeal signs, higher incidence of symmetrical polyneuropathy than that of mononeuropathy, occurrence of myasthenia and myopathy. Therefore it is doubtful that vasculitis plays as an important role as has been supposed in production of the neurological picture. Blood and serum factors may be of significance in some occasions.

Important from a clinical point of view is the frequent complication by fungal and certain bacterial infections of the nervous system. This probably results from altered immunological responses inherent to SLE and not just from taking large amounts of steroids or from debilitation. Prompt recognition and institution of appropriate treatment are important in lieu of all such cases reported thus far having ended fatally. Frequent occurrence of herpes zoster noted by Dubois et al. and confirmed by the present study is another indication of abnormal response to infections and suggests that some cases of aseptic meningitis in SLE may also be viral.

In a number of cases, muscular weakness in SLE has improved with cholinergics. Because of the similarities in age and sex distribution of SLE and myasthenia gravis and because of the fact that in both diseases antinuclear factors are found with a significant frequency, it is interesting to postulate, as has been done by many others that the two diseases are etiologically related. The fact that myasthenic weakness almost always develops preceding the onset of other signs and symptoms of the disease, may be important in considering the relationship between the 2 diseases.

Neurological signs and symptoms may be primary presentation in the initial stage of the disease. However, in reviewing cases in literature and our cases, it is found very rare that the patients have had no systemic signs of SLE prior to or at the time of neurological involvements and it is unlikely that the disease is confused with primarily neurological diseases.

**SUMMARY**

The literature and case records of 46 patients with neurological manifestations of systemic lupus erythematosus were reviewed. A variety of neurological signs and symptoms representing involvements at all levels of neuraxis were found to occur in the course of this disease. Most of them were due directly to the disease but the psychoses were more often caused by the steroid treatment than by the disease itself. The mechanisms by which the disease caused the signs and symptoms appeared multiple and the vascular involvement did not seem to play as an important role as has been thought. Infections of the central
The nervous system were not infrequent. Other than the muscular weakness improved by cholinergics, neurological manifestations rarely preceded systemic signs of SLE.

Lately much interest has been aroused and more than a few studies have been published concerning neurological involvements of primarily non-neurological diseases of unknown etiology, including carcinomas of various organs, sarcoidosis, periarteritis nodosa, Bechet's disease to name a few. It is hoped that they will cast a light not only on the nature and pathogenesis of the neurological signs and symptoms, but also on the etiology of the underlying diseases.

REFERENCES

NEUROLOGICAL ASPECTS OF LUPUS ERYTHEMATOSUS

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Fig. 1 Brain from Case 3. Note marked swelling and congestion of blood vessels of the left hemisphere which was infarcted.

Fig. 2 Circle of Willis from the same case as above, with obstruction of the left internal carotid artery.

Fig. 3 Microscopic picture of the obstructed internal carotid artery, showing normal structures of the vessel wall.

M. HONDA
Fig. 4  Brain from Case 2. Note atrophy of the right hemisphere which was infarcted.

Fig. 5  Cut sections of the cerebral hemispheres and brain stem from the same case as above. Note old, cystic, infarcted lesions in the right hemisphere and atrophy of the right cerebral peduncle.