



## Wolves in the brain - A rare case of neuropsychiatric lupus

**Abdul S. Mohammed, Prajwal Boddu, Abdalla Hassan, Punam Rajput, Dennis Levinson**

*Advocate Illinois Masonic Medical Center, Department of Internal Medicine, 2356 North Elston Avenue, # 306, Chicago, Illinois. 60614*  
*Corresponding email: [abdalla.hassan@advocatehealth.com](mailto:abdalla.hassan@advocatehealth.com)*

### ABSTRACT

21 year old female with no significant past history presented with altered mental status as noted by her family members. Two days prior to presentation, she started becoming increasingly restless, tearful, loud and irritable. Social or functional status has been reported as well. Of note, she was evaluated for a skin rash involving her mouth, palms and soles two month prior to presentation and was diagnosed with possible hand-foot-mouth disease. On admission, patient vital signs were notable for. A Petechial rash was noted in the mouth, palms and soles bilaterally. Mental status examination was notable for severe agitation, labile mood, tangential thought process and delusions. Initial laboratory studies were significant for white blood count of  $2100/\text{mm}^3$ , red cell count of  $3.24/\text{mm}^3$  and platelets of  $77000/\text{mm}^3$ . EKG confirmed sinus tachycardia. Urine drug screen was negative. Lumbar puncture showed normal CSF cell count was normal with normal protein. Patient was started on quetiapine and Haldol. Further laboratory testing revealed erythrocyte sedimentation rate of 24 mm/h, positive ANA with titer of 320, Anti dsDNA of  $>300$ , low C3 and C4 complement level of 38 mg/dl and 3 mg/dl respectively. MRI and MRA were normal and EEG revealed mild diffuse background slowing indicating mild diffuse cerebral dysfunction. Rheumatology was consulted due to concern for lupus cerebritis based on high ANA titers, evidence of vasculitis on skin examination, abnormal EEG and exclusion of other more common etiologies. Patient was started on 1 gram methylprednisolone after which she showed considerable improvement in mentation with normalization of her thought content and process. Our case also illustrates the importance of maintaining a high degree of clinical suspicion of NPSLE even with a paucity of evidence of clinical systemic activity.

**Keywords:** Neuropsychiatric lupus; Lupus cerebritis; altered mental status

### INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease predominantly affecting women with a prevalence of 20 to 150 cases per 100,000 (1-3). Neuropsychiatric lupus (NPSLE) is the most prevalent manifestation of lupus affecting 14% to over 80% adults (4-6) and is associated with increased morbidity and mortality. Though rheumatologic diseases are difficult to diagnose, a delay may lead to serious consequences. We present the case of a 21 year old female who did not receive timely treatment due to a delay in diagnosis of SLE which led to patient presenting with NPSLE and requiring ICU admission due to sudden alteration in mental status. The American College of Rheumatology (ACR) has identified 19 different ways that lupus can affect nervous system, including the brain. This complication of lupus is known as neuropsychiatric lupus, or NPSLE. Compiled research suggests that as many as 90 percent of adults, adolescents, and children with lupus will at some time experience the devastating effects of NPSLE (7).

Despite this, involvement of the Central nervous system is one of the least understood areas in rheumatology at the moment. Even after decades of extensive research, the mechanisms of how lupus attacks the nervous system or how

to prevent damage is unclear. The most common complication of NPSLE is cognitive dysfunction, meaning difficulty concentrating or reasoning and problems with memory and recall. These symptoms can disrupt all aspects of life, including the ability to plan, work, organize, and learn, visual-spatial processing, and language. For children and adolescents especially, this effect of NPSLE on school performance is a major concern. Added to this burden is that NPSLE occurs frequently, early in the course of the disease, and with great severity in children with lupus.

Yet other symptoms can be life-threatening, including seizures and strokes. These manifestations can be a major cause of illness, severely diminished quality of life, and even brain damage and death (8).

### **CASE PRESENTATION**

21 year old female with no significant past medical history presented to our emergency department for altered mental status as noted by her family members. Two days prior to presentation, she started becoming increasingly restless, tearful, loud and irritable. She was also noticed by her family to be pacing up and down in her room, speaking gibberish, disoriented to her surroundings and refusing to eat or shower. Collateral history from the father revealed that the patient did suffer a decline in her social or functional status prior to this episode. Patient's father did not endorse any prior history of psychiatric problems in the patient or any of the family members. Of note, she was evaluated for a skin rash involving her mouth, palms and soles two month prior to presentation and was diagnosed with possible hand-foot-mouth disease. There was no evidence of illicit drug use. On admission, patient had stable vitals but for tachycardia with heart rate around 140/min. A Petechial rash was noted in the mouth, palms and soles bilaterally. Mental status examination was notable for severe agitation, labile mood, tangential thought process and delusions. Initial laboratory studies were significant for white blood count of  $2100/\text{mm}^3$ , red cell count of  $3.24/\text{mm}^3$  and platelets of  $77000/\text{mm}^3$ . EKG confirmed sinus tachycardia. Urine drug screen was negative. CT scan of the head was negative for acute intracranial process. Lumbar puncture was performed due to concern for possible encephalitis but the CSF cell count was normal with normal protein. Patient was later transferred to intensive care unit for further monitoring and works up of sudden alteration in mental status. Neurology, infectious disease and psychiatry were consulted. Patient was started on quetiapine and Haldol. Further laboratory testing revealed erythrocyte sedimentation rate of 24 mm/h, positive ANA with titer of 320, Anti dsDNA of  $>300$ , low C3 and C4 complement level of 38 mg/dl and 3 mg/dl respectively, ribosomal P protein of 6.8, RNP Ab of  $>8$ , Smith antibody of  $>8$ , chromatin Ab  $>8$  and SM/RNP Ab  $>8$ . Extensive laboratory testing was negative for herpes simplex, EBV, HIV, Lyme disease, Coxsackie, Bartonella, West Nile virus. NMDA receptor antibody IgG was  $<1:10$ . Blood and urine cultures were negative. MRI and MRA were normal and EEG revealed mild diffuse background slowing indicating mild diffuse cerebral dysfunction. Rheumatology was consulted due to concern for lupus cerebritis based on high ANA titers, evidence of vasculitis on skin examination, abnormal EEG and exclusion of other more common etiologies. Patient was started on 1 gram methylprednisolone after which she showed considerable improvement in mentation with normalization of her thought content and process. She was diagnosed with mood disorder secondary to NPSLE based on the absence of a history of psychiatric illness, lack of a prodromal period, the sudden onset of behavioral alteration and rapid response to medical pharmacotherapy. She was switched 3 days later to oral prednisone and hydroxychloroquine.

### **DISCUSSION**

In 1999, the American College of Rheumatology (ACR) helped standardize determination of neuropsychiatric manifestations in SLE by establishing case definitions for 19 neuropsychiatric syndromes, dividing them into two broad categories: central and peripheral (9). Since our patient did not have a previous diagnosis of SLE, we first had to confirm the diagnosis of SLE based on the ACR criteria (10). Our patient had oral ulcers, hematologic abnormalities leukopenia and thrombocytopenia with laboratory evidence of elevated ANA titer, positive Anti Smith and Anti ds DNA antibodies which meets the diagnostic criteria for SLE.

Once the diagnosis criteria of SLE were met we excluded all the diseases that could have been causing the presenting symptoms of acute alteration in mental status and psychosis in our patient. ACR criteria for NPSLE requires at least one of the 19 case definitions to be met to diagnose NPSLE. Our patient did have acute confusional state and psychosis which was confirmed on initial evaluation by our psychiatry department. The next step was to determine the etiology of neuropsychiatric manifestations as to having a functional or organic basis. The diagnosis of NPSLE is a clinical challenge and needs to be made on a case-to-case basis after careful exclusion of other possible etiologies and supportive evidence from serological and neuroimaging studies. Various etiological

mechanisms have been proposed to be causal to NSPLE including autoantibody, vasculopathic and inflammatory-cytokine (11).

Various serological markers have been proposed to be associated with CNS lupus, most notably anti-Ribosomal NP. However, a recent meta-analysis reported anti-RNP to have limited specificity of 80% for NPSLE (14). Our patient had normal CRP and ESR (0.3, 24), uncharacteristic of an actively inflammatory state. Studies have noted that neurological manifestations can occur even in the absence of clinical systemic activity and that there are no significant difference in clinical characteristics between NPSLE patient and a SLE patient without neuropsychiatric manifestations suggestive of the fact that no clinical factors predict NPSLE (12,13)

MRI imaging is very sensitive and is the imaging study of choice for detecting subtle vascular ischemic lesions noted in CNS lupus characteristically showing multiple, small, punctate areas of increased signal at periventricular or subcortical white matter of both cerebral hemispheres (14). However, studies have shown normal MRI scans in upto 40% of patients with a wide variety of 1999 ACR-defined NPSLE syndromes (15). NPSLE patients with no findings on the conventional MRI scans may have detectable abnormalities on more advanced quantitative MRI techniques including Magnetic resonance spectroscopy and Magnetic transfer imaging(16). Using MTI, diffuse grey matter damage has been observed reflecting neuronal injury from possible anti-neuronal antibody mediated processes undetectable on the conventional MRI scans (20). Studies have noted EEG to be 80% sensitive in SLE patients irrespective of CNS lupus activity, with delta and theta wave activities observed to be unique findings (17). EEG in our patient revealed presence of mild diffuse background predominating in the delta and theta range indicating mild diffuse cerebral dysfunction. Our patient improved considerably after receiving methylprednisolone which corroborates with the suspected diagnosis of NPSLE.

### CONCLUSION

NPSLE is major diagnostic challenge that should be made on a case to case basis after careful exclusion of other etiologies and supportive evidence from serological markers, CSF analysis, and neuro-imaging studies. Our patient met the ACR 1999 criteria for NPSLE and had high ANA titers, positive anti-RNP, EEG abnormalities. MRI was normal which might have warranted more advanced MRI imaging techniques given the fact that significant percentages of NPSLE patients have undetectable abnormalities on the conventional MRI scans. However, these imaging modalities might not be available in most treatment centers and should not delay treatment in cases with high clinical suspicion. Our case exemplifies the challenges faced in making a diagnosis and determining the basis for the underlying psychosis of NPSLE. Our case also illustrates the importance of maintaining a high degree of clinical suspicion of NPSLE even with a paucity of evidence of clinical systemic activity.

### REFERENCES

- [1] Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Lawrence RC<sup>1</sup>, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH, Heyse SP, Hirsch R, Hochberg MC, Hunder GG, Liang MH, Pillemer SR, Steen VD, Wolfe F. *Arthritis Rheum.* 1998 May; 41(5):778-99.
- [2] Prevalence of adult systemic lupus erythematosus in California and Pennsylvania in 2000: estimates obtained using hospitalization data. Chakravarty EF<sup>1</sup>, Bush TM, Manzi S, Clarke AE, Ward MM. *Arthritis Rheum.* 2007;56(6):2092-4.
- [3] Understanding the epidemiology and progression of systemic lupus erythematosus. Pons-Estel GJ<sup>1</sup>, Alarcón GS, Scofield L, Reinlib L, Cooper GS. *Semin Arthritis Rheum.* 2010;39(4):257-68.
- [4] The prevalence of neuropsychiatric syndromes in systemic lupus erythematosus. Ainiola H<sup>1</sup>, Loukkola J, Peltola J, Korpela M, Hietaharju A. *Neurology.* 2001;14(3):496-500.
- [5] Neuropsychiatric syndromes in lupus: prevalence using standardized definitions. Brey RL, Holliday SL, Saklad AR, Navarrete MG, Hermosillo-Romo D, Stallworth CL, Valdez CR, Escalante A, del Rincón I, Gronseth G, Rhine CB, Padilla P, McGlasson D. *Neurology.* 2002;58(8):1214-20.
- [6] Prospective analysis of neuropsychiatric events in an international disease inception cohort of patients with systemic lupus erythematosus. Hanly JG, Urowitz MB, Su L, Bae SC, Gordon C, Wallace DJ, Clarke A, Bernatsky S, Isenberg D, Rahman A, Alarcón GS, Gladman DD, Fortin PR, Sanchez-Guerrero J, Romero-Diaz J, Merrill JT, Ginzler E, Bruce IN, Steinsson K, Khamashta M, Petri M, Manzi S, Dooley MA, Ramsey-Goldman R, Van Vollenhoven R, Nived O, Sturfelt G, Aranow C, Kalunian K, Ramos-Casals M, Zoma A, Douglas J, Thompson K, Farewell V; Systemic Lupus International Collaborating Clinics (SLICC). *Ann Rheum Dis.* 2010;69(3):529-35.

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- [7] Systemic lupus erythematosus with neuropsychiatric manifestation incurs high disease costs: a cost-of-illness study in Hong Kong. Zhu TY<sup>1</sup>, Tam LS, Lee VW, Lee KK, Li EK. *Rheumatology (Oxford)*. 2009;48(5):564-8.
- [8] Neurologic manifestations of systemic lupus erythematosus in children and adults. Muscal E, Brey RL. *Neurol Clin*. 2010;28(1):61-73.
- [9] Neuropsychiatric syndromes in patients with systemic lupus erythematosus and rheumatoid arthritis. Hanly JG<sup>1</sup>, Fisk JD, McCurdy G, Fougere L, Douglas JA. *J Rheumatol*. 2005;32(8):1459-6.
- [10] Dilemmas in neuropsychiatric lupus. Kovacs JA, Urowitz MB, Gladman DD. *Rheum Dis Clin North Am*. 1993;19(4):795-814.
- [11] The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum*. 1999;42(4):599-608.
- [12] Hanly JG. Neuropsychiatric lupus. *Rheum Dis Clin North Am*. 2005;31(1):273-298.
- [13] Accuracy of anti-ribosomal P protein antibody testing for the diagnosis of neuropsychiatric systemic lupus erythematosus: an international meta-analysis. Karassa FB, Afeltra A, Ambrozic A, Chang DM, De Keyser F, Doria A, Galeazzi M, Hirohata S, Hoffman IE, Inanc M, Massardo L, Mathieu A, Mok CC, Morozzi G, Sanna G, Spindler AJ, Tzioufas AG, Yoshio T, Ioannidis JP. *Arthritis Rheum*. 2006;54(1):312.
- [14] Aggressive CNS lupus vasculitis in the absence of systemic disease activity. C. M. Everett<sup>1</sup>, *Rheumatology* (2008) 47 (1): 107-109
- [15] Neuroimaging in neuropsychiatric systemic lupus erythematosus. Sibbitt WL Jr, Sibbitt RR, Brooks WM. *Arthritis Rheum*. 1999;42(10):2026.
- [16] Griffey RH, Brown MS, Bankhurst AD, et al. Depletion of high-energy phosphates in the central nervous system of patients with systemic lupus erythematosus, as determined by phosphorus-31 nuclear magnetic resonance spectroscopy. *Arthritis Rheum* 1990; 33:827.
- [17] Selective gray matter damage in neuropsychiatric lupus. Steens SC<sup>1</sup>, Admiraal-Behloul F, Bosma GP, Steup-Beekman GM, Olofsen H, Le Cessie S, Huizinga TW, Van Buchem MA. *Arthritis Rheum*. 2004;50(9):2877-81.