CASE REPORT

Severe lupus leukoencephalopathy – a case report

Khean Jin GOH MBBS MRCP, *Sazilah AHMAD SARJI MBBS FRCR, Salem OMAR MBBS and Chong Tin TAN FRCP MD

Division of Neurology, Department of Medicine and *Department of Radiology, University of Malaya, Kuala Lumpur, Malaysia.

Abstract

This is the report of a 27 year old Chinese woman who presented with severe, progressive headache as a manifestation of central nervous system lupus erythematosus. She had no focal neurological deficits and had relatively clear mentation. Magnetic resonance imaging revealed a striking, diffuse signal change in the white matter of the cerebrum, cerebellum and brainstem. The mechanism of the severe headache was postulated to be due to raised intracranial pressure or the involvement of a headache “generator” within the brainstem. The widespread white matter change on neuroimaging with relative paucity of neurological and cognitive dysfunction suggests that the pathogenic mechanism may be a direct immunologic attack rather than a small-vessel vasculopathy.

Key words: systemic lupus erythematosus, central nervous system, headache, white matter disease, magnetic resonance imaging

INTRODUCTION

Nervous system involvement in systemic lupus erythematosus (SLE) is heterogeneous and may reflect varied underlying pathophysiological mechanisms. Involvement of the central nervous system can be diffuse, focal or a combination of both. Diffuse nonfocal manifestations may range from limited cognitive dysfunction to dementia, psychiatric disturbances, altered consciousness, seizures (including status epilepticus) and headache.1

Headache is not uncommon in patients with SLE and may be due to various secondary abnormalities, i.e., cerebrovascular disease, central nervous system infection and benign intracranial hypertension. It has been also previously thought to be a manifestation of SLE involvement of the central nervous system.1-3 However, we have recently found in a prospective survey of SLE patients compared to non SLE inpatient and community controls that headaches (including migraine headaches) in SLE patients were not significantly more prevalent compared to controls.4 This does not however exclude the possibility that in the individual SLE patient with central nervous system involvement headache may be the result of the underlying disease process.

The pathophysiological mechanism of neuropsychiatric lupus is often thought to be a non-inflammatory vasculopathy but anti neuronal antibodies have been described which may play a role in direct immunologic attack on the brain.1 We describe here a young woman who had central nervous system lupus erythematosus who presented with severe headache and a diffuse leukoencephalopathy on neuroimaging suggesting a direct immune insult to the cells as the pathogenic mechanism.

CASE REPORT

Ms. SLK was a 27 year old Chinese woman first started in November 1996 while she was working in a factory in Singapore. She complained of headaches which were bifrontal, pressing in nature and associated with nausea and vomiting. She also complained feeling weak and lethargic and reported weight loss although she was unable to quantify. In February 1997 she noted an erythematous rash over the upper extremities and subsequently over the face, neck, chest and back. The rash subsequently became scaly and hyperpigmented. She also developed alopecia and oral ulcers but had no complaints of joint pains. She returned home to Petaling Jaya, Malaysia because of her illness. She initially sought traditional treatment and did not present to the University Hospital, Kuala Lumpur till
June 1997 when she complained of recurrence of headache for two weeks prior to admission. This was described as severe, arising from the frontal area radiating to the occiput. She also complained of fever but no chills and rigors. There was no blurring of vision, photophobia, neck stiffness or any focal neurological symptoms.

On admission, she was conscious and alert. She was clear in her history and relevant in her answers. Clinical examination showed that she had marked alopecia and an extensive hyperpigmented rash over the face, neck and trunk. Vasculitic lesions were noted over her palms. She was afebrile, had no signs of meningism and no focal neurological deficits. Blood pressure was 97/56. A diagnosis of systemic lupus erythematosus with central nervous system involvement was suspected.

Investigations: The initial investigation revealed a haemoglobin of 89 g/L, leucocyte count of 4.7 x 10⁹/L and a platelet count of 149 x 10⁹/L. Blood urea, creatinine and electrolytes were normal. Her erythrocyte sedimentation rate (ESR) was 65 mm/hour. C-reactive protein was <0.4 mg/dL (0.0 -0.8). Coagulation profile was normal.

A CT scan of the brain carried out on admission showed diffuse white matter hypodensity with effacement of the cortical sulci suggestive of some degree of cerebral oedema. No focal abnormalities were detected. Cerebrospinal fluid examination revealed normal glucose, protein and cell count. Examination for acid fast bacilli, cryptococcal antigen and culture and bacterial culture were negative.

Serological tests: Antinuclear antibody was 1 in 1280 (speckled) and anti double-stranded DNA measured by enzyme-linked immunosorbent assay (ELISA) was 457 IU/ml (negative < 200 IU/ml). Serum complements were reduced. Anti cardiolipin antibody was negative. Based on the SLE disease activity index (SLEDAI), disease activity score at the time of admission was 30.

MRI: Magnetic resonance imaging (MRI) scan of the brain was carried using a Siemens 1.5 Tesla scanner. T1-weighted (TR = 570.0, TE = 14.0), T2 weighted (TR = 3800.0, TE = 90.0) and T2 FLAIR (fluid attenuated inversion recovery) sequences in the axial plane were carried out. This showed a striking diffuse and symmetrical signal change in the cerebral and cerebellar white matter. There was also involvement of white matter of the midbrain and upper pons. There were no infarcts, haemorrhage or other focal abnormalities. There were no abnormal focal lesions or enhancement in post contrast images.

Treatment: The patient was diagnosed to have SLE with severe central nervous system involvement. She was pulsed with intravenous methylprednisolone 1 gram daily for 3 days and subsequently oral prednisolone 50 mg/day. Her headache gradually resolved and she was subsequently discharged on oral prednisolone.

Progression: She returned two weeks later with the complaint of severe continuous generalised headache which recurred 4 days prior to admission and severe vomiting on the day of admission. The patient was extremely distressed by the headache and she required opioids analgesia to afford some relief. On clinical examination, she looked ill but was conscious and alert with clear mentation and no papilloedema, focal neurological signs or meningism. A repeat lumbar puncture revealed a raised cerebrospinal fluid (CSF) pressure of 30 cm H₂O but CSF cell count, protein and glucose were normal. The headache remained severe despite strong analgesics and a second intravenous pulse methylprednisolone was administered. Her condition however worsened and two days after admission, the patient suddenly went into cardiorespiratory arrest and had to be resuscitated and ventilated. Post-resuscitation, she was unresponsive and her pupils were unreactive. A repeat CT scan at this time showed cerebral oedema but the white matter changes remained the same. Despite assisted hyperventilation, she died two days later. Post-mortem examination was refused by her next-of-kin.

DISCUSSION

Central nervous system (CNS) involvement in SLE is difficult to assess because of its protean manifestations and lack of definitive diagnostic markers. The challenge in the evaluation of such patients would be to classify the nervous system dysfunction and determine the cause, so that appropriate therapy can be instituted. Diffuse nonfocal CNS lupus often manifest as cognitive dysfunction, dementia, states of altered consciousness or psychiatric disturbances.

Our patient, however, presented with severe progressive headache. In an SLE patient, this would warrant an exclusion of serious secondary
FIG. 1: Magnetic resonance imaging (MRI) scan of the brain using a T2-weighted FLAIR sequence:

a) diffuse symmetrical hyperintensity of the cerebral white matter

b) white matter signal changes within the midbrain
disorders such as CNS infection, haemorrhage, cerebral infarction, cerebral sinus thrombosis, aseptic meningitis and subdural haematoma.\textsuperscript{1,5} Investigations revealed no evidence of CNS infection (normal cerebrospinal fluid examination and C-reactive protein) and neuroimaging showed diffuse white matter changes but no focal intracranial lesions. Her symptoms were therefore the result primary CNS lupus. An SLE headache has been suggested by some investigators but these are chronic recurrent headaches suggestive of migraine\textsuperscript{2,3} and our controlled study of chronic headache in SLE has not supported this entity.\textsuperscript{4} Atypically, this patient’s headache was the result of diffuse progressive CNS disease. A possible mechanism for headache could be a developing raised intracranial pressure (the CSF pressure on lumbar puncture was raised) which could have led finally to brain herniation and death. Another possibility is that there was involvement of a centre in the brainstem which may function as a “generator” for headache. A migraine “generator” in the brainstem has been postulated\textsuperscript{6,7} based on persistent increased cerebral blood flow in the brainstem on positron emission tomography (PET) studies. In our patient, MRI showed involvement of the brainstem and progression of the brainstem lesions may have worsened the headache and led to cardiorespiratory arrest.

Cerebral white matter lesions on MRI have been reported in several case series.\textsuperscript{8-13} These lesions have mostly been patchy, multiple at the periventricular or subcortical white matter. The significance of these lesions is unclear and have been thought to reflect small vessel vasculopathy.\textsuperscript{8-10,13} because of similar changes in healthy elderly individuals with risk factors for cerebrovascular disease\textsuperscript{14} and because they could fit with the presumed pathogenic mechanism of small vessel disease based on observations of previous post-mortem series.\textsuperscript{15,16} Clinical correlation of the lesions with neurological symptoms has not been consistent and it is uncertain whether the brain abnormalities on MR imaging is related to the presence and severity of neuropsychiatric disease.\textsuperscript{11,12} Diffuse CNS disease may have larger and more widespread signal changes compared to focal disease.\textsuperscript{9}

MRI in our patient showed an extremely striking diffuse symmetric white matter involvement on both T1 and T2 weighted images. Such findings are uncommon. We have found...
two previous case reports, both women aged 56 years and 43 years respectively presenting with features of severe organic brain syndrome where there were extensive widespread white matter involvement on CT and MRI. In both patients there was evidence of active SLE disease and in the latter patient, the cerebrospinal fluid interleukin 6 (IL-6) was elevated suggesting an inflammatory process within CNS and paralleling the CNS disease activity consistently. Similarly in our patient, the extensive white matter involvement reflected severe active CNS disease as evidenced by the severity of the headache at clinical presentation, the high disease activity score (SLEDAI = 30), the evidence of raised intracranial pressure and finally her poor outcome. In the two earlier reports, the global neurological dysfunction of their patients correlated well with the diffuse findings on neuroimaging. Our patient was remarkable however, in that her main complaint was headache with little evidence of disturbance of mentation or consciousness.

The diffuse white matter changes on neuroimaging were postulated to reflect oedema (as there was some reversibility) as well as irreversible demyelination and gliosis. The pathogenesis was assumed to be widespread changes due vasculopathy or a direct immunologic attack on the brain. In our patient, the paucity of dysfunction of cognition and consciousness despite diffuse MR changes suggest a sparing of the cortical neurons, making a widespread vasculopathy unlikely. We feel the pathophysiological mechanism for such widespread leuкоencephalopathy may be more likely a direct immunologic insult to the neurons. In an earlier MRI series, patients with diffuse CNS disease had symmetrical lesions and elevated titres of antibodies to neurofilaments. Magnetic resonance spectroscopy (MRS) imaging provides a non-invasive method of studying tissue metabolites in vivo of lupus brains. A recent study showed abnormalities characterised by decreased N-acetylaspartate (NAA), elevated choline and normal lactate, suggesting neuronal loss and demyelination rather than ischaemia. It is probable that in a heterogeneous disorder such as neuropsychiatric lupus, more than one single pathophysiological process is involved.

Unlike the two earlier case reports mentioned above where the patients improved on steroids, our patient's symptoms ameliorated initially after pulse methylprednisolone but recurred and then worsened. The severity of disease was such that high dose steroids were ineffective.

REFERENCES
15. Johnson RT, Richardson RP. The neurological manifestations of systemic lupus erythematosus, a

189

