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CASE BASED REVIEW

# A child with recurrent headache, fever and diffuse meningeal enhancement on MRI

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**Abstract**
Juvenile neurolupus presents primarily with neuropsychiatric manifestations which may also be the initial presentation. Such primary neuropsychiatric SLE (NPSLE) events are a consequence either of microvasculopathy and thrombosis, or of autoantibodies and inflammatory mediators. Diagnosis of NPSLE requires the exclusion of other causes, and clinical assessment directs the selection of appropriate investigations. These investigations include measurement of autoantibodies, analysis of cerebrospinal fluid, electrophysiological studies, neuropsychological assessment and neuroimaging to evaluate brain structure and function. In our patient, the disease presented with chronic headache initially diagnosed as migraine, followed by fever and paraparesis. Fundoscopy showed retinal haemorrhages. Investigations revealed anaemia, neutrophilic leucocytosis, thrombocytopenia and raised inflammatory markers (ESR 119 mm/h CRP 58 mg/L) and high globulin. MRI brain showed diffuse meningeal enhancement resembling meningitis but CSF analysis was normal. ANA and dsDNA were positive with low C3, C4. All diffuse meningeal enhancements may not be meningitis and one needs to corroborate all the clinical, biochemical and imaging analyses to come to a diagnosis.

**Keywords** Cerebral venous sinus thrombosis · Juvenile neurolupus · Systemic lupus erythematosus

## Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterised by the presence of autoantibodies and by intermittent flares and remissions [1]. The clinical presentation is diverse, ranging from a mild disease to severe life-threatening disease involving multiple organs. Approximately 25% [1] of children with SLE have neuropsychiatric manifestations of SLE which are a major cause of morbidity and mortality. Neuropsychiatric symptoms may be the initial presentation of SLE in children. The mortality rate is relatively low, but morbidity may be significant and permanent damage can occur [1, 2]. The most frequent neuropsychiatric manifestations are headache 28.3%, mood disorders 20.7%, cognitive dysfunction 19.7%, seizures 9.9% and cerebrovascular disease 8.0% [3]. SLE can have a myriad of clinical presentations. We present a child with recurrent headache labelled as migraine by the neurologists. With the onset of low-grade fever, cervical lymphadenopathy, she was managed as tuberculosis. Our aim is to share the diagnostic dilemmas that we faced, and the clinical reasoning that was applied to reach the final diagnosis.

## Clinical description

A 10-year-old female presented with recurrent headache since 6 months which was considered migraine, intermittent fever and multiple left cervical lymphadenopathy for 30 days and weakness of both lower limbs for 7 days. Biopsy from the cervical lymph nodes showed reactive lymphocytes and epitheloid granulomas; anti-tubercular therapy (intensive phase) was empirically started 2 weeks prior to admission.

Low-grade, intermittent fever persisted along with headache, with new onset paraparesis. This was followed by an episode of generalised seizure, for which she was admitted at our institute. At admission, she was conscious, alert and oriented. She was hypertensive (BP, 130/90 mm Hg) with weakness of bilateral lower limbs. She was

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febrile (100.8 f), with a heart rate of 110/min; respiration was quiet with no signs of respiratory distress. There was pallor, with left-sided cervical lymphadenopathy. Lymph nodes palpated were small, 8–9 mm, discrete and painless with no discharging sinus. There was no rash. The spine was normal. There were no signs suggestive of meningeal irritation. CNS examination revealed power 3/5 in bilateral lower limbs with mild hypotonia, normal deep tendon reflexes and flexor plantar response. There were no involuntary movements. Sensory system examination was normal. Fundoscopy revealed retinal haemorrhages.

Investigations showed anaemia, leucocytosis (predominantly neutrophilic), thrombocytopenia (90,000/cumm) and raised inflammatory markers (ESR, 119 mm/h; CRP, 58 mg/L; and serum albumin:globulin ratio 0.84).

MRI brain with contrast (Fig. 1 A–C) showed diffuse meningeal enhancement, cerebral venous sinus thrombosis in superior sagittal and right transverse sinuses with mild to moderate dilatation of the ventricles and focal oedema in frontal-parietal regions. FLAIR axial screening of the brain showed irregular focal lesions in the bilateral frontal and parietal regions with oedema around. MRI of the cervical spine showed no obvious abnormality. T2W sagittal screening of the dorsal spine showed ill-defined signal abnormalities in the mid-dorsal region. T2W sagittal screening of the lumbar spine was normal. CSF analysis was near normal with CSF protein 59 mg/dl, glucose 57 mg/dl and mononuclear cells 10/uL. CSF CBNAAT, India ink staining and culture were negative. Evaluation of other organ systems was non-contributory. Based on these suggestive radiological findings (sinus thrombosis) and laboratory parameters (low platelets, inverse serum albumin globulin ratio, persistently elevated ESR and retinal haemorrhages), a detailed evaluation of an underlying autoimmune pathology was undertaken. Results highlighted that ANA (hep-2 cell line) was positive at titre 1:1000 (homogenous pattern) with positive anti-dsDNA, hypocomplementemia (C3, 49.7; C4, 6.9) and positive direct Coombs test. Other parameters of the extractable nuclear antigen (ENA) panel, anti-phospholipid antibody profile and EEG were normal.

Final diagnosis of systemic lupus erythematosus (SLE) was made based on corroborative clinical, laboratory and radiological parameters. The chronological monitoring of biochemical parameters are outlined in Table 1.

Anti-tubercular treatment was stopped and she was initiated on pulse methylprednisolone, monthly pulse cyclophosphamide, hydroxychloroquine, amlodipine and ecosprin. The patient responded well to the management. The headache resolved after 3 days of initiation of treatment and gradually she was able to walk on her own. At present, she is asymptomatic with no neurological deficits. She is being maintained on tapering oral corticosteroids and monthly pulse cyclophosphamide, and remains asymptomatic.

## Discussion

SLE is a multi-systemic autoimmune disease with a higher incidence of neurological involvement in childhood-onset disease. In approximately 75–80% of patients having CNS involvement, it tends to occur during the first year of SLE diagnosis [4–6]. The prevalence of NPSLE in various series ranges from 21 to 95% [4–8]. NPSLE tends to have diverse psychiatric and neurologic symptoms.

Proposed pathogenic mechanisms in NPSLE include the following [9]:

1. Vasculopathy—characterized by hyaline degeneration, proliferation of endothelial cells, thrombosis and gliosis around vessels [10].
2. Various cytokines that alter the blood–brain barrier and recruit more immune cells [11].
3. Autoantibodies—direct reactivity to dsDNA or cross-reaction of anti-dsDNA with N-methyl-d-aspartate (NMDAR) receptors [12]. Anti-phospholipid antibodies (aPL) induce a procoagulant state that produces thrombosis of arterial and venous cerebral vessels leading to cerebrovascular accidents and cerebral venous sinus thrombosis.

Diagnosis of NPSLE proposes a great challenge since we lack a ‘gold standard’ diagnostic test to differentiate NPSLE from non-NPSLE patients with neuropsychiatric manifestations. Hence initial diagnostic evaluation should be similar to that in a non-SLE patient, aiming to exclude secondary causes of neuropsychiatric events. Our patient had presented with low-grade fever, cervical lymphadenopathy, headache, seizures and gradual onset paraparesis. The notable findings in the present case were that the diagnosis of SLE was delayed and she was initially treated as a case of migraine/ tuberculosis.

Following admission, the profound leptomeningeal enhancement on MRIs caused a diagnostic dilemma. The usual causes of leptomeningeal enhancement consist of viral and bacterial meningitis, CNS cryptococcal infection, tumors, haemorrhage and granulomatous conditions like neurosarcoidosis, vasculitis and trauma. The possibility of infectious meningitis or encephalitis was ruled out by a negative CSF study.

Very few cases of CNS lupus with leptomeningeal enhancement on MRI brain have been described. Okano et al. reported 1 case in which a 41-year-old patient was admitted with mental symptoms which improved with steroid therapy [13]. Özlem et al. reported a similar case

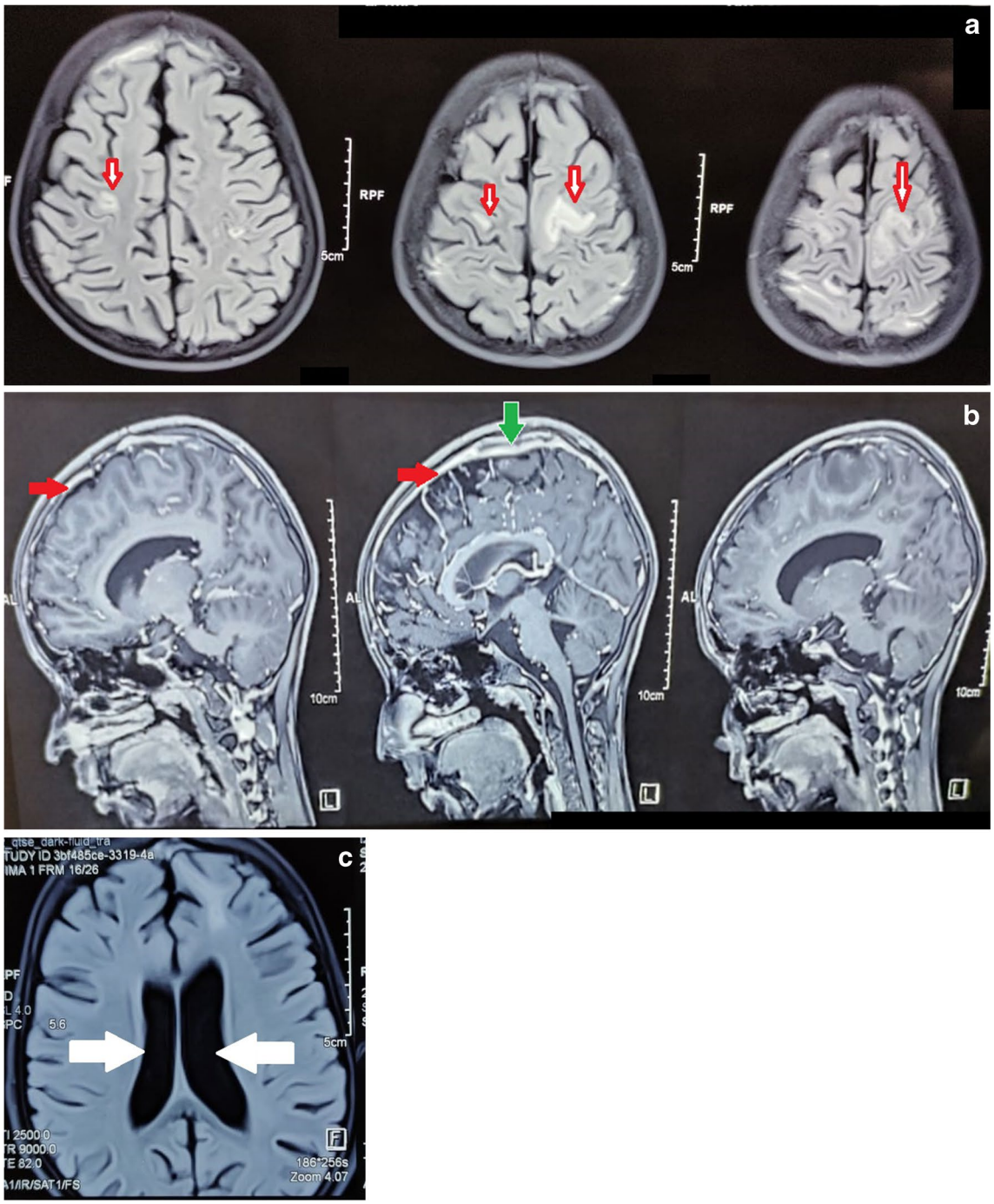


**Fig. 1** MRI brain with contrast showing multiple areas of focal oedema in frontal and parietal regions (**A**), diffuse meningeal enhancement (red arrow) with cerebral venous sinus thrombosis (green arrow) in superior sagittal and right transverse sinus (**B**) with mild to moderate dilatation of ventricles (**C**)

of aseptic leptomeningitis in a 17-year-old female who presented with complaints of vertigo, nausea, vomiting, headache, diplopia, ptosis on the left and weakness of the left leg. A diagnosis of SLE was established, with diffuse leptomeningeal involvement on MRI. The clinical symptoms resolved almost completely after steroid therapy [14].

Also, cerebral venous sinus thrombosis (CVST) is a relatively rare manifestation in SLE. Compared to SLE patients without CVST, SLE patients with CVST had a higher prevalence of thrombocytopenia [15]. Superior sagittal sinus was reported to be the most frequently involved site (62.5%)

**Table 1** Chronological monitoring of blood parameters

| Parameters | Day 1 of admission at outside hospital | Day 5 of admission at outside hospital | Day 1 of admission at our hospital (day 14 of illness) | Day 5 of admission at our hospital |
|---|---|---|---|---|
| Haemoglobin (gm/dl) | 11.6 | 8.4 | 8.5 | 9.2 |
| TLC (cu/mm) | 9100 | 15,000 | 10,000 | 9800 |
| DLC (%)<br>N = neutrophils<br>L = lymphocytes | N35<br>L54 | N76<br>L16 | N78<br>L18 | N53<br>L40 |
| Platelets (cu/mm) | 2.3 | 1.42 | 90,000 | 85,000 |
| CRP (mg/L: cut off < 5) | 9.5 | 31.5 | 57.6 | 16.7 |
| ESR (mm/h) | 34 | 40 | 118 | |
| PT-INR (s) | | 1.38 | | 1.0 |
| Serum albumin (gm/dl) | | | 3.7 | |
| Albumin:globulin ratio | | | 0.84 | |

giving rise to seizures and paralysis, and transverse sinus was the second (41.2 ~ 44.7%) [15, 16].

From this case, we would like to highlight the fact that not all diffuse meningeal enhancements have a CNS infection as its etiology. Lupus, the great mimicker, can too manifest as the same.

**Author contribution** All authors contributed equally.

## Declarations

**Disclosures** None.

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