

CASE REPORT

Juvenile systemic lupus erythematosus with primary neuropsychiatric presentation

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SUMMARY

Systemic lupus erythematosus (SLE) is an autoimmune disease with multiple manifestations in several organs and systems. Neuropsychiatric manifestations can occur in 22–95% of paediatric cases, being much less frequent as an initial clinical event. We report a case of SLE, presenting primarily with neuropsychiatric symptoms. An African-descendant 7-year-old girl was admitted with a 4-day history of ataxia, diplopia and morning vomiting, as well as severe headache, psychiatric symptoms and cognitive dysfunction beginning 1 year prior to admission. Brain MRI was suggestive of encephalitis. Investigation excluded infectious aetiology. Immunological markers revealed high titre of antinuclear and anti-double-stranded DNA antibodies. Neuropsychiatric lupus (NPL) was considered, and cyclophosphamide and methylprednisolone pulses were started, with good initial response. Clinical deterioration motivated therapy with azathioprine with subsequent clinical stabilisation and a latent cognitive dysfunction. In unusual encephalitis presentation, a wide range of differential diagnosis has to be considered. Primary NPL presents difficult diagnostic and therapeutic challenges.

BACKGROUND

Systemic lupus erythematosus (SLE) is an autoimmune disease with multiple manifestations in several organs and systems and with a wide range of clinical severity.

The American College of Rheumatology defines the neuropsychiatric manifestations of SLE in 19 different clinical syndromes, which constitute a severe complication of SLE. The nervous system involvement prevalence is estimated in 22–95% of all paediatric SLE cases^{1–5} but is extremely rare as the initial clinical manifestation of the disease.

We report a case of juvenile lupus, presenting primarily with neuropsychiatric symptoms.

CASE PRESENTATION

We report the case of an African descendant, 7-year-old girl, with an unremarkable family history. She was admitted to our hospital with a 4-day history of ataxia, diplopia and morning vomiting. She had a history of severe headache, recurrent vomiting, cognitive dysfunction and psychiatric symptoms, such as auditory hallucination, irritable mood and aggressive behaviour, beginning 1 year prior to admission. She never had seizures.

On clinical examination, she had no fever or meningeal signs; she presented with a broad-based,

unsteady gait, bilateral dysmetria, horizontal nystagmus and hypor reflexia of the lower members. Fundoscopic examination was normal.

INVESTIGATIONS

Laboratory studies showed a normocytic, normochromic anaemia with haemoglobin value of 107 g/l; a normal leucocyte count; a raised erythrocyte sedimentation rate (ESR) of 25 mm/h with a normal C reactive protein (CRP); normal renal function, electrolytes, glycaemia and blood coagulation tests and negative toxicology urine screening.

Brain CT showed bilateral widening of the horizontal sulcus of the cerebellum with doubtful hypodensity in the left cerebellar hemisphere, which led to the diagnostic hypothesis of a cerebellar mass.

For a better characterisation of the brain imaging, a brain MRI was performed which showed multiple cortico-subcortical lesions in both cerebral hemispheres with increased signal intensity in long repetition time sequences, highly suggestive of encephalitis, being acute disseminated encephalomyelitis (ADEM) a less probable diagnosis (figure 1). The EEG showed a diffuse slowing of cerebral activity, without paroxysmal activity.

Lumbar puncture was performed with normal cytochemical markers. Cerebrospinal fluid (CSF) bacteriological, mycological and mycobacteriological cultures were negative. Venereal diseases research laboratory–CSF test was negative. PCR testing for the detection of cytomegalovirus (CMV), Epstein-Barr virus (EBV), varicella-zoster virus (VZV), herpes simplex (HSV) virus type 1 and 2, influenza, enterovirus, paramyxovirus, borrelia, brucella, mycoplasma and mycobacterium tuberculosis in CSF were negative for all the mentioned agents.

CSF immunoelectrophoresis showed intrathecal synthesis of IgM and oligoclonal IgG bands with a normal hematoencephalic barrier.

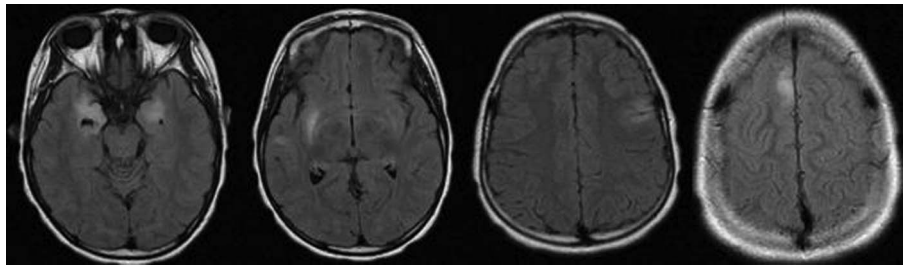
Blood serological testing for syphilis, HIV type 1 and 2, HSV type 1 and 2, CMV, EBV, enterovirus, influenza, adenovirus, brucella, borrelia and mycoplasma were all negative.

Serum ammonia and lactate levels were within normal values.

Immunological investigation revealed normal immunoglobulin and complement levels. Rheumatoid factor, antimitochondrial, anti-ribonucleoprotein, anti-Sjögren's syndrome B (La), anti-Sjögren's syndrome A (Ro), anti-Smith (Sm), anti-cardiolipin and anti-b2 glycoprotein antibodies were all negative. Both antinuclear antibody (ANA) and anti-double-stranded DNA(anti-ds DNA) antibodies were positive. ANA

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Figure 1 First brain MRI: multiple lesions of both cerebral hemispheres, with irregular borders and intermediate intensity on T2-weighted images, located at the grey matter–white matter junction, in both temporal lobes (with hippocampal involvement), right insula, right anterior superior frontal lobe and left frontal lobe; marked cerebellar atrophy. These aspects were described as ‘highly suggestive of encephalitis’.



revealed a high titre in the haemagglutination test of 1 : 5120 and a nuclear mitotic apparatus (NuMA) pattern.

TREATMENT

When encephalitis was initially suspected, empiric treatment was started with ceftriaxone, acyclovir and tuberculostatics in order to cover bacterial, viral and mycobacterial agents. Dexamethasone was also started regarding the possibility of ADEM diagnosis. As the investigation results ruled out the different infectious agents, empirical treatment was stopped. Neuropsychiatric lupus (NPL) diagnosis was then established and immunosuppressive treatment was started. Cyclophosphamide and methylprednisolone were given as intravenous monthly pulses for a 6-month induction while maintaining continuous oral prednisolone. Adjuvant psychotropic treatment with risperidone was also started.

OUTCOME AND FOLLOW-UP

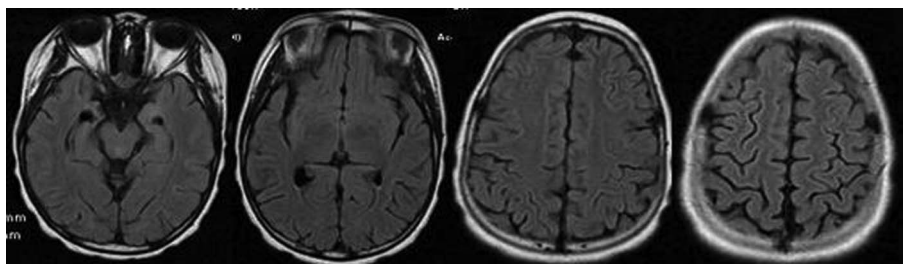
After the first cyclophosphamide and methylprednisolone pulse, there was marked clinical response improvement with regression of the ataxia, dysmetria and nystagmus. After the second pulse, brain MRI was repeated, showing marked improvement with nearly complete regression of all lesions (figure 2).

She completed 6 monthly pulses of cyclophosphamide and methylprednisolone with neurological and psychiatric improvement, maintaining a latent cognitive dysfunction assessed with a score of 60 months in the Griffiths Mental Development Scale.

Six months later, there was marked clinical deterioration with psychomotor lentification, recrudescence of aggressive behaviour and mood disorder, headaches, dysmetria, nystagmus and ataxia with disability in walking independently. It was also noticed de novo lesions of vasculitis and arthritis affecting the small joints of hands and feet. A brain angio-MRI was then repeated, showing marked diffuse cortical atrophy without images of vasculitis.

Psychotropic treatment was adjusted with valproic acid and quetiapine. Azathioprine was started as maintenance therapy, with good clinical response and recovery of autonomous gait.

Figure 2 Brain MRI after two pulses of methylprednisolone and cyclophosphamide: nearly resolution of all lesions; there is only an image of hyperintensity in the inner portion of both temporal lobes, involving the hippocampus, with complete resolution of all the other lesions.



Currently, after 11 months of azathioprine, there is clinical stabilisation, with residual ataxia, dysmetria, psychomotor slowing and an important cognitive dysfunction.

DISCUSSION

SLE affects multiple organ and systems and is more common among women and African descendants.⁶ The central nervous system (CNS) involvement seems to be more serious in children than in adults, leading to higher rates of permanent organ damage.^{7–9} It also seems to occur in earlier stages of the disease in which there may not be involvement of the disease in other organs.

The pathogenic aetiology of NPL is likely multifactorial and may involve a non-inflammatory vasculopathy of the small vessels, non-thrombotic effects of CNS-specific auto-antibodies against neuronal, astroglial or endothelial cells, and inflammation caused by intrathecal production of proinflammatory cytokines.^{10 11}

The American College of Rheumatology classifies the neuropsychiatric manifestations of lupus in 19 different syndromes.¹² According to the prospective study of Sibbitt *et al*,² the most common manifestations in the paediatric population are headache (72%), mood disorder (57%), cognitive dysfunction (55%), seizures (51%), acute confusional state (35%), peripheral nervous system dysfunction (15%), psychosis (12%) and stroke (12%).

In this clinical report, we describe a female African-descendent child (the most prevalent groups in SLE) with primary nervous system involvement presenting with headache, mood disorder, psychosis, cognitive dysfunction and movement disorders, which are common manifestations in NPL. However, these manifestations usually do not occur as the initial clinical presentation of the disease, leading to some difficult diagnostic challenges.

NPL diagnosis must be made based on a high index of clinical suspicion and evidence of the American College of Rheumatology criteria for SLE diagnosis,^{13 14} which may be not present in the early stages of the disease. There are no specific diagnostic tests for NPL. As we can see in this case, an

exhaustive investigation is needed in order to exclude neurological, infectious, metabolic and neoplastic pathologies.

A full blood count may show anaemia, as in this case, leucopenia or thrombocytopenia. The ESR is a sensitive but non-specific indicator of disease activity in SLE. Usually, as we can see here, in active SLE, ESR is raised and CRP is low, which may help to distinguish between bacterial infection and active SLE. The most specific blood tests are the assay of autoantibodies. High titres of ANA (usually >1/300) and positive anti-DNA antibodies are the most specific diagnostic tests for SLE. Anti-NuMA antibodies detection is very uncommon, and is mostly associated with connective tissue disease, mainly SLE and Sjögren syndrome.¹⁵

CSF analysis may be useful in NPL investigation. In this case, CSF immunoelectrophoresis showed oligoclonal bands, as it is reported in 15–80% of NPL cases.¹¹

Brain imaging is important in NPL evaluation and brain MRI is the most sensitive exam.¹¹

Although there are no specific MRI patterns for NPL diagnosis, some characteristic changes have been proposed:^{16–17} acute lesions with irregular borders, intermediate intensity on T2-weighted images with a lacy/filamentous pattern and a semi-lunate shape, located at the grey-white matter junction along sulci and gyri or in the white matter with overlying grey matter hyperintensity. These acute lesions usually resolve with corticotherapy.

One of the most consistent imaging findings is the cortical atrophy. This may be a direct result of lupus acute neuronal lesion, or secondary to microinfarcts or long-term corticotherapy. Total duration of the disease, total steroids dosage and a high number of systemic manifestations outside the CNS, including cognitive dysfunction, seem to be related with hippocampus atrophy in NPL.¹⁸

This clinical report is very interesting in what concerns the brain imaging. It shows the initial acute lesions (located at the white matter, along sulci, with intermediate intensity on T2-weighted images) that resolved with the aggressive corticotherapy and cyclophosphamide. We can also see the progressive atrophy, located initially at the hippocampus, which gradually evolved to a severe atrophy of the entire cortex, related with the subsequent severe cognitive dysfunction presented by the patient.

The therapeutic approach in NPL includes symptomatic and immunosuppressive therapies.

Symptomatic therapy consists in psychotropics (antidepressants and antipsychotics), which may have an important adjunctive role in NPL, allowing the control of affective or psychotic disorder manifestations.¹⁹

The first-line immunosuppressive treatment in NPL treatment is corticotherapy. Although it is the only approved drug for the treatment of juvenile SLE, its well-known side effects and the association with cortical atrophy and steroid-induced psychosis contribute to long-term morbidity in patients with NPL. There are no published NPL treatment trials in paediatric population, but in some studies with NPL adult patients,^{20–21} cyclophosphamide appears as a good therapeutic option, as it seems to have better overall therapeutic control of SLE-related neurological manifestations than methylprednisolone.

Although cyclophosphamide has high successful rates of remission induction, there are some refractory cases and patients who recur after treatment, like the reported one. Azathioprine has been used as an effective and safer second-line immunosuppressive agent for long-term maintenance, with good outcomes in some published cases.^{22–23}

Learning points

- ▶ In an unusual encephalitis presentation, a wide range of differential diagnosis has to be considered.
- ▶ The clinical presentation of neuropsychiatric systemic lupus erythematosus is highly variable and neurological features may precede systemic signs, leading to some difficult diagnostic challenges.
- ▶ Neuropsychiatric lupus requires early and aggressive immunosuppressive treatment.
- ▶ Neurological involvement in systemic lupus erythematosus represents important long-term morbidity with high rates of permanent organ damage.

This clinical report illustrates the diagnostic and therapeutic challenges in juvenile neuropsychiatric lupus. Early diagnosis and aggressive precocious treatment may be important to control neurological sequelae that contribute to the high morbidity of this disease.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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