NEUROLOGICAL INVOLVEMENT IN SYSTEMIC LUPUS ERYTHEMATOSUS

By C. H. Tay
(Senior Medical Registrar and Clinical Teacher)

and

O. T. Khoo
(Professor of Clinical Medicine, University of Singapore)
(Department of Clinical Medicine, Medical Unit II, Outram Road General Hospital, Singapore 3)

INTRODUCTION

With the improved diagnostic facilities and the widespread uses of immunosuppressive drugs over the past fifty years, the incidence of systemic lupus erythematosus (SLE) has increased rapidly. Thus much more cases are seen because the survival rate is comparatively longer than the pre-steriod era.

Although brief descriptions of the neurological aspects in SLE were reported by earlier writers (Kaposi, 1872; Osler, 1895; Libman and Sacks, 1924), its importance is only recently recognised. The reported incidence of neurological involvement in several large western series varied from 25% to 75% (Harvey *et al*, 1954; Clark and Bailey, 1956; Johnson, 1962; Dubois and Tuffanelli, 1964; Berry and Hedge, 1965; O'Connor and Musher, 1966). Recently, the literature on this subject has been reviewed by Dubois (1966) and by Johnson and Richardson (1968).

This paper presents a detail neurological analysis of 75 cases of SLE found in a medical unit over a period of 15 years. Neurological involvements due to the primary disease, its systemic complications and the side-effects of its medication are the subjects to the present study.

MATERIAL AND METHODS OF STUDY

All cases diagnosed as SLE between January 1955 through 1969 inclusive, in the Medical Unit II, Outram Road General Hospital, Singapore, were included in this study.

The criteria for diagnosis were based on:—

1. A positive L.E. preparation;
2. a typical skin or/and renal histology of SLE with other confirmatory immunological tests and
3. a classical SLE picture with multi-systems involvement.

Complete neurological as well as general physical examinations were made on the patient's first admission and at subsequent follow-up visits. Neurological assessment included psychiatric evaluation and the detailed examination of the central and peripheral nervous systems including the musculature and the ocular fundi. Appropriate haematological, biochemical and radiological investigations were done in each case. Whenever indicated, cerebrospinal fluid examinations, E.M.G., E.E.G., cerebral angiogram and other special tests were also performed.

In this study, neurological involvements are divided into 3 groups:—

1. Involvement by the disease itself (SLE).
2. Involvement by systemic complications, and
3. Involvement as a result of chemotherapy.

RESULTS

General Clinical Findings

The data of the 75 patients with SLE have been reported elsewhere (Tay and Khoo, 1970; Tay, 1970, 1971). In 70% of cases of this series, the age of onset of the disease was in the second and third decades. The majority were Chinese (88%) females (Female : Male—8 : 1).

Besides fever (73·3%), the principle systems affected were: the skin (69·3%), the joints (65·3%), the urinary system (46·7%), the cardiovascular system (30·7%), the neurological system (29·3%), the respiratory system (26·7%), the haematological system (17·3%), the lymph glands (17·3%), the eyes (16%), and the gastro-intestinal system (10·7%).

Significant laboratory results were: High E.S.R. (88%), Hypergammaglobulinaemia (60%), Positive L.E. cells (70·7%), Positive

A.N.F. (antinuclear factor) (74·1%). Positive Rheumatoid arthritis factor (37·2%) and Positive Coomb's test (16%).

Neurological Findings

The three groups of neurological involvement are:—

(i) *Neurological Involvement due to SLE*

There were 21 patients (or 29·3%) in this series, with one or more neurological deficits belonging to this group.

Details of the involvement are summarized in (Table I).

TABLE I

NEUROLOGICAL INVOLVEMENT DUE TO SLE LESIONS

(a) **Specific Neurological Disorders**	
1. *Central Nervous Systems*	
(*a*) Convulsions or seizures	3 cases
(*b*) Cerebral thrombosis	2 cases
(*c*) Subarachnoid haemorrhage	1 case
(*d*) Hemichorea	1 case
(*e*) Unexplained headache	5 cases
2. *Cranial Nerves*	
(*a*) Partial third nerve palsy	1 case
3. *Spinal Cord*	
(*a*) Paraplegia	1 case
4. *Peripheral Nerves*	
(*a*) Peripheral neuropathy	5 cases
(*b*) Paraesthesia	1 case
5. *Fundal Changes*	
(*a*) "Cytoid" bodies	5 cases
(*b*) Retinal haemorrhage	2 cases
(*c*) Optic atrophy	3 cases
6. *Muscle Changes*	
(*a*) Myopathies	7 cases
(*b*) Muscle atrophy and contratures	2 cases
(b) **Psychological Disorders**	
(*a*) Anxiety states	10 cases
(*b*) Endogenous depressions	4 cases
(*c*) Suicidal tendencies	1 case
(*d*) Frank psychosis	2 cases

(ii) *Neurological Involvement due to Systemic Complications in SLE*

20 patients (or 26·6%) in this series had neurological manifestations secondary to various systemic complications of the disease. The results are listed in (Table II).

TABLE II

NEUROLOGICAL INVOLVEMENT DUE TO SYSTEMIC COMPLICATIONS IN SLE

Coma and fits—	
secondary to terminal uraemia	7 cases
secondary to liver failure	1 case
secondary to septicaemia	3 cases
Cerebral haemorrhage secondary to hypertension	1 case
Subarachnoid haemorrhage secondary to thrombocytopenia	1 case
Pyogenic meningitis—due to lowered resistance	3 cases
Cryptococcal meningitis—due to lowered resistance	2 cases
Herpes zoster—due to lowered resistance	4 cases

(iii) *Neurological Involvement due to Therapeutic Complications*

Table III presents the neurological involvement found in 15 patients (or 20%) in this study with complications arising from drug administrations.

TABLE III

NEUROLOGICAL INVOLVEMENT DUE TO THERAPEUTIC COMPLICATIONS IN SLE

(i) **Corticosteriods**	
(*a*) Depression	3 cases
(*b*) Frank psychosis	2 cases
(*c*) Distal muscle wasting	2 cases
(*d*) Caratact formation	1 case
(ii) **Chloroquine**	
(*a*) Retinal damage	2 cases
(iii) **Immunosuppressive Drugs**	
(*a*) Depression	3 cases
(*b*) Herpes zoster	1 case

DISCUSSION

All parts of the nervous system may be affected by Systemic Lupus Erythematosus (SLE) but the disease itself has no characteristic neurological pattern or course. In addition, some cases may have neurological deficits from other systemic complications and from the side-effects of drugs. At times, it is not possible to distinguish one form of neurological involvement from another as they are closely inter-related. The diagnosis is often made by exclusion, clinical observation, various investigations, and histology studies. In this study of 75 cases, about a third of them had neurological manifestations of SLE, a quarter had neurological changes from various systemic involvement and a fifth had neurological complications attributed to medication.

(a) General Clinical and Laboratory Findings

The detailed study and general discussions of the clinical and the laboratory findings of these 75 cases of SLE have been published elsewhere (Tay, 1969; Tay and Khoo, 1970; Tay, 1970, 1971). Except for some minor differences in clinical features, our cases were not dissimilar to those reported from other centres (Harvey *et al*, 1954; Larson 1961; Dubois, 1966). The incidences of most of the laboratory investigations too, were comparable to those reported in the West.

(b) Neurological Findings

(i) *Neurological Involvement due to SLE*

In the literature, the frequency of involvement in this group ranged from 20% to 75%, with an average of about 50%—a much higher incidence than our series (29·3%) (Clark and Bailey, 1956; Hill, 1957; Armas-Cruz *et al*, 1958; Larson, 1961; Berry and Hodges, 1956; Dubois and Tuffanelli, 1964; O'Connor and Muscher, 1966; Johnson and Richardson, 1968).

The entire gamut of neurological lesions can be found. These are the sequelae of the widely scattered vascular damage in the central and peripheral nervous systems. Neuropathological studies had demonstrated microinfarcts in these systems due to occlusions of arteries, arterioles, and veins which showed inflammatory changes and fibrinoid necrosis (Jarcho 1936; Johnson and Richardson, 1968).

One of the common neurological manifestations of SLE was convulsive seizures occurring in a variety of clinical forms and at various stages of the disease. Although the known incidence for seizures varied from 52% to 75%, with an average of 14%, only three cases (4%) were found in this series. Unlike terminal seizures which were often the result of some systemic involvement (i.e. uraemia), these fits often appeared early in the course and had been reported to be responded favourably to steriod administration (Gold and Yahr, 1960; Jessar *et al*, 1953; Russel *et al*, 1951). Electroencephalograms in these cases were often nonspecific and were of little diagnostic value as there was poor correlation between the clinical presentation and the EEG tracings. In most instances, there were diffuse cortical microinfarcts in various parts of the cerebrum and the brain stem.

Cerebral vascular thrombosis and haemorrhage, infrequent findings in SLE, were found in 2% to 5% elsewhere and 2·6% (2 cases) in this series. One woman with right hemiplegia and motor aphasia had radiological evidence of left middle cerebral artery occlusion. The other was a 44-year old man with Gerstmann's syndrome due to a left parietal vascular thrombosis. Arterial occlusions leading to cortical infarction and sometimes, to various forms of haemorrhages, were often caused by the proliferative and destructive changes of the cerebral vasculature. (Hanrahan, 1954; Silverstein, 1963; Johnson and Richardson, 1968). Thus, diffuse cerebral angiitis with perivascular infiltration and fibrinoid necrosis of the arterioles and capillaries may give rise to various focal signs like extrapyramidal symptoms, cranial nerve palsies, brain stem lesions, myelitis and so forth. The above-named conditions are on the whole extremely rare as 16 cases of Chorea and 14 cases of cord involvement have been documented in the literature so far. (Cammarata *et al*, 1963; Bailey *et al*, 1956; Copeland *et al*, 1958; Melle, 1959; Greenhouse *et al*, 1966). Of the cranial nerves, the third and sixth nerves are more affected than the rest. (Siekert and Clark, 1955; Granger, 1960). In the present study we had a single case each of Chorea, cranial nerve palsy and transverse myelitis. Of special interest were 5 patients who presented with nonspecific bitemporal headache without any organic lesions during the course of illness. In two, the headache was severe enough to warrant numerous neurological investigations for the exclusion of possible intracranial neoplasm. However, no abnormalities were detected and none were available for neuropathological studies. The

symptoms could probably be explained by the small and transient, microinfarctions in the 'silent areas' of the brain.

The peripheral nervous system too was not entirely spared from SLE—the reported incidence ranged from 3% to 18% (Goldberg, 1959; Benett *et al*, 1961; Berry and Hodges, 1965; Dubois and Tuffanelli, 1964; Honda *et al*, 1966). Six patients (8%) in this series had evidence of peripheral neuropathy due to SLE. Of these, 4 presented as the distal sensorimotor type, one had signs and cerebrospinal fluid changes simulating Gillian-Barre syndrome, and another had subjective symptom of paraesthesia, but without any other neurological signs. The third type of neuropathy, not found in this study, was the mononeuropathy multiplex, due to vascular lesions within the nerves. The two former conditions, however, were attributed to primary degeneration of posterior spinal ganglia with secondary changes in the spinal nerves rather to a primary vasculitis. (Bailey *et al*, 1956). Various types of ocular fundal changes in SLE have been observed, but none were characteristic for the disease. "Cytoid bodies" appearing as fluffy cotton-wool or well-demarcated whitish exudates were found in 5 patients (7%) of this study and 9% to 24% in other series (Dubois, 1966; Harvey, 1954; Jessar *et al*, 1953). Retinal vascular lesions were also responsible for retinal haemorrhage (2 cases) and secondary optic atrophy (3 cases).

Nine patients (12%) had evidence of Lupus myopathy. Generalised myalgia, muscle tenderness and atrophy, especially of the limb girdles, were not uncommonly found in SLE—a 20% to 48% incidence (Dubois 1966; Madden, 1950).

Psychological disturbance in SLE is well-known. Almost all types of psychosis and psychoneurosis may be encountered, and the recorded incidence varied between 12% to 55% (Clark and Bailey, 1956; Brody, 1953; Stern and Robbins, 1960; Dubois, 1966). 17 cases in this study presented with several varieties of mental changes, not related to drugs or other systemic conditions. The commonest manifestations were anxiety states and depressions. Fessel and Solomon (1960) on reviewing this subject of psychoses associated with SLE, stressed the organic nature of the psychosis, which in most instances, were caused by cerebral angiitis. The usual error, as pointed out by Dubois (1966) was to blame the steriods for the neurosis or psychosis. However, it has been demonstrated that the mental changes were part of the disease and corticosteriods would, in fact, improve the mental states of these patients (O'Connor, 1959; Harvey *et al*, 1956; Cares and Weinberg, 1958; Tumulty, 1954).

(ii) *Neurological Involvement due to Systemic Complications in SLE*

Terminal coma and fits in 11 patients were due to uraemia, septicaemia and liver failure. In one case, an associated hypertension was the main cause of a fatal cerebral haemorrhage. Thrombocytopenia with subarachnoid bleeding was observed in another patient. Secondary bacterial and fungal infections of the nervous systems were partly due to the lowered immunological state of the disease and to the long-term steriod and other immunosuppressive therapy. In this series, there were 3 pyogenic and 2 fungal (Cryptoccocal) meningitis. The association of Cryptoccocal meningitis with SLE (found in two patients in this series) have been previously reported. (Harvey, 1956; Pariser *et al*, 1961; Pierce and Logothetis, 1962). Thus torula should always be vigorously sought for in CSF of SLE patients who present with ill-defined neurological manifestations. Early treatment with specific therapy such as amphotericin B may prevent an early fatal outcome in these cases. Secondary viral infection like herpes zoster were also observed in 4 cases during the course of the illness.

(iii) *Neurological Involvement Secondary to Therapeutic Complications in SLE*

Drugs commonly used in SLE were the corticosteriods and other immunosuppressive agents like Cyclophosphomide, Methrotexate, 6-Mercaptopurine and Azathioprine. Until lately, antimalarials too were popular medications. Steriod-induced mental disorders varying from depression, hallucinations with catatonia, to frank psychosis were well-known side-effects (Trethowan 1954). Nine of our patients were adversely affected by steriod administration, of these 6 had mental disturbance of varying degrees, 2 developed distal muscle wasting (from Dexamethasone) and one had bilateral retinopathy with caratact formations. Immunosuppressive agents too were responsible for 4 cases with neurological changes. Chloroquine-induced retinal damage in SLE patients has been fairly well documented before (Goldman and Preston, 1957; Hobbs *et al*, 1961; Wilson, 1961). This drug has not been extensively used nowadays because of the serious side-effects.

SUMMARY

A neurological analysis of 75 cases with SLE over a 15-year period in one medical unit revealed 29·3% neurological involvement due to the disease itself, 26·6% with neurological signs attributed to systemic complications, and 20% with neurological deficits secondary to medications.

A detailed list of each of these three groups of neurological involvement was presented and the literature of each condition was briefly reviewed and discussed.

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