

CASE REPORT

Cerebellar ataxia in systemic lupus erythematosus

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Neuropsychiatric manifestations are commonly observed in systemic lupus erythematosus (SLE) patients; however, cerebellar involvement has rarely been reported. In the presence of acute cerebellar ataxia, etiologies related (focal edema and ischemia) and not related (infections, malignancy and paraneoplastic syndromes) to lupus have to be considered and they imply different treatment strategies. We report the clinical and radiological features of 3 SLE patients who presented with acute cerebellar ataxia. A review of the literature was performed by documenting cases of cerebellar ataxia in SLE and the importance of neuroimaging in the evaluation of these patients. *Lupus* (2008) 17, 1122–1126.

Key words: cerebellar ataxia; MRI; SLE

Introduction

Neuropsychiatric (NP) manifestations are present in 50–70% of the patients with SLE and include a variety of central and peripheral neurological manifestations.^{1,2} The prevalence of cerebellar involvement in SLE has been estimated to occur in less than 2% of the cases.^{2–12} Cerebral ischemia, vasogenic oedema and antibody-mediated cerebral dysfunction are possible etiologies of acute cerebellar ataxia related to SLE.^{2–12}

We report the clinical and radiological features of three patients who showed signs of acute cerebellar ataxia. A review of the literature was performed by documenting cases of cerebellar dysfunction in SLE and the importance of neuroimaging in the evaluation of these patients.

Case report

Patient 1

A 34-year-old Caucasian patient was referred to the emergency unit with a 6-h history of acute onset of unsteadiness of gait and difficulty in walking. One

month before she had experienced the onset of Raynaud's phenomenon, inflammatory arthralgias and oral ulcers. She had been treated for high blood pressure in the previous 2 years. On clinical examination, her blood pressure was 140/90 mmHg and heart and lung sounds were normal. No arthritis was noted on physical examination. On neurological examination, she presented limb and truncal ataxia, bilateral nystagmus and diplopia. No muscle weakness or sensory disturbance was noted. Deep tendon reflexes were normal. Meningeal signs were absent. Complete blood count showed leukopenia, positive ANA (1/320 homogenous), negative dsDNA, normal complement levels and positive anti-Sm and anticardiolipin antibodies (IgG isotype, moderate/high titers) confirmed on two other posterior occasions. Blood urea, glucose, liver function, thyroid tests and chest X-rays were normal. Carcinoembryonic antigen (CEA 125) was negative. The patient was diagnosed with SLE based on leukopenia, oral ulcers, positive anti-Sm, ANA and anticardiolipin antibodies. There was no history of previous miscarriages or thrombotic events. Her cranial CT was normal and lumbar puncture revealed slight pleocytosis (10 white blood cells; 51% neutrophils with normal protein and glucose levels and cultures were negative for bacteria, fungi and mycobacterium). She was treated with pulse methylprednisolone (1 g for 3 days) for NP-SLE, with improvement of neurological symptoms. Her MRI performed 2 days after corticosteroid initiation

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showed hyperintense white-matter lesions in the deep white matter, but there was no evidence of edema and no abnormality in signal intensity within the cerebellum. Prednisone 1 mg/kg with progressive tapering over the next 6 months and azathioprine 2.5 mg/kg were prescribed. After 6 months, the patient was completely asymptomatic with normal neurological examination. Her follow-up MRI revealed dilatation of the fourth ventricle and hyperintense white-matter lesions in the deep white matter.

Patient 2

A 29-year-old non-Caucasian female patient with diagnosis of SLE was sent to the rheumatology unit for evaluation of cranial nerve palsy and headache. She was followed up at a private clinic with the diagnosis of SLE for the past 10 years (polyarthritis, photosensitivity, positive ANA (1/1280; speckled), positive dsDNA and anti-Sm antibodies and negative anticardiolipin and lupus anticoagulant). She had a family history of multiple sclerosis. On examination, her blood pressure was 120/82 mmHg, her heart and lung sounds were normal and no musculoskeletal abnormalities were found. On neurological examination, she was found to have truncal ataxia without limb dysmetria, nystagmus, diplopia and mild right-facial palsy. No myosis, ptosis or muscle weakness of the extremities was observed. Deep tendon reflexes were normal. Lumbar puncture was normal, including negative oligoclonal bands. Her MRI showed an isolated lesion in the brainstem (Figure 1). Her evaluation for malignancy (chest x-ray, endoscopy, gynecological examination, CEA 125) was negative. Anticardiolipin antibodies and lupus anticoagulant were repeatedly negative. She was treated with pulse methylprednisolone (1 g for 3 days), followed by oral prednisone 1 mg/kg with progressive tapering and intravenous cyclophosphamide over the next 6 months with complete improvement of symptoms. Her MRI carried out 1 month after the beginning of the therapy showed complete remission of the brainstem lesion. After 6 months, azathioprine (2 mg/kg) was introduced. Two months later she presented to the emergency unit with dysarthria and severe headaches. Her MRI showed multiple lesions in the deep white matter and recurrence of the lesion in the brainstem (Figure 2). A repeated lumbar puncture ruled out the presence of infection (negative for bacteria, fungi, syphilis, toxoplasmosis and mycobacterium). A new evaluation for malignancy was negative. Prednisone (1 mg/kg) and azathioprine (3 mg/kg) were reintroduced with progressive improvement of symptoms and MRI.

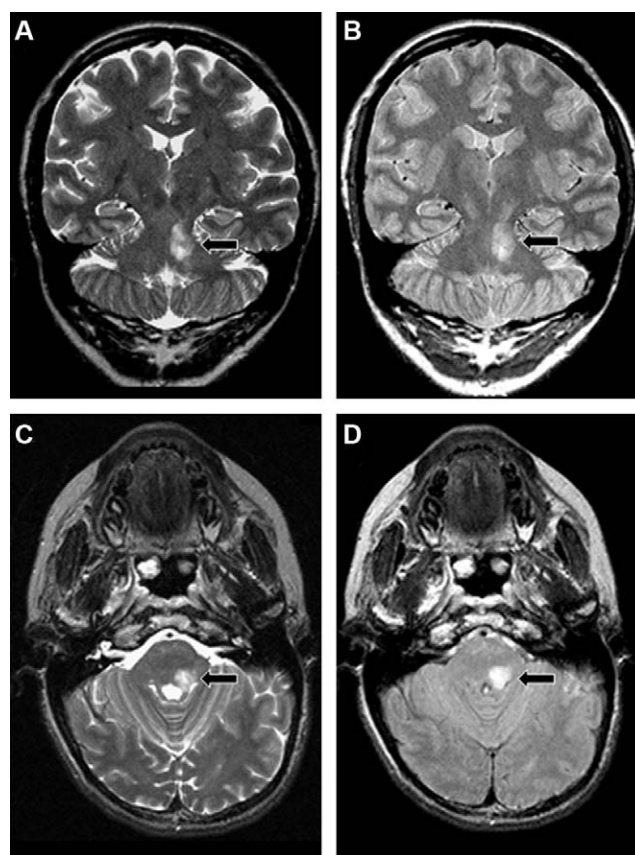


Figure 1 Coronal (A, B) and axial (C, D) MRI at onset of symptoms in patient #2 showing an isolated lesion in the brainstem in (A, C) T2 weighted images and (B, D) fluid attenuated inversion recovery (FLAIR) images.

Patient 3

A 15-year-old non-Caucasian female patient diagnosed with SLE in 2003 (arthritis, malar rash, photosensitivity, pericarditis, ANA 1/1280 and positive dsDNA antibody) presented with nystagmus, diplopia, dysarthria and vertigo in December 2006. On neurological examination, truncal ataxia with upper- and lower-limb dysmetria, positive Romberg sign and normal fundoscopic examination were observed. Deep tendon reflexes were normal. Lumbar puncture had increased protein (75 mg/dl), normal glucose levels, 3 white blood cells and 37 red blood cells. Cultures were negative for bacteria, fungi and mycobacterium. Her MRI showed in the cortex of the vermis cerebellaris a small area of increased signal in fluid attenuated inversion recovery (FLAIR) with slight contrast enhancement. The diagnosis of an ischemic cerebellar lesion with blood-brain barrier rupture secondary to vasculitis was suggested. Her evaluation for malignancy (chest x-ray, endoscopy, gynecological examination and CEA 125) was negative. Anticardiolipin antibodies and lupus anticoagulant were negative

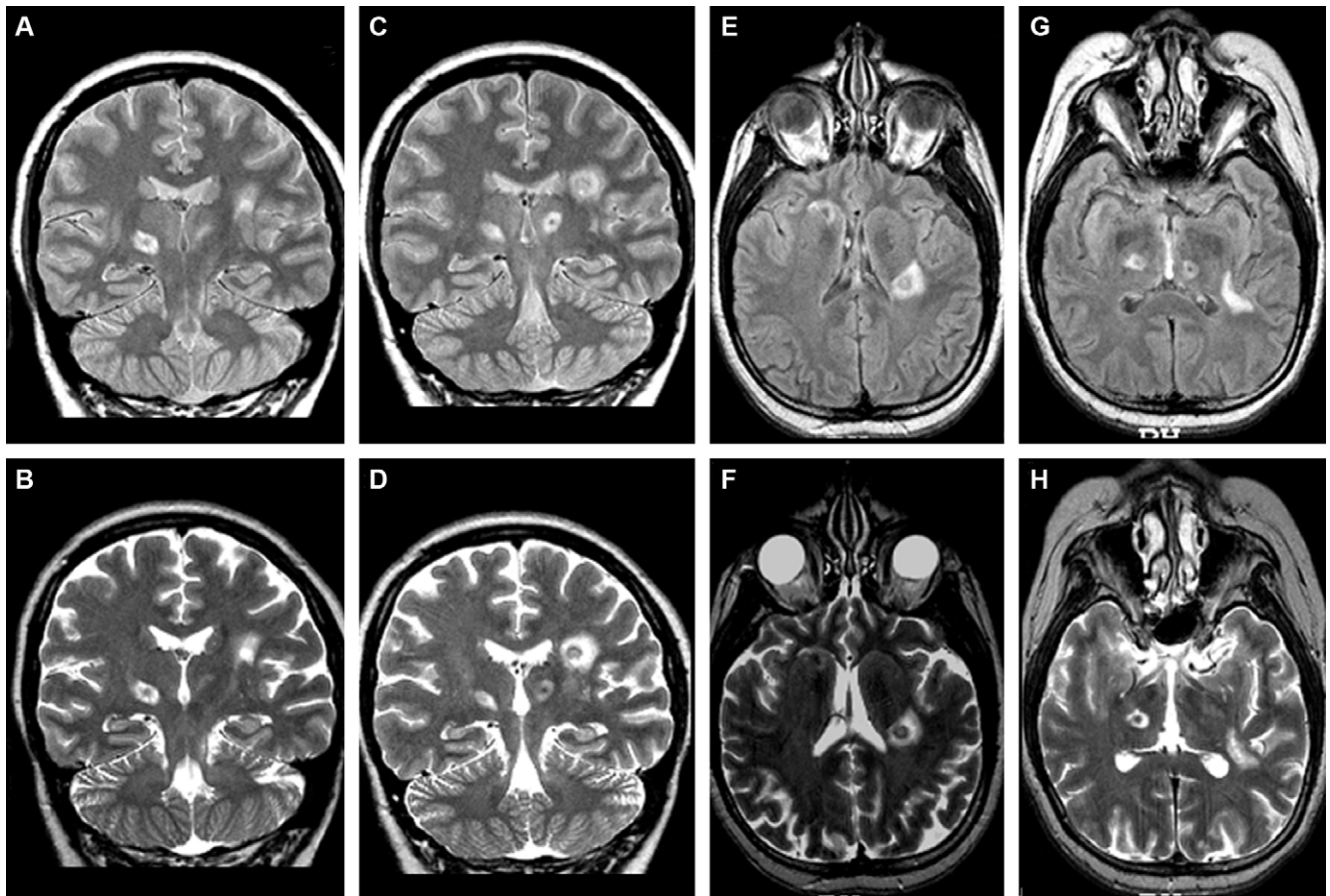


Figure 2 Coronal (A, B, C, D) and axial (E, F, G, H) MRI at follow-up of patient #2 showing multiple deep white-matter lesion. (A, C, E, G) T2 weighted images and (B, D, F, H) fluid attenuated inversion recovery (FLAIR) images.

on several occasions. She was treated with pulse methylprednisolone (1 g for 3 days), followed by oral prednisone 1 mg/kg with progressive tapering and pulse cyclophosphamide over the next 6 months with complete improvement of symptoms.

Discussion

NP-SLE may present as focal or diffuse CNS involvement. Focal CNS manifestations secondary to cerebellar involvement has rarely been described in SLE.²⁻¹² The sudden onset of nystagmus and ataxia suggests the presence of cerebellar dysfunctions that may occur as an isolated presentation, associated with brainstem or more widespread CNS manifestations.⁷⁻⁹

We report three SLE patients who presented in our clinic with acute cerebellar ataxia. An isolated involvement of the cerebellum was present in two patients (patients #1 and #3). In patient #2, a lesion in the brainstem was responsible for the neurological signs and symptoms at presentation and the recurrence of

symptoms was, however, associated with a more widespread CNS involvement.

Previous studies suggested that cerebral infarction and vasculopathy are possible pathogenic mechanisms involved in cerebellar ataxia in SLE patients.⁴⁻⁶ In our patients, cerebral ischemia was less likely seen in patients #1 and #2 because of the absence of typical ischemic MRI abnormalities on initial and follow-up MRI. Although patient #3 had an ischemic cerebellar lesion, her MRI also showed slight contrast enhancement, suggesting blood-brain barrier rupture secondary to an underlying vasculitis. The presence of reversible, edematous lesions as shown in patient #2 are consistent with areas of brain oedema. The absence of significant disease in most necropsy studies suggests that the reversible high-intensity lesions do not represent infarct or necrosis.^{2,12} Reversible oedema of brain could be induced by acute changes in the blood-brain barrier secondary to vasculopathy, which would reverse when the barrier defect improved.¹² However, the presence of an isolated reversible, edematous lesion in the brainstem has

been previously reported only once in SLE.³ Most patients present with lesions in cortical and sub-cortical brain areas.¹² In addition, the patient had a positive family history of multiple sclerosis. But the observation of negative oligoclonal bands on CSF examination and the appearance of lesions on MRI led to the conclusion that multiple sclerosis was unlikely in this patient. Interestingly, the patient presented with recurrence of the lesion in the brainstem and appearance of new lesions in the cerebral hemisphere after prednisone was tapered. She responded to a new course of prednisone and an increase in the azathioprine dose.

Immunosuppressive therapies with high-dose corticosteroids, azathioprine and cyclophosphamide, mycophenolate mofetil and rituximab have all been used in association with corticosteroids (oral or intravenous pulse therapy) in SLE patients with CNS involvement.¹³ Corticosteroids given at presentation improved the cerebellar manifestations in all patients and could explain the absence of MRI abnormalities in patient #1. But follow-up MRI showed a dilated fourth ventricle, suggesting that a cerebellar involvement was present at the beginning. The rapid improvement observed in our patients after the treatment with corticosteroid corroborated with the diagnosis of an underlying vasculitis. Controlled studies for treatment of CNS manifestations in SLE are rare.¹⁴ Most authors suggest the use of pulse cyclophosphamide in patients with acute CNS manifestations.^{14,15} Because of the risk of premature ovarian failure, patient #2 refused cyclophosphamide. Azathioprine was chosen instead.

The heterogeneous nature of CNS manifestations in SLE suggests that different disease mechanisms may be involved. Deposition of immune complexes in the choroid plexus, the effects of specific antibodies such as anticardiolipin and anti-neuronal antibodies, resulting in direct neural cell dysfunction, and immune-mediated vascular disease have each been invoked as pathogenic.⁹ Large-vessel vasculitis and embolic disease secondary to Libman–Sachs endocarditis has also been described.⁹ However, conventional MRI is normal in most patients and hyperintense white-matter lesions are frequently found in both symptomatic and asymptomatic SLE patients.¹²

Lupus anticoagulant and anticardiolipin antibody have been found to be associated with various neurological manifestations in SLE patients.^{16–18} In addition to thrombotic events, antiphospholipid antibodies have been shown to cross-react with epitopes on CNS phospholipids like sphingomyelin, causing neuronal dysfunction.^{9,17,18} Although previous authors have linked this mechanism to the presence of CNS

manifestations in SLE,¹⁶ we identified anticardiolipin antibodies in only one patient. The remaining two patients had negative anticardiolipin antibodies on several occasions.

Anti-neuronal antibodies have also been associated with CNS involvement in SLE. The presence of such antibodies would be consistent with the absence of extensive infarction, and the presence of reversible oedema of neural tissue, and they are more frequently associated with diffuse, rather than focal NP manifestations in SLE.^{12,18,19} Unfortunately, anti-neuronal antibodies were not measured in our patients.

Although CNS manifestations are often observed in SLE, other causes have to be considered. Differential diagnoses involving the cerebellum include acute disseminated encephalomyelitis, Lhermitte–Duclos disease, diffusely infiltrating glioma or lymphoma, and drug-related inflammatory processes.²⁰ Brain CT is particularly useful in the acute phase to detect acute hydrocephalus, cerebellar edema or brainstem compression. MR imaging is the modality of choice to demonstrate cerebellar pathology, which may remain undetected on CT. Although the imaging appearances may vary considerably, MRI is useful in the diagnosis of acute cerebellar ataxia.²⁰

In addition, acute cerebellar ataxia may occur secondary to paraneoplastic manifestations associated with anti-Hu and anti-Yo antibodies. Unfortunately, investigations for anti-Hu and anti-Yo antibodies were not performed, but our patients were carefully investigated to rule out lung, ovarian and breast malignancies, most commonly associated with these antibodies.²¹

Two deaths were reported in previous series, suggesting that cerebellar involvement is a rare but serious CNS manifestation in SLE.⁹ The predominant histological findings reported in both cases were multiple perivascular hemorrhages and classical vasculitic changes.⁹ All our patients were treated with corticosteroids within 24 h of onset of symptoms. This could explain the good evolution in the three cases. Previous reports have suggested that delay in the initiation of therapy may be associated with poorer prognosis.⁷

In conclusion, we report 3 SLE patients with acute cerebellar ataxia due to an underlying small-vessel vasculopathy. Treatment with immunosuppressants improved clinical and MRI findings.

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