

CASE REPORT

CEREBRITIS AND NEUTROPENIA IN A CHILD WITH ANA NEGATIVE LUPUS

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Abstract

Objective

Systemic lupus erythematosus (SLE), an autoimmune systemic disease with unknown etiology, affects virtually every part of the body; involvement of the central nervous system (CNS) is one of the major causes of morbidity and mortality in systemic lupus erythematosus (SLE) patients and is the least understood aspect of the disease. neutropenia is very uncommon in childhood lupus. True negative anti nuclear antibody (ANA) tests in patients with lupus are now very rare. The patient reported here was a 12-year-old girl with ANA negative lupus cerebritis who presented with left hemiparesia after a generalized seizure, with neutropenia observed during its course.

Key words: lupus cerebritis, neutropenia, ANA negative lupus, children

Introduction

Systemic lupus erythematosus (SLE), an autoimmune disease involving multiple organ systems, has been defined clinically and is associated with antibodies directed against cell nuclei. Its multisystem manifestations and complications induced by use of immunosuppressive agents make the diagnosis and management of this disorder challenging (1).

Childhood-onset SLE is often reported as being more severe than adult-onset disease. In a published series, a large proportion of both children and adolescents with SLE have been reported with significant renal or central nervous system (CNS) involvement (2). The spectrum of CNS manifestations varies widely, from those with severe, life-threatening presentations, such as transverse myelitis or stroke, to those with more subtle and subclinical abnormalities in neurocognitive function, such as memory, intellect and learning. The different pathogenic mechanisms involved are poorly understood and the therapy available is often disappointing (3). Leukopenia also occurs in up to 50% of patients with systemic lupus erythematosus (SLE) at some point during the course of the disease (4), but neutropenia (<1000 neutrophils/mm³) is very uncommon in childhood lupus (5).

Antinuclear antibody (ANA), an antibody to nucleosomal DNA-histone complexes, is present in over 90% of children and adolescents with SLE (2). True negative ANA test in patients with lupus are now very rare, perhaps 2% of sera at most (6). We report here a case of lupus cerebritis who presented with left hemiparesia after a generalized seizure; this case deserved reporting, because in addition to an unusual clinical presentation, she had also uncommon paraclinical signs such as neutropenia and negative ANA tests.

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Case Report

The patient was a 12-year-old child was admitted due to lethargy and hemiparesia. Her illness began suddenly with a generalized tonic-clonic seizure, lasting about an hour (status epilepticus), following which left hemiparesia and lethargy occurred; she had 3-year history of idiopathic epilepsy (Complex Partial Seizure), that had been controlled by carbamazepine and sodium valproate.

At admission she was lethargic and asthenic with a low-grade fever and normal blood pressure. She had bilateral conjunctivitis and an ulcerated papule at mucocutaneous junction of nasal septum. Bilateral pulmonary fine crackles were present. Cardiac and abdominal examination was normal. There were few ecchymotic lesions on the lower limbs and an upward left plantar reflex.

A complete workup for infections was done except for lumbar puncture (her parents did not consent); broad-spectrum antibiotics and acyclovir were started. Phenytoin was prescribed for seizure control due to patient's low level of consciousness and focal pattern of seizures.

Axial brain CT-scan was normal. Her brain MRI showed diffuse right hemispherical abnormal signals at T2W (figure 1). Electroencephalography showed diffuse theta (θ) waves that were compatible to diffuse parenchymal lesions. In echocardiography only there was a mild tricuspid regurgitation without any vegetation.

Laboratory values in first few days were significant for WBC=5000cells/ μ l (Neutrophil=88), HCT=43% (MCV=83), PLT=112000/ μ l, Reticulocyte count=0.3%. Urea=80mg/dL, Creatinine (Cr) =1 mg/dL, Na⁺=135 mEq/L, K⁺=4 mEq/L, Blood Sugar=84 mg/dL, PT=20.2 sec (control of 13 seconds) (INR=2.2), aPTT=35 sec(control of 26 to 36 seconds), ABG was normal. ESR was 30mm/1h and CRP was positive. Liver function tests were abnormal (SGOT=134 (15-46 U/L), SGPT=57(8-36 U/L), ALP=179U/L). Wright, Widal and PPD tests all were negative. The anti nuclear antibody (ANA) was also negative. Two blood cultures performed were negative after 48 hours.

On the third day of hospitalization (DOH), the patient's renal function worsened (Urea=134 mg/dL, Cr=3 mg/dL). Urine analysis showed a mild hematuria (WBC=1-

2, RBC=6-7, SG=1010). Urine culture was negative. Renal ultrasonography showed normal sized kidneys, but their parenchymal echogenicity was increased.

On the 8th DOH, fever with diffuse purpura and petechia on lower limbs, buttocks and trunk appeared, some being palpable purpuras. She complained from left upper and left lower limb pain. Color Doppler ultrasonography of limb vessels was normal; the following day she became ill and toxic. Edema and limb pain was accentuated. Other positive clinical signs were a moderate fever, bilateral pulmonary fine crackles, facial plethora which was more prominent in cheeks, significant lip edema and a painful edema in her left leg that was compatible with a deep vein thrombosis. One pulse of methyl prednisolone was administered with clinical diagnosis of SLE followed by oral prednisolone after 48 hours. Before corticosteroid administration, serologic tests for connective tissue disorders were controlled. The results were C3=100 (normal range 83 to 177mg/dL), C4=37(normal range 15 to 45mg/dL), ANA=6 u/ml (normal<10), ANCA was negative, anti ds-DNA=64 u/ml (normal<27) ESR=118 mm/1h, Rheumatoid factor was negative and CPK=17U/L.

After steroid infusion, fever, facial plethora, malar rash and lip edema disappeared. Her coughs, pain, edema and petechia in the extremities decreased significantly after 24 hours, and respiratory symptoms and signs also improved. PT and PTT were normal. Renal function tests improved (Urea=29 mg/dL, Cr=0.8 mg/dL). Liver function was still abnormal (AST=92U/L, ALT=96U/L).

On the 19th DOH, neutropenia appeared (WBC=1700/ μ l (Neutrophil=24%, Lymphocyte=68%, Monocyte=8%)). Carbamazepine was discontinued. Because of poor seizure control, Primidone was added to sodium valproate. Bone marrow aspiration reported hypocellular without other abnormalities. Due to accentuation of neutropenia in the following days, granulocyte colony-stimulating factor (G-CSF) was started for two consecutive days. On the 30th DOH, her general condition was very good and vital signs were stable. Her CBC returned to normal and she was discharged with outpatient follow up; at discharge her laboratory tests were as follows: WBC=10200/ μ l (Neutrophil=64, Monocyte=8.8, Eosinophil=0.1), Hb=12.8 g/L, PLT=336000/ μ l, AST=62U/L, ALT=43U/L.

L, ESR=25mm/h ,U/A (SG=1017, protein++, blood+, WBC=4-5/hpf,RBC=9-10/hpf,PH=6,CAST=negative), C3=100 mg/dL, C4=40 mg/dL, Anti Phospholipid Antibody (IgG) =1 (<10 U/mL). ANA was checked that was negative again.

One month after discharge she had improved

significantly and laboratory data were stable except for hematuria and mild proteinuria. According to active urine, azathiopurin was started for her. At present her disease is controlled completely. Her anti-ds DNA level and CBC are within normal ranges now.

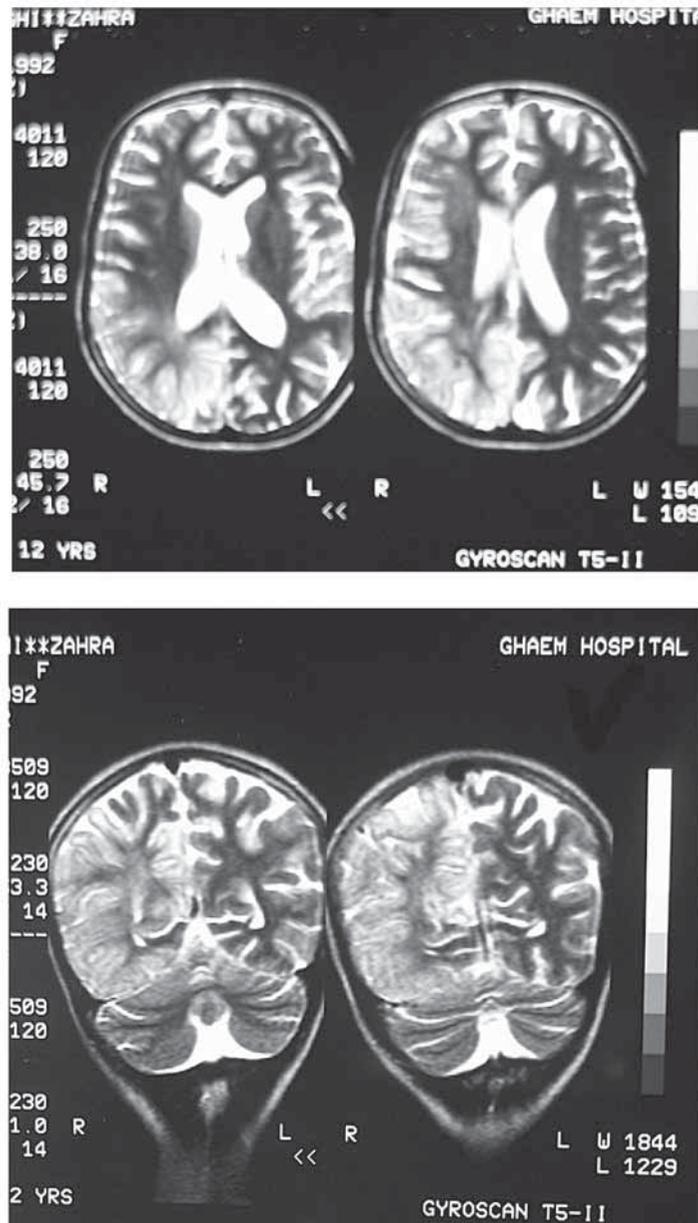


Figure 1: Brain MRI of patient showing diffuse right hemispherical abnormal signals at T2W imaging.

Discussion

This is the rare documented case of cerebritis and neutropenia in a child with ANA negative Systemic Lupus Erythematosus.

Based on leucopenia, positive anti-ds DNA and neurologic manifestations, our patient had only 3 criteria according to the American College of Rheumatology (ACR) criteria for Diagnosis of SLE (7); hence she can be classified as probable SLE. We know that Anti-dsDNA is virtually 100% (96-100) specific for SLE (it is ONLY positive in pts with SLE) (8). Rapid response to corticotherapy, and renal involvement (appearance of proteinuria) in follow up confirmed this diagnosis.

Neurologic complications of systemic lupus cerebritis are not as well known in children as in adults (9). Stroke syndromes secondary to Neuropsychiatric-SLE (NP-SLE) can affect any area of the brain. Strokes usually occur within the first 5 years of the onset of SLE. Cerebrovascular accidents occur in 5-15% of all SLE patients (10). Parikh and colleagues noted neurologic abnormalities in 25 of 108 (23 percent) of a series of patients with onset of SLE before the age of 20 years. Cerebrovascular accidents with hemiplegia or diplegia occurred in 7 of 25 and generalized tonic clonic seizures in 5 (9). In a study by Steinlin and coworkers, CNS abnormalities were noted in 40 of 91 patients, with onset of SLE before 18 years of age. Seizures occurred in 8 patients and were followed by a cerebrovascular accident in 2 (11). In a recent study, twenty-five children with neurologic complications were identified after reviewing the hospital medical records of 86 children with systemic lupus erythematosus. Seven children (28%) had neurologic symptoms at the time of initial diagnosis of systemic lupus erythematosus, sixteen children had seizures, and 12 children had seizures as the initial central nervous system involvement. Five children had diffuse lupus cerebritis, three had stroke, and two had isolated cranial neuropathies (12). According to the history of onset of epilepsy in our patient during her school age period we can suppose that this epilepsy may be secondary to SLE.

Severe CNS disease may present as a focal manifestation, usually thrombotic in nature, or as a diffuse manifestation, consequent to various pathogenic mechanisms, such as vasculitis, antibody mediated

injury, multifocal thrombosis or a combination of these. However, precise attribution to one particular mechanism is not always easy and in some cases, as in our patient, focal (unilateral involvement in MRI) and diffuse manifestations (generalized theta waves in EEG) may coincide in the same patient (3).

The exact pathophysiological process of lupus cerebritis is unknown. The proposed mechanisms are likely due to the assault of several immune system changes, including the following:

1. Circulating immune complexes: The immune complexes, which consist of DNA and anti-DNA, cause an inflammatory response as well as a disruption of the blood-brain barrier. As mentioned anti ds-DNA was positive in our case.
2. Anti-neuronal antibodies: The three identified anti-neuronal antibodies postulated in CNS involvement are lymphocytotoxic antibodies (LCAs), which somehow react with brain tissue and interfere with the neuron's ability to respond. the anti-neuronal membrane antibodies that are targeted directly to neuronal antigens, and the third, the intracytoplasmic antibodies that target the constituents of the neuron cells (i.e., ribosomes and neurofilaments). They are also called anti-SSA or anti-SSB antibodies, seen in 90% of SLE patients with psychosis. These antibodies were not checked in our patient.
3. Antiphospholipid antibodies: The lupus anticoagulant antibody prolongs coagulation. Stroke-like disorders, such as pulmonary emboli, thrombocytopenia, and arterial/venous thrombi, are seen in 30%–50% of SLE patients. In our patient antiphospholipid antibody was negative, two weeks after steroid therapy.
4. Cytokine release: The cytokines trigger edema, endothelial thickening, and infiltration of neutrophils in brain tissue (13).

Suppression of the hematopoietic system, especially of the myeloid lineage, is a severe complication of systemic lupus erythematosus (SLE) (14). In a recent report Euler et al suggested G-CSF as an effective treatment of neutropenia during SLE (15). Our patient also had a rapid and significant response to Granulocyte colony-

stimulating factor (G-CSF) administration.

The pathophysiology of neutropenia in SLE is complex and appears to involve both cellular and humoral immune mechanisms. Increased neutrophil margination and increased peripheral neutrophil destruction, possibly due to autoantibodies directed against polymorphonuclear neutrophils, may contribute to the development of neutropenia in some patients. In addition, suppression of neutrophil production and maturation by T lymphocytes (CD4+, CD8+, and CD57+) and autoantibodies against CD34+ hematopoietic progenitor cells has been demonstrated. If an immune-mediated pathogenesis is suspected, potential targets of immune injury are not only myeloid cells, but also mediators involved in the regulation of myelopoiesis. It has been demonstrated that cytokines and hematopoietic growth factors can indeed be the target of autoimmunity for autoimmune diseases as well for lymphoproliferative disorders (4).

The presence of lupus cerebritis and neutropenia in a patient may suggest a common mechanism. According to the above mentioned mechanisms for neutropenia and lupus cerebritis, one types of anti neuronal antibodies may contribute to both neuronal and neutrophil damage.

In our patient, ANA was reported negative three times during the first month of diagnosis. ANA negative patients with lupus usually fall into three categories: 1) anti phospholipid antibody syndrome, 2) early disease, and 3) previously positive ANA made negative by steroids, cytotoxic drugs, or uremia. Several reports have documented the delayed appearance of ANA in patients suspected of having SLE. Based on results of the Wallace group studies, documenting a mean of 3 to 4 years between onset of symptoms and time of diagnosis, ANA negative SLE is not surprising (6). In our patient the most probable possibility may be the second category i.e. early disease.

Since 1945, many drugs have been reported as having the potential to cause lupus-like illness. The more notorious of these drugs, such as procainamide and hydralazine, are no longer in common use, but others such as anticonvulsants, isoniazid, and chlorpromazine are still widely prescribed. Differentiating drug-induced lupus from idiopathic lupus, or systemic lupus erythematosus (SLE), is important as it has greatly different prognostic

and therapeutic implications. Fever, arthralgia, serositis and ANA occur at least as frequently in drug-induced disease as idiopathic SLE, hematological, renal and CNS involvement and ds-DNA are rare (16). Antibodies against double-stranded DNA (ds-DNA) are both sensitive and specific for active SLE in childhood but may occur in other conditions (2). According to positive ds-DNA and diffuse involvement of brain in EEG and MRI, drug induced lupus is less probable. Although drug induced disease can explain some symptoms and signs of our patient, but according to the persistence of renal problems in follow-up the diagnosis of SLE was confirmed. We must also consider that neutropenia in this patient may be an adverse reaction of carbamazepine. But considering her normal neutrophil count at admission this possibility is less likely.

Liver function tests may be mildly elevated in acute SLE or in response to therapies such as azathioprine or nonsteroidal anti-inflammatory drugs (17). This patient also had a slight elevation in aminotransferases. The partial thromboplastin time (PTT) may be elevated secondary to lupus anticoagulant (antiphospholipid antibody), which is associated with thrombosis. In our patient the PTT was normal, while the prothrombin time (PT) was elevated; we have no specific explanation for this condition. It may be secondary to nutritional state of patient before admission or the mild hepatitis due to lupus.

In summary it is important to consider lupus in differential diagnosis of childhood epilepsy and stroke-like conditions. ANA is not necessarily positive in some patients at onset of SLE. Neutropenia in a patient with lupus cerebritis may suggest the presence of anti neuronal antibodies as the possible mechanism causing cerebritis.

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