Leukoencephalopathy and cerebral edema as the presenting manifestations of SLE in an ANA-negative adolescent female: A case report and review of literature.

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Case Report

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Abstract

Background: Systemic lupus erythematosus (SLE) is an autoimmune disease with various clinical manifestations involving multiple organ systems. Neuropsychiatric manifestations of SLE has been associated with increased morbidity and mortality, thus it is important to recognize and diagnosis the disease entity and treat early. When neuropsychiatric symptoms are involved, typically there are many other systemic features to aid in the diagnosis of SLE. Many autoantibodies have been discovered and are used to help diagnose SLE. The antibody present in most cases of pediatric SLE, as well as in many other rheumatic diseases, is the nonspecific antinuclear antibody (ANA), making it a commonly used screening tool by primary care physicians when evaluating a patient with a possible rheumatic disorder. However, a small subset of SLE patients, 1-5%, present with a negative ANA, and it is important to keep SLE on the differential diagnosis in specific instances when a thorough infectious and neurological workup has been completed and proven to be inconclusive.

Case Presentation: This case involves a Hispanic adolescent female with a negative ANA who presented with diffuse cerebral edema secondary to leukoencephalopathy due to SLE with central nervous system involvement. She had an extensive workup while inpatient involving metabolism, infectious disease, rheumatology, and neurology prior to obtaining the diagnosis of SLE. She was treated with both cyclophosphamide and rituximab and showed improvement.

Conclusions: A review of the literature revealed 8 cases with SLE presenting with or developing diffuse cerebral edema and/or leukoencephalopathy. Our patient's case differs in that she was also ANA negative despite other autoantibody positivity. While she did have low complements and transient leukopenia, she did not present with other signs of organ involvement, which made the diagnosis of SLE with neuropsychiatric involvement quite challenging. We discuss the importance of keeping SLE on the differential despite a negative ANA in complex cases without any other cause and to consider initial screening with not only the ANA but also dsDNA and complements to avoid missed diagnoses.

Background

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease that is characterized by multisystem clinical manifestations and associated autoantibodies, most commonly an antinuclear antibody (ANA) which is present in up to 95-99% of cases of pediatric SLE. Neuropsychiatric involvement in SLE (NPSLE) includes both the central and peripheral nervous system manifestations such as stroke, seizures, myelopathy, chorea, and psychosis, and more subtle findings such as mood disorders, cognitive impairment, and headaches (1-5). Currently, there are 19 NPSLE syndromes as defined by the American College of Rheumatology (4, 6). The prevalence of neuropsychiatric manifestations in various cohorts ranges from as low as 20% to as high as 95% (1, 3, 4). In 40% of patients with SLE-related CNS disease, the initial symptom will be at presentation, and approximately 70% of children will have CNS manifestations within the first year of diagnosis of SLE (4). Neuropsychiatric lupus (NPSLE) has been associated with increased morbidity and mortality, thus is it extremely important to recognize and treat early if present. The most frequent NPSLE manifestations are headaches, psychiatric manifestations (including mood disorders, psychosis, cognitive dysfunction, and acute confusional state), cerebrovascular disease and seizures (4-6).

We present a case of pediatric SLE with primarily neuropsychiatric symptoms but manifesting as cerebral edema secondary to acute leukoencephalopathy. Cerebral edema and leukoencephalopathy have been rarely reported as manifestations of NPSLE in the literature. Many of these patients already carried a diagnosis of SLE, previously had manifestations of NPSLE, and/or had other systemic symptoms related to their disease (Table 1). Furthermore, many of these patients were ANA-positive, which made this case challenging since our patient was ANA negative.

Case Presentation

A 13-year old previously healthy Hispanic female presented with 1 week of nighttime fevers (Tmax 38.8 degrees Celcius orally), 3-4 days of occipital headache with blurry vision, and 1 day of neck pain. Initial vital signs were normal. She was afebrile and awake, alert, and oriented. Her physical exam was significant for grade IV papilledema on ophthalmologic exam. She otherwise had a normal neurologic exam, without meningeal signs. All other systems were normal. Her initial differential was most concerning for infectious, metabolic or neurologic causes. Initial laboratory studies showed leukopenia with a white blood cell count of 3.9k/cum (normal value 5-10 k/cum), normocytic, normochromic anemia (Hgb 10.4), and normal platelet count. Leukopenia was noted on 2 occasions but was not sustained and resolved prior to treatment. Her erythrocyte sedimentation rate (ESR) and C-Reactive protein (CRP) were normal. Her urinalysis was without proteinuria or hematuria. She had normal renal function, electrolytes, toxicology screening, thyroid studies, folate, and vitamin B12 levels. Initial head CT showed diffuse cerebral swelling without herniation. Follow up brain MRI/MRA with and without contrast showed “symmetric diffuse T2 hyperintensity on the white matter of both cerebral hemispheres, brainstem, corpus callosum and cerebellar white matter with mild cerebellar tonsillar ectopia and no mass or midline shift”. This was consistent with diffuse brain swelling secondary to acute leukoencephalopathy. Brain MRA without contrast was without abnormalities. A lumbar puncture was unable to be performed due to severity of cerebral edema.

During her hospitalization, multiple subspecialty services were consulted including neurosurgery, neurology, genetics, metabolism, infectious disease, ophthalmology, and rheumatology. Infectious studies were significant for positive EBV NA IgG, EA IgG, VCA IgG and negative VCA IgM, positive CMV IgG and IgM, and positive Mycoplasma IgG and IgM. Immunofluorescent antibody testing for mycoplasma pneumoniae IgM was negative. Arbovirus panel testing (which includes STL Encephalitis virus, California encephalitis virus, eastern equine virus, western equine virus) was sent twice and was inconclusive on both occasions due to specimen producing a “non-specific fluorescence”. Other infectious studies were negative including serum CMV PCR, EBV PCR, herpes simplex (HSV) virus type 1 and 2, Cryptococcus blood antigen, human Immunodeficiency virus (HIV) 1 and 2 antibody and antigen, influenza A/B, adenovirus, parainfluenza 1-4, chlamydia pneumoniae, bocavirus, coronavirus, RSV A/B, rhinovirus/enterovirus, metapneumovirus, Lyme disease serologies, Brucella IgM/IgG, and West Nile IgM/IgG. TB spot testing was negative. An extensive metabolic workup was done and results were normal, including serum amino acids, urine organic acids, lactate, pyruvate, very long chain fatty acids, lysosomal panel, carnitine, homocysteine, and CK. An MR spectroscopy was completed which showed “elevation of the glutamine/glutamate complex in short echo MRS in both the left frontal lobe and right basal ganglia” without “significant abnormal elevated lactate peaks in the white matter basal ganglia”. Her lab workup did not support a primary metabolic disorder.

She was managed medically for her cerebral edema with sodium supplementation for therapeutic hypernatremia and acetazolamide. She remained afebrile until day 4 of her hospitalization, however on hospital days 5, 6, and 7 she developed fevers. At this time, she was initiated on doxycycline for presumed mycoplasma infection due to positive IgG and IgM mycoplasma titers. On day 7 of her hospitalization she had acute deterioration and became unresponsive and obtunded, requiring emergent intubation. A repeat head CT done at that time showed stable cerebral edema without new changes or herniation. EEG was negative for seizure activity. She was successfully extubated to room air within 24 hours and remained stable throughout the remainder of her hospitalization.

Rheumatology was consulted on day 8 of her admission for concern for CNS vasculitis or other autoimmune etiologies. She had an initial rheumatologic workup that included ANA of <1:40 by immunofluorescence (IF), but elevated anti-dsDNA (82.2), low C3 (21) and low C4 (2). Antiphospholipid antibodies were significant for beta 2-glycoprotein IgA 7.0 (reference range being < 7.0), with beta-2 glycoprotein IgG and IgM negative, anti-cardiolipin antibodies negative, and lupus anticoagulant negative. The hypocomplementemia and positive anti-dsDNA antibody prompted further evaluation, specifically for SLE. Additional lab testing revealed positive Smith (>8), SSA (>8), SSB (1.2, reference range <1.0), RNP (2.1, reference range <1.0), Ribosomal P (>8) and neuronal (>400, reference range 0-54) antibodies. ANA was repeated and again noted to be <1:40 by IF. She was ultimately diagnosed with SLE with CNS involvement. At this point in her disease process she had no other apparent organ involvement or other SLE features.

She was started on treatment for SLE and received 5 days of IV methylprednisolone (1gm) in addition to IV cyclophosphamide (initial dose 500 mg/m2) and IV Rituximab (500 mg/m2). Repeat MRI prior to discharge showed stable cerebral edema and leukoencephalopathy (Figure 1). Her headaches subjectively improved with therapy, and repeat ophthalmologic exam showed improvement of papilledema from grade IV to grade II-III by time of discharge. She was discharged home on day 19 of hospitalization on prednisone 60mg daily, hydroxychloroquine, and acetazolamide, with the outpatient management plan of second Rituximab infusion and monthly cyclophosphamide infusions and with IV solumedrol pulse dose therapy.

Discussion

This case report describes a pediatric patient with a new diagnosis of ANA-negative SLE with the initial findings of diffuse cerebral edema and acute leukoencephalopathy on imaging, characterized symptomatically only by headache, blurry vision and Grade IV papilledema on examination. According to the literature, the finding of diffuse cerebral edema with or without leukoencephalopathy in NPSLE is extremely rare, and if present, develops later in the disease course and typically with other systemic signs of the disease. SLE patients with concern for neuropsychiatric involvement most commonly present with headaches, seizures, stroke, depression, and/or cognitive dysfunction as the sign of central neurologic involvement (4-6). It is uncommon to see diffuse cerebral edema with leukoencephalopathy as the primary finding of CNS disease in SLE and no other signs of systemic disease. There have been case reports of patients with isolated intracranial hypertension as the only sign of neuropsychiatric lupus, and a few with intracranial hypertension with associated leukoencephalopathy (see table 1), but we were unable to find an instance of a patient with isolated diffuse leukoencephalopathy as the only presenting sign of lupus upon initial diagnosis. Many other patients described had other systemic signs/symptoms and already carried the diagnosis of SLE. Furthermore, most

cases in the literature had a positive ANA in their workup to further assist in the diagnosis of SLE. Additional risk factors associated with development or worsening of NPSLE include generalized SLE activity or damage, history of previous or concurrent other major NPSLE, and antiphospholipid antibodies (3, 4). Our patient did not have any of these risk factors.

As shown in Table 1, most of the case reports reviewed described intracranial hypertension with or without leukoencephalopathy in 5 of 8 adult patients (7-15). Of the three cases that were children (ages, 7y, 11y, and 12y), at least two of them had a positive ANA (one patient's ANA result was not mentioned in the case report), and one out of the three pediatric cases had a previous diagnosis of SLE. All cases reported other clinical manifestations of SLE in addition to CNS involvement, unlike our patient. Imaging findings reported were consistent in showing diffuse hyperintensities on MRI suggestive of leukoencephalopathy, similar to our patient. Patient outcome across case reports were variable, with some making a full recovery and others unfortunately succumbing to their disease. Various methods were used for treatment, with high-dose steroids being a unifying treatment choice.

The pathophysiology has been explored in SLE cases of idiopathic intracranial hypertension (IIH) with diffuse leukoencephalopathy. There are multiple theories, including the possibility of immune-complex mediated damage, autoantibodies interacting (either directly or indirectly) with antigens on neuronal cell membrane, intrathecal cytokine production, and microangiopathy (1, 2). Various autoantibodies have been found to have a relation with increased incidence of NPSLE, including anti-phospholipid antibodies, anti-ribosomal P antibodies, and microtubule-associated protein-2 antibodies. These autoantibodies have been theorized to target endothelial cells, prostacyclins, protein C-S complex, and platelets, leading to acute impact on coagulation and chronic proliferative vasculopathy (2). Cranial MRI is currently the anatomic imaging modality of choice for these patients, and displays high sensitivity but low specificity for NPSLE. Most NPSLE patients (40-80%) show small punctate focal lesions in periventricular and subcortical white matter areas on imaging, not necessarily associated with diffuse brain edema as was the case with our patient, and cerebral angiography typically is normal (2). A vast array of findings in the literature make it very difficult to determine exact pathophysiology of diffuse leukoencephalopathy with associated cerebral edema. Pathophysiology is likely multifactorial, involving autoantibody reactivity as well as an underlying propensity for cerebral damage.

Interestingly, our patient is also unique in that she was diagnosed with SLE but had a negative ANA test noted on two occasions during her hospitalization and again after discharge. Additionally, she had a positive dsDNA antibody, multiple antibodies to extractable nuclear antigens (ENA) and low complements. When considering our patient's infectious workup, this was likely representative of a diffuse polyclonal B-cell response and cross-reactivity resulting in false positive mycoplasma, EBV,CMV and the abnormal fluorescent for California virus, western and eastern equine viruses, and St. Louis virus antibodies. Additional autoantibody testing was not pursued until a thorough infectious, metabolic and neurologic workup was negative or inconclusive. Ultimately, it was the evidence of hypocomplementemia and a highly positive dsDNA antibody that led to the additional autoantibody testing and ultimately her diagnosis. She had multiple positive ENA antibodies (Smith, RNP, SSA, SSB), ribosomal P antibody and neuronal antibody. Our patient is a unique representation of SLE, but her case may suggest that for some specific instances, where thorough infectious and neurological testing are inconclusive, that ANA testing alone may not be sufficient for screening for SLE. There are few descriptions of such cases in the literature but some do describe the importance of screening patients with suspected

rheumatologic disorders with more than just the basic ANA screen (16). Testing with other markers specific to SLE disease activity, e.g. complement levels and anti-dsDNA, proved critical in the diagnosis of SLE for our patient.

Several reasons are given in various studies as to why some patients with the diagnosis of SLE have negative ANA screenings. These include the prozone or hook effect, the entity of an ANA negative SLE patient, or technical issues with the ANA screen itself (17). We believed the prozone effect may have been responsible for our patient's negative ANA result. This occurs in cases of very high antibody concentrations. It is thought to be responsible for negative immunoassays that involve the detection of antigen-antibody complexes (18). With these assays, there is dependence on agglutination to reveal the presence of the antibody and thus confirm a positive test. With the prozone effect, the antibody concentration is so high, it interferes with the clumping of antigen-antibody complexes resulting in a seemingly negative result. ANA testing was repeated in our patient on two occasions and was "negative" in both cases. With the prozone effect suspected to be responsible for this result, it is likely future ANA tests of our patient will remain negative, though could turn positive with treatment of the patient's disease and reduction in antibody burden.

Conclusion

Our patient presented with a very rare form of NPSLE, and in addition was found to be ANA-negative on serological testing making this a challenging diagnosis of SLE. Isolated diffuse cerebral edema and leukoencephalopathy in SLE has rarely been reported in the literature. Resolution is possible with appropriate therapy, but mortality is a major concern due to the diffuse and severe vasogenic edema with lymphocytic infiltration. Therefore, it is important to recognize diffuse cerebral edema with leukoencephalopathy as being on the differential for possible NPSLE manifestation, despite ANA results, in order to improve patient outcomes.

List Of Abbreviations

ANA: antinuclear antibody

NPSLE: neuropsychiatric systemic lupus erythematosus

SLE: systemic lupus erythematosus

Declarations

- **Ethics approval and consent to participate:** not applicable
- **Consent for publication:** Obtained from patient's mother
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- **Authors' contributions:**
    - AT: Background literature search regarding NPSLE, Abstract, Background section, Conclusions section, evaluation of case reports, importation of pictures and tables, reviews/edits with Melissa Oliver.

- RB: Case Presentation section and revision
- CK: Background literature of prozone effect and negative ANA and revision
- MO: Obtained consent for participation and publication from patient's mother, reviews/edits of case report write-up, guidance regarding journal for submission and appropriate source citation

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Table

Table 1: Historical SLE cases in the literature with diffuse leukoencephalopathy.

Patient (ref)	Age/Sex at presentation	Initial Presentation	Previous diagnosis of SLE	Previous neurological involvement	Neuroimaging	Positive ANA?	Treatment	Outcome
1 (7)	38yo/F	Severe headache, syncope	YES	NO	CT: diffuse cerebral edema MRI: diffuse white matter hyperintensities	YES (1:2560)	3 day pulse-dose steroids→ oral prednisone, plaquenil	Herniation → death
2 (8)	11yo/F	Malar rash, photosensitivity, prolonged fever, hemolysis, generalized convulsions, unconsciousness	NO	N/A	MRI: high signal intensity in b/l basal ganglia and thalami, hyperintensities in deep white matter, pons, b/l caudate heads, putamens, thalami	Unknown	3 day pulse-dose steroids, IV 500 mg/day methylprednisolone	Return to baseline 1 year after insult
3 (9)	12yo/F	HA 1 mo, progressive vomiting 1 week, abducens palsy 5 days	YES	NO	CT: Diffuse white matter hypodensity without ventricular dilatation. MRI: diffuse high-intensity signal	YES (1:320)	3 day pulse-dose steroids w/steroid taper, ranitidine, hydroxychloroquine 200mg.	No further recurrence, stable neurologically
4 (10)	35yo/F	Headache, mild Papilledema, skin eruption, fever	NO	N/A	MRI: diffuse hyperintense white matter lesions	YES	Unknown	Unknown
5 (11)	49yo/F	5wk constant HA, AMS, somnolence	YES	YES	CT: diffuse cerebral edema, small SAH MRI: diffuse sulcal hyperintensity	Unknown	Mannitol, 7 day high-dose steroids, IVIG, steroid taper	4 weeks from discharge, no recurrence
6 (12)	28yo/F	fever, malaise, facial edema, diplopia	NO	N/A	MRI: asymmetrical, multifocal high signal intensity lesions in subcortical white matter Gadnolinium: leptomeningial enhancement	Unknown	3 days high-dose methylprednisolone	Unclear
7 (13)	7yo/F	4 day ataxia, diplopia, morning vomiting; 1yr hx	NO	N/A	CT: bilateral widening of the horizontal	YES (1:5120)	Methylprednisolone pulse monthly, Cyclophosphamide	stabilization w/residual ataxia, dysmetria,

		of HA, recurrent vomiting, cognitive dysfunction			sulcus of cerebellum MRI: multiple cortico-subcortical lesions in both cerebral hemispheres with increased signal intensity.		monthly, continuous oral prednisolone	psychomotor slowing.
8 (14, 15)	34 yo/F	headache, swelling of the extremities, joint pain for 1 month. Bilateral papilledema on exam.	NO	N/A	CT: Extensive cerebral edema MRI: diffuse white matter lesions; MRA/MRV normal.	YES (1:10000)	Unclear	Unclear

Figures

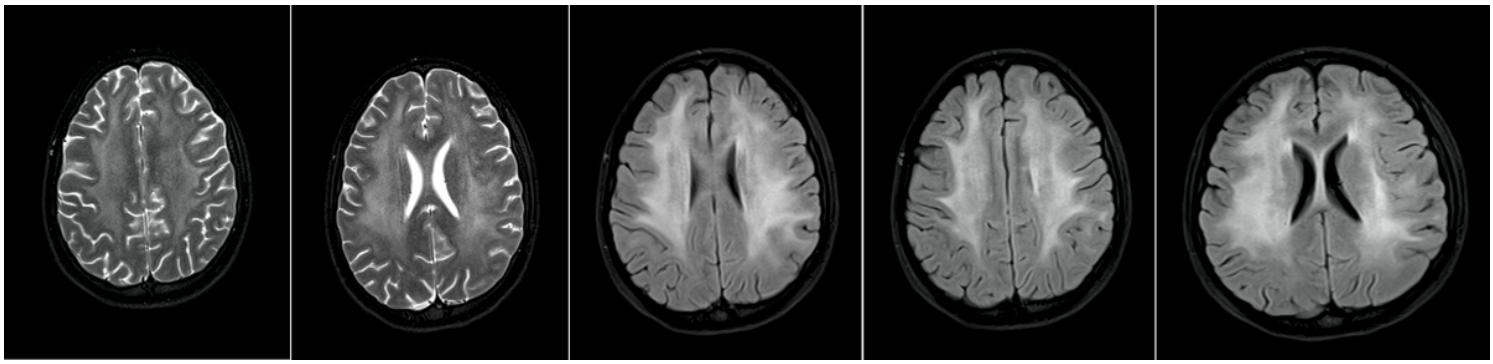

Figure 1

MRI brain with/without contrast. Figure 1 formal read: “Symmetric and confluent T2 intensity within white matter. Involvement of the corpus callosum splenium, internal and external capsule, brainstem at the dorsal tegmental tracts of the pons. Moderate degree of gray matter involvement at the anterior temporal lobe on the right and posterior left frontal lobe around the area of the precentral gyrus. No abnormal areas of reduced diffusion”. MRI shows stable cerebral edema and leukoencephalopathy after 5 days IV methylprednisolone, 1x dose IV cyclophosphamide, and 1x dose IV Rituximab.