MEDICAL PRACTICE

Clinical Problems

Neuropsychiatric Problems in Systemic Lupus Erythematosus

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Kaposi,¹ in his original description of systemic lupus erythematosus (S.L.E.), noted recurrent delirium in 2 out of 11 patients. During the past few years there has been a resurgence of interest in the central nervous system manifestations of S.L.E., together with an increasing awareness of their importance. In a recent large prospective study of S.L.E., central nervous system involvement, including psychosis, was seen in 59% of patients and was second only to renal involvement as a cause of death.² The use of sensitive tests for the diagnosis of S.L.E., in particular deoxyribonucleic acid (DNA) antibody titres³ and cerebrospinal fluid complement levels,⁴ may contribute to a more widespread recognition of this complication. The most difficult diagnostic and therapeutic problems have related to cases where psychiatric symptoms predominate.⁵ In this review case histories of five patients with central nervous system lupus seen recently at Hammersmith Hospital are reported to illustrate some of the clinical problems.

Case Reports

CASE 1

A 53-year-old Jamaican woman was initially seen as an outpatient with labile hypertension and depression for which she was treated with imipramine. Four years later she was noted to have active synovitis in the small joints of the hands and ankles. In addition she was severely depressed and had a peripheral sensory neuropathy, generalized muscle weakness (without wasting or tenderness), and an

easily audible pericardial friction rub. Investigations included E.S.R. 98 mm in one hour, haemoglobin 10.5 g/100 ml, W.B.C. 4,600/mm³, with an absolute lymphopenia, a positive W.R. with negative Treponema pallidum immobilization test, and a small pericardial effusion on the echocardiogram. Radiography of the joints showed no erosions. The Rose-Waaler test was negative, L.E. cell and A.N.F. tests were positive, DNA binding activity was 78%, (normal less than 20%) and the aspartate transaminase was 113 K.A. units.

Over the course of 10 days she progressively became more withdrawn and uncommunicative. In addition she had ideas of reference about other patients. Then over the course of about 24 hours her level of consciousness deteriorated rapidly and she was rousable only on vigorous stimulation, but apart from a mild dysarthria no abnormal neurological signs were found. The spinal fluid was normal. E.E.G. showed frequent abnormal runs of symmetrical and synchronous slow waves which were maximal in the anterior quadrants. A diagnosis of S.L.E. with central nervous system involvement was made and it was decided to start her on corticosteroids in an initial dose of hydrocortisone 200 mg intramuscularly daily. Within 24 hours there was noticeable improvement in her level of consciousness. She was more aware of the time and began to take note of what was going on around her and to show an interest in food. Three days later a normal sleep pattern was restored and she was fully orientated and feeding herself. Within a week she was walking about the ward and talking normally with other patients. During a 12-month follow-up period, in which the prednisone was reduced to 10 mg, there was no active synovitis or recurrence of depression, but the peripheral neuropathy remained unchanged. The DNA binding activity was less than 20%. It was apparent that she was a highly intelligent woman with considerable insight who could recount in detail what went on when she was in a state of apparent stupor.

CASE 2

A 15-year-old right-handed girl had complained for one year of intermittent abdominal pains and episodic arthralgia. Twenty-four hours before admission she had experienced a sharp pain above the eyes associated with nausea, followed by a sensation of multicoloured flickering lights in both visual fields. Within 24 hours these had become lateralized to the left homonymous temporal fields, and 12 hours later she was found to have a complete left-sided homonymous hemianopia.

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In addition she had a facial "butterfly" rash, subungual splinter haemorrhages, and livedo reticularis over the forearm and dorsum of the right hand. E.E.G. showed frequent irregular low to medium voltage delta waves at 1.5-3.5 Hz in the right posterior quadrant. A technetium brain scan, skull x-ray picture, spinal fluid were all normal. Thrombocytopenia (40,000/mm³), a weakly positive direct Coombs test, a positive A.N.F., and a DNA binding activity of 81% (normal less than 20%) were found. At this stage she was started on oral prednisone 30 mg/day reducing to 7.5 mg/day over the course of two months.

Ten days after discharge she suddenly felt faint and unsteady, the left hand became numb, and she was unable to move her left arm. She had an expressive dysphasia, but consciousness was never impaired. Over about one hour her speech returned to normal and power returned to the left arm. She was readmitted as an emergency, the only new finding on physical examination being some cortical sensory loss in the left hand and forearm. She was started on hydrocortisone 200 mg/day intravenously, and the new symptoms and signs regressed over the next few days. Subsequently she had several episodes in which a "veil" descended over the remaining areas of peripheral vision. These episodes were always accompanied by subungual vascular lesions and exacerbation of the livedo reticularis, and responded to increases in corticosteroid therapy. Over the last 12 months she remained well on decreasing prednisone dosage. The DNA binding activity remained normal. Apart from the left homonymous hemianopia there were no abnormal neurological findings or psychiatric changes.

CASE 3

A 35-year-old woman first developed discoid lupus erythematosus on her face, sternal region, and left arm three years before admission. The diagnosis was confirmed histologically and she was treated with topical steroids. Three months before coming under our care she became gradually unwell with polyarthralgia, hair loss, limb girdle pain, and vague visual disturbances. On admission she was very anxious and emotionally labile, with widespread lesions of discoid lupus on her face, arms, chest, and legs. There was patchy alopecia and active synovitis of the wrists and small joints of the fingers. In addition she had a rotatory tremor of her head and choreiform movements of her hands. Investigations showed an E.S.R. of 65 mm in one hour, haemoglobin 11.7 g/100 ml, W.B.C. 4,200/mm³ (16% lymphocytes), normal A.S.O. titre, positive A.N.F. and L.E. cell tests, and a DNA binding activity of 70%. X-ray examination of her joints and skull and an E.E.G. showed nothing abnormal. In view of the systemic features of the disease, together with evidence of involvement of the central nervous system she was started on oral prednisone 20 mg/day. Within a few days she became noticeably less anxious and more emotionally stable and the tremor had disappeared. DNA binding activity returned to normal over the next seven days. Corticosteroids were gradually withdrawn over the next four months, with no return of the signs of systemic disease.

CASE 4

A 27-year-old woman first became unwell two years previously with an unexplained anxiety state which was treated with antidepressant drugs. Eight months before admission to this hospital she was diagnosed as having schizophrenia and admitted to a psychiatric hospital for treatment. While there she had episodes of severe headaches and vomiting and developed a facial rash and haematuria. Within two months she developed a right homonymous hemianopia and weakness of the right arm. She was transferred to a general hospital where an E.E.G. and brain scan showed a focal abnormality in the left temporal region. A left carotid arteriogram and lumbar cerebrospinal fluid were normal. Laboratory investigations were: E.S.R. 95 mm in one hour, W.R. positive and *Treponema pallidum* immobilization test negative, A.N.F. positive, L.E. cells negative, raised gammaglobulin level, and microscopic haematuria. A diagnosis of arteritis of unknown type was made and she was started on prednisone 15 mg/day. Three months later she suddenly developed a dense right-sided hemiparesis, an expressive aphasia, and left retinal artery thrombosis. It was noted that she bruised easily, and blood coagulation studies pointed to a circulating anticoagulant (antifactor VIII). She was transferred to this hospital, where on admission apart from a faint erythematous rash in a "butterfly" distribution the clinical findings were unchanged. A brain scan showed total infarction of the left temporal lobe and a partial infarction of the right temporal lobe. A carotid arteriogram

showed a completely occluded left common carotid. On the basis of the clinical history and findings, the positive A.N.F., false-positive W.R., and circulating anticoagulants the diagnosis was thought to be S.L.E. with cerebral involvement. The DNA binding activity was slightly raised at 23% despite the corticosteroid therapy. Steroid dosage was increased to 100 mg prednisone daily with great improvement in her conscious level but not in the focal neurological signs. Forty-eight hours later she again deteriorated and remained in coma for the last six days of her life.

Necropsy showed thrombosis of the left common carotid, internal carotid, and middle cerebral arteries with resultant cerebral infarction. Histological examination showed onion skin lesions in the spleen and wire loop lesions in the kidney. Sections of uninfarcted areas of the brain showed endothelial hyperplasia of small vessels plugged with acidophilic thrombi. The pathological diagnosis was "small vessel vasculitis with features suggestive of both S.L.E. and thrombotic thrombocytopenic purpura."

CASE 5

A 14-year-old Jamaican girl presented at another hospital with a two-week history of painful swelling of the knees, ankles, and wrists associated with fever, rigors, and haematuria. Apart from her obvious pyrexia and arthritis she was also noticed to have palpable cervical lymph nodes and a blood pressure of 180/95 mm Hg. Investigations showed E.S.R. 100 mm in one hour, haemoglobin 11.5 g/100 ml, W.B.C. 4,000/mm³, (63% neutrophils and 31% lymphocytes), and aspartate transaminase 100 K.A. units. L.E. cell preparations were negative. She was initially thought to have rheumatic fever and was treated with aspirin. However, the arthritis spread to involve both wrists, the small joints of the hands, and the elbows. Subsequently she developed chest pain and a productive cough, a chest x-ray picture showing a small left basal effusion. The E.S.R. rose to 121 mm in one hour and the blood urea to 41 mg/100 ml. She was transferred to this hospital, where it was noticed that she had pitting oedema to the level of both knees and pronounced alopecia.

Investigations showed a urinary protein excretion of 9.56 g over 24 hours and a creatinine clearance of 31 ml/min. L.E. cell preparations were positive, and an A.N.F. titre was 1:1,250. The direct Coombs test was positive. She was treated with prednisone 60 mg/day, hydrochlorothiazide 10 mg/day, and Slow K 600 mg three times daily. Her blood urea continued to rise over the next two weeks to 172 mg/100 ml and her blood pressure rose to 178/120 mm Hg. Treatment with betanidine 200 mg four times daily rapidly controlled the hypertension. Shortly after this, while remaining normotensive, she developed grand mal convulsions and was started on phenobarbitone 50 mg three times daily. This did not stop her convulsions, however, which were thought to be due to cerebral arteritis. Prednisone dosage was therefore increased to 150 mg/day. The convulsions stopped but returned when the dosage was again reduced to 30 mg/day. At the time of discharge she was on prednisone 50 mg/day and her blood urea was 10 mg/100 ml, creatinine clearance 76 ml/min, 24-hour urinary protein 4.2 g and blood pressure 150/110 mm Hg lying and 110/70 mm Hg standing. During three months of follow-up she remained well but subsequently failed to attend.

Clinical Manifestations

As in neurosyphilis, almost any neurological or psychiatric abnormality may occur in S.L.E. While neuropsychiatric abnormalities are frequently multiple they will be considered separately for the sake of clarity.

Disorders of Mental Function.—These are probably the commonest central nervous system abnormality in S.L.E. In their mildest form they are easily overlooked, even in patients known to have S.L.E., and Case 1 shows the importance of considering S.L.E. in any patient with "rheumatoid" disease developing mental abnormalities. Mental symptoms can antedate the better-known manifestations of S.L.E. by several years, as in Case 4, where the diagnostic progression was from chronic anxiety state to schizophrenia to focal neurological changes ending in a massive and fatal cerebral infarction. Endogenous depression was the commonest mental change found by Shearn and Pirofsky,⁶ being seen in about half of patients. In the present Case 1 the patient was for many years thought to have

rheumatoid arthritis with an associated chronic depressive illness, which suddenly progressed into a catatonic-like state. Schizophrenia is not uncommon⁷ and can antedate other features of S.L.E. by months or years, as in Case 4. In addition Johnson and Richardson⁸ described patients presenting with confusional states, hypomania, and paranoia, while Clarke and Yoss⁹ reported cases in which there was a general falling off in intellectual functions leading to progressive dementia. An acute deterioration in the level of consciousness has been described in relation to a disseminated encephalomyelitis in S.L.E.¹⁰ While it is generally thought that these disorders in mental function are the result of cerebral vasculitis leading to multiple micro-infarcts and haemorrhage,^{11 12} this is rarely borne out by pathological studies.⁸ In a recent necropsy study of two patients known to have had cerebral lupus Atkins *et al.*¹³ found immunoglobulin deposits in the small vessels of the choroid plexus.

Epilepsy.—Epilepsy has been reported in 17-50% of patients with central nervous system lupus,^{3 8} usually of the grand mal type, but focal epilepsy,¹⁴ temporal lobe seizures,¹⁵ and petit mal attacks¹⁶ have all been reported. Convulsions generally occur during exacerbations of the disease, although reports have appeared in which epilepsy antedated other manifestations of S.L.E. by several years,¹⁷ and recurrent convulsions occur frequently enough during the terminal stages to be of bad prognostic import.¹⁷ Convulsions occurring in S.L.E. may also result from uraemia and hypertension and from the use of corticosteroids and antimalarials. In addition patients with idiopathic epilepsy can develop an S.L.E.-like syndrome when using anticonvulsant drugs such as hydantoins¹⁸ and primidone,¹⁹ the clinical picture usually regressing after withdrawal of the drug.

Cranial Nerve Disorders.—These occur in 5-33% of patients with cerebral lupus.^{3 8} Both nuclear and peripheral lesions of the cranial nerves have been described. Cranial nerve disorders usually appear suddenly and unexpectedly without any premonitory symptoms, as did the homonymous hemianopia in Case 1. Visual defects as in Case 1 are the most common, with homonymous hemianopia,²⁰ blindness,²¹ papilloedema,²² abnormalities of extraocular movements, and pupillary changes²³ also being reported. In some patients ptosis and disturbances of extraocular movements are seen due to a myoneural junction dysfunction resembling myasthenia gravis.²⁴ Such cases are sometimes atypical in that they do not respond well to anticholinesterase therapy. Neuropathological studies in these cases usually show brain-stem vasculitis with multiple areas of infarction and, more rarely, perivascular haemorrhage. In those patients presenting with infranuclear palsies no lesions have been found in the peripheral nerves, unlike polyarteritis nodosa or diabetes mellitus.

Paralysis.—Hemiplegia is an uncommon complication of S.L.E., being found in 5% of patients with central nervous system manifestations,³ although its transient recurrence in a young doctor associated with aphasia over a 14-year period first led Osler²⁵ to focus attention on the systemic nature of the disease. As with convulsions, most cases of hemiplegia occur at some intermediate stage of the disease, but some antedate other symptoms by several years,²⁶ while others occur at a terminal event.²⁷ Occlusion of the major arteries is rare; only two cases in the literature were found to have occlusions of large or medium-sized arteries at necropsy.^{20 28} A few cases of paraplegia due to myelopathy have been described.²⁹

Disorders of Movements.—Chorea has been the most widely-reported disorder of movement in S.L.E.³⁰ In its early stages such chorea is easily overlooked, as its only manifestation is a slight exaggeration of semipurposeful movements. The awareness of this particular feature is of special significance in children thought to have rheumatic fever, as an alternative diagnosis of S.L.E. may call for the early use of corticosteroids. In the present Case 3 the patient was unusually old, the average age for this complication being 17 and the oldest recorded case being 33.³¹ A few patients have been reported as having Parkinsonian-like

tremor and rigidity³² and even cogwheel rigidity without tremor.³³ Cerebellar ataxia has occasionally been seen but with associated signs suggesting a brain-stem lesion rather than cerebellar cortical involvement.⁹

Peripheral Neuropathy.—This is less commonly seen in S.L.E. than in rheumatoid arthritis. When present it is usually symmetrical, with mixed sensory and motor loss.³⁴ A pure sensory neuropathy of a "stocking" type distribution as in Case 2 is unusual. Less commonly a mononeuritis multiplex similar to that seen in polyarteritis nodosa develops.³⁵ Also described is an exclusive motor loss with raised levels of spinal fluid protein without a pleocytosis, as in the Guillain-Barré syndrome.³⁶

Diagnosis

There is no one test or group of tests that will establish a definite diagnosis of cerebral lupus. While most neuropsychiatric symptoms occur during an exacerbation of the disease—with fever, arthralgia, a high E.S.R., and a high titre of DNA antibodies—occasionally central nervous system manifestations occur as isolated events and even antedate the better-known features by several years. The difficulties involved in the diagnosis and management of the more subtle neuropsychiatric changes in S.L.E. were reviewed by Dubois,⁵ who emphasized the importance of distinguishing S.L.E. psychosis from more benign emotional problems encountered in the disease. The implications are numerous. If current impressions are borne out psychosis may come to be recognized as one of the most common manifestations of S.L.E., and many such episodes may in the past have been wrongly attributed to corticosteroid therapy.

The progression of such early changes to more florid disease is illustrated in Cases 2, 4, and 5. Clinically the finding of a vasculitis, as manifested by subungual or periungual haemorrhages, livedo reticularis, or nephritis is of major importance, as many of the cerebral symptoms may also result from cerebral vasculitis.³⁷

Examination of the cerebrospinal fluid should be performed mainly to exclude meningitis, particularly fungal or tuberculous.⁵ In those cases where an abnormal cerebrospinal fluid is found it is reasonable to assume an organic basis of the neuropsychiatric manifestations being investigated. Failure to show abnormalities, however, does not preclude an organic lesion. A protein content over 50 mg/100 ml was found in only 48% of cases in the literature.⁸ Values over 100 mg/100 ml are very unusual except in patients with Guillain-Barré-type neuropathy or myelopathy. In the same series 32% of patients had a pleocytosis of over 5 cells/ml, and only nine cases were reported with cell counts over 50 cells/ml in the absence of a bacterial or fungal meningitis. More recently Petz *et al.*⁴ described abnormally low levels of C4 in the cerebrospinal fluid of patients with cerebral lupus and produced evidence to suggest that this was a result of an immune reaction within the central nervous system rather than a reflection of a low fourth component of complement (C4). If confirmed, these findings suggest that this investigation may prove helpful in the diagnosis and management of cerebral lupus.

Measurement of DNA antibodies has proved to be both a sensitive and specific guide to disease activity in S.L.E.,^{3 38-41} and increased anti-DNA activity has been found in patients in whom psychosis was the only manifestation of disease activity.⁹

E.E.G.s, when abnormal, have most commonly shown diffuse slowing. While having little localizing value⁸ in this disease, an abnormal result provides help in the differentiation between organic and purely functional mental changes. Cerebral arteriograms are almost always normal in patients with cerebral lupus, possibly because the fundamental disorder is that of small vessel obliteration. The only indication for undertaking this line of investigation in a patient with known S.L.E. is if there is clear collateral evidence of an alternative and treatable cause for the central nervous system manifestations. Crawford⁴² suggested that massive thrombosis after carotid arteriography is unusual except in those patients whose large vessels are already

abnormal. It is possible in Case 4 that the carotid occlusion was related to the initial carotid arteriogram.

Other causes of neuropsychiatric symptoms should be borne in mind, especially in patients with advanced renal involvement and hypertension. Fluctuations in the levels of consciousness and convulsions occur in uraemia, hypokalaemia, and hyponatraemia, while encephalopathy and intracerebral haemorrhage can result from secondary hypertension. Patients on long-term corticosteroids may develop benign intracranial hypertension,⁴³ while those on "immunosuppressive" therapy have an increased incidence of cerebral abscess and intracerebral lymphomas.⁴⁴ Drugs used in the treatment of S.L.E. may cause neuropsychiatric changes of an iatrogenic nature; antimalarials may produce personality changes, convulsions, and psychotic episodes,⁴⁵ and corticosteroids lower the epileptogenic threshold⁴⁶ as well as producing euphoria and frank psychosis.⁴⁷

Diagnostic difficulties might also occur in patients on some psychotropic drugs such as phenothiazines, in which a lupus-like syndrome has been described.⁴⁸ Thrombotic thrombocytopenia may cause diagnostic difficulties, as neuropsychiatric symptoms are commonly associated with fever, haemolytic anaemia, and thrombocytopenia.⁴⁹

MANAGEMENT

Corticosteroids are the mainstay of treatment in cerebral lupus; indeed Dubois⁵ claimed that if steroids are used in "massive" doses it is unusual for a patient to succumb to central nervous system involvement unless there is severe renal disease or iatrogenic complications. By comparing his results in cerebral lupus since the use of large amounts of corticosteroids became routine practice, there has been a decline in the mortality from 52% to 18%. Initial steroid dosage is largely a matter of empirical judgement. In patients with recurrent convulsions or profound disturbances in consciousness, corticosteroids by intravenous infusion may be required in a dose of hydrocortisone 500 mg every 24 hours. This should be increased by 50% each 24 hours until clinical improvement is noted. As much as 2,300 mg of cortisone has been used successfully in treating an acute episode of cerebral lupus.⁵⁰ In less severe cases 50 mg of prednisone given by mouth is usually required as the initial starting dose, usually being tapered off according to clinical response. While measurement of anti-DNA antibodies has not been adequately assessed in the diagnosis and monitoring of central nervous system lupus, DNA antibody titres generally fall towards normal, often rapidly with the use of corticosteroid therapy.⁵¹ Thus finding a high titre in an S.L.E. patient on corticosteroids may prove of use in the differentiation of S.L.E. psychosis from steroid psychosis.

The decision to subject an S.L.E. patient with psychiatric symptoms to high-dose corticosteroid therapy, with its attendant risks, must be made in the knowledge that such symptoms can herald more severe and even fatal neurological disease. Until more is known about the incidence and natural history of central nervous system lupus, especially psychosis, such decisions must remain somewhat arbitrary.

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