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ORIGINAL PAPER

A study of Neurological manifestations in systemic lupus erythematosus

Das Marami[1], Singh SK[2], Goswami Munindra[3], Kayal AK[4], Basumatary LJ[5], Borah Papori[6]

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ABSTRACT

Objectives: *To analyze clinical, immunological, electrophysiological and radiological spectrum of the patients of Systemic Lupus Erythematosus (SLE) presented with neurological manifestations in Gauhati Medical College & Hospital, Guwahati.* ***Materials and methods***: *Hospital based prospective study carried out in Neurology department. Diagnosed cases of SLE who presented with neurological manifestations at the time of diagnosis or develop during the course of the disease were included in the study. Subjects undergone detailed clinical, immunological and laboratory analysis & appropriate statistical methods were applied as required.* ***Results***: *A total number of 82 cases were evaluated. Median age of presentation was 22 years with female to male ratio 3.5:1. CNS diseases were predominant in 72(87.8%) and rests were symptoms referable to PNS. Among the CNS diseases most common was seizure in 28(38.9%) followed by acute confusional state, headache, myelopathy, stroke, psychosis. Among PNS diseases, most common was polyneuropathy in 12(63.2%), followed by cranial neuropathy, plexopathy, AIDP and myasthenia gravis. ANA was found to be the most common autoantibody in 81(98.7%) cases followed by Anti-ds DNA. Mean SLEDAI was 8.9 ± 5.7. Disease activity is significantly more in CNS as compared to PNS diseases. It was found that SLEDAI, values on 4-point liker scale and SLICC/ ACR damage index significantly decreased at 6 months during follow up.* ***Conclusion***: *Neurological manifestations are not uncommon in SLE. They correlate with disease activity, and results in high morbidity if not diagnosed early. It is necessary to detect subclinical NPSLE by having a high index of suspicion, and evaluation by clinical, immunological, neuroimaging and neurophysiological tests.*

Keywords: *Acute confusional state; neurolupus; seizure.*

INTRODUCTION

Systemic lupus erythematous (SLE) is an autoimmune disease in which organs and cells undergo damage initially mediated by tissue binding autoantibodies and immune complexes.[1] People of all genders, ages and ethnic group are susceptible, but it frequently affects women of child bearing age group. The prevalence is approximately 130/100000 in United States, with African Americans, Hispanic and Asians more frequently affected than non-hispanic whites.[2] In Indian population the prevalence is 3/100000.[3] The nervous system is commonly affected in both children and adults with SLE. It is also associated with a worse prognosis and more cumulative damage in children[4] and adults.[5]

Neuropsychiatric symptoms can be among the earliest manifestations of SLE, and some reports suggest up to 40% of neuropsychiatric symptoms appear during the first year of SLE diagnosis.[4] NPSLE symptoms can be a devastating manifestation of SLE, and a recent study demonstrated a standard mortality ratio of 9.5, markedly with acute confusional state.[5]

Autoantibodies are central for the diagnosis of SLE; however, note that the prevalence of anti-nuclear antibodies in healthy

Address for correspondence:
[1]Associate Professor
Email: moromi13das@yahoo.co.in
Mobile: +919954742007
[2] Senior Resident
[3]Professor & Head (**Corresponding author**)
Email: goswamimunindra@yahoo.com
Mobile: +919435014264
[4]Retired Professor, [5]Assistant Professor, [6]Assistant Professor
Department of Neurology
Gauhati Medical College & Hospital, Guwahati, Assam

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subjects may reach 20% at certain ages[6] and many non-SLE patients with mild CNS symptoms, such as weakness or headache, might have weakly positive anti-nuclear antibodies testing. For patients with established SLE, several autoantibodies were found to correlate with neuropsychiatric symptoms: APLA with stroke and vascular dementia, seizures, chorea, headache, and transverse myelitis; anti-ribosomal-P with depression or psychosis; anti-neuronal with cognitive dysfunction and depression; anti-ganglioside antibodies with migraine, acute confusional state, depression, and peripheral neuropathy;[7] yet, none of these antibodies can serve as a definite marker of NPSLE.

NPSLE is not uncommon in India and affects younger age group. Early diagnosis and management of NPSLE is a clinical challenge. During the last few decades, overwhelming efforts were made to elucidate the pathophysiology as well as to improve the classification, diagnosis, and management of NPSLE. This accumulated information has enhanced our understanding and ability to help patients. Our study will help in better understanding the disease pathogenesis, which will help in early diagnosis and treatment of the disease that will lead to decreased mortality and morbidity and reduce the burden of disease in the society.

METERIALS AND METHODS

Study Population: The present study is a prospective single centre hospital based study which was undertaken at the Department of Neurology, Gauhati Medical College and Hospital, Guwahati, Assam from October 2015 to September 2017.

Selection of the Cases: The cases for the present study were selected from the Neurology outpatient and inpatient departments as well as from other departments of Gauhati Medical College and Hospital who sought referral for such cases.

Inclusion Criteria: (i) Any diagnosed SLE patient presented with neurological symptoms and (ii) Any patient presenting with neurological symptoms that are fulfilling the A.C.R diagnostic criteria of SLE.

Exclusion Criteria: Patients having neurological manifestations which can be explained by other concomitant diseases.

All included cases were subjected to a detailed clinical history and clinical examination.

- Investigations including serological, radiological and electrophysiological were done as per clinical symptoms.
- Immunological parameters were analysed as per standard protocol.
- Diagnosis of SLE made by applying the Systemic Lupus International Collaborating Clinics (SLICC) group revised ACR SLE classification criteria 2012.[6]
- Patients were put in various clinical syndromes as per American College of Rheumatology (ACR) case definition and classification criteria for 19 Central Nervous System (CNS) and Peripheral Nervous System (PNS) syndromes.
- Seizures are classified as per ILAE 2017 classification of seizures.
- Disease activity was measured by the SLE disease activity index (SLEDAI)[8] in 1st visit and 6 months follow-up. Patients were categorized according to their disease activity score into three groups: mild (<10), moderate (10-20), severe (20).[9]
- Organ damage was assessed by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC-ACR) Damage Index (SDI)[10] at time of 1st visit and after 6 months.
- A four-point Likert scale was used to assess the clinical outcome of every NP event between the first visit and re-assessment (1-worsening of symptoms, including death; 2-no change; 3-improvement of symptoms; 4-resolution of symptoms). Likert scales have been previously used by other groups as physician-reported outcome in NP SLE studies.[11]

Statistical analysis:

Statistical analysis was done using Statistical Package for Social Sciences (SPSS) software version 16. Data were presented as mean, standard deviation, median and percentage. The p-value was considered significant if <0.05.

RESULTS

A total of 82 cases were included in the study. Median age of presentation was 22 yrs with most common age-group 10-20 yrs. Most of the cases were females (78%) with F: M ratio was 3.5:1. Mean duration of first neurological symptom from diagnosis of SLE was 17.7 ± 20.1 months. CNS diseases were predominant manifestation in 72 (87.8%) and rest were symptoms referable to PNS.

Table 1 Neurological manifestations

CNS		**PNS**	
Diseases	No (%) n=72	Diseases	No (%) n=19
Seizures	28 (38.9)	Cranial neuropathy	4 (21.1)
Acute confusional state	17 (23.6)	Polyneuropathy	12 (63.2)
Psychosis	4 (5.6)	Plexopathy	1 (5.3)
Stroke	6 (8.3)	Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)	1 (5.3)
Headache	9 (12.5)		
Myelopathy	8 (11.1)	Myasthenia gravis	1 (5.3)

Common autoantibodies that are known to be associated with SLE were studied. ANA was found to be the most common autoantibody occurring in 81(98.7%) cases, followed by Anti-dsDNA (**Table 2**). One patient with ANA negativity was found to have positive anti-dsDNA. Because of resource poor setting, APLA was studied only in 34 cases and found to be positive in 19(55.9%), among this anticardiolipin antibody in 11(32.4%) followed by lupus anticoagulant 6(17.6) cases. Both antibodies were found in 2(5.9%) cases.

Table 2 Immunological parameters

Antibody	**Cases No. (%) n=82**
ANA	81 (98.7)
Anti-dsDNA	67 (81.7)
Anti Sm	31 (37.8)
Anti Ro-52	28 (34.1)
Anti RNP	37(45.1)
Anti Ro (SS-A)	44 (53.7)
Anti La (SS-B)	8 (9.8)
Anti Histone	28 (34.1)
Anti scl-70	1 (1.2)
Anti nucleosome	44 (53.7)
Anti mitochondrial (AMA-M2)	18 (22)
Anti Ribosomal-P	43 (52.4)
Antiphospholipid (APLA) {Done in 34 cases }	19 (55.9)

Mean SLEDAI was 8.9 ± 5.7. Highest mean SLEDAI was found in stroke followed by seizures. All the patients had mild (0-10) to moderate (11-20) disease activity. Mean SLEDAI was significantly more in CNS as compared to PNS diseases (**Figure 1**). Majority of patients improved and only 5% expired due to intercurrent illness. Patients who expired had significantly high SLEDAI as compared to those who survived (**Figure 2**). 69 patients turned up for regular follow-up and we could compare SLEDAI, values on 4 point likart scale, and SLICC/ACR damage index at time of discharge and 6 month follow-up (**Figure 3,4,5**).

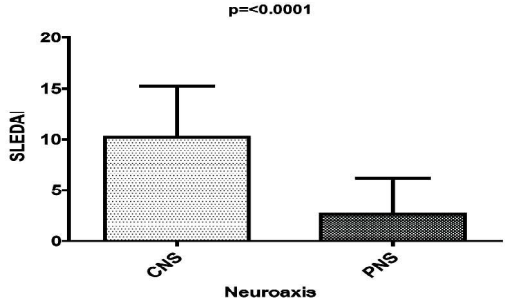

Figure 1 Comparison of SLEDAI between CNS and PNS diseases

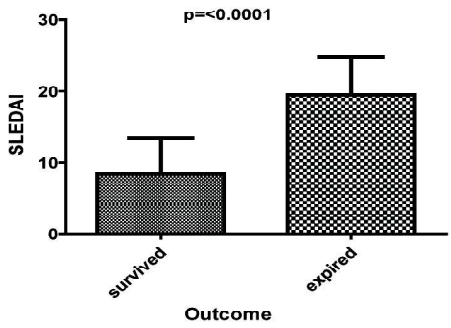

Figure 2 Comparison of SLEDAI with outcome

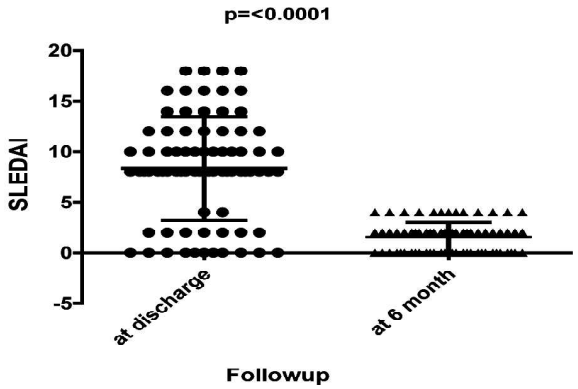

Figure 3 Comparison of SLEDAI in follow up

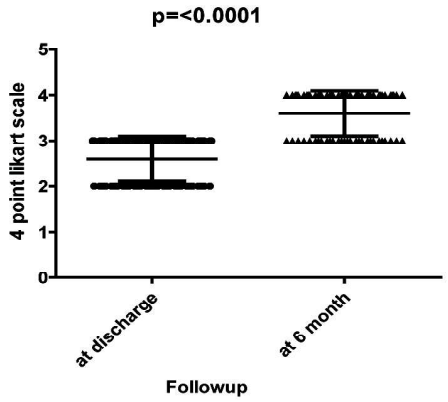

Figure 4 Comparison of 4 point likert scale in followup

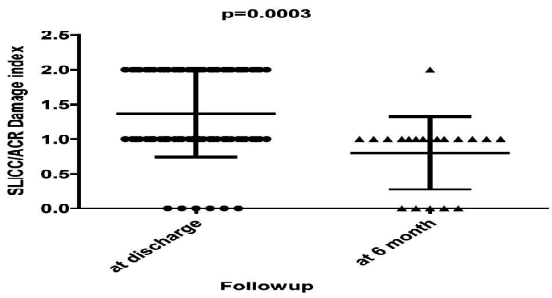

Figure 5 Comparison of SLICC/ACR damage index in follow up

DISCUSSION

Cases are classified according to American college of rheumatology nineteen case definitions for neuropsychiatric SLE (NPSLE) syndrome.[12] CNS was commonly involved as compared to PNS which correlates with previous study.[9,10] Seizure can occur in SLE in any time of disease course and any semiology can occur. In our cases most common semiology was found to be generalized tonic-clonic seizure which correlates with the recent study of Kakati S et al done in north east India.[11] Due to application of strict exclusion criteria, we have ruled out infective and metabolic causes of seizures. However, in many of the cases, we could not ascertain the definite cause for it, due to financial constraint for further investigations. One (1.2%) case of AIDP was found in our study. The prevalence of SLE in AIDP or GBS has been reported to be 0.6-1.7% in literature,[13] which correlates with our study. In a present study one case of myasthenia gravis (MG) was found which is a rare association described in the literatures. A case series by Jallouli et al[14] showed the prevalence of myasthenia gravis 1.3% in SLE cases, which correlates with our study. The frequency of myasthenia gravis in our study is higher than in general population[15] as our study is hospital based which may not reflect whole population.

Most common antibody found in our patients was ANA which correlates with most of the studies from India and all over the world. A study by Malaviya et al[3] compared case series on SLE from different regions of India and found ANA in more than 96% of cases, which correlates with our study. Other studies from India like study by Saigal et al[16] showed 65%, Malaviya et al[3] 55% and Santhanam et al[17] 45% anti-dsDNA positivity in SLE. dsDNA antibodies rise in active disease and in the evolution of lupus nephritis in most patients.[18] As in our study most of the cases are of CNS disease having high disease activity index (described further) and also associated with lupus nephritis; therefore large number of anti-ds DNA positivity found in comparison to available literatures in India.

Regarding disease activity (SLEDAI and SLICC/ACR damage index), most of our cases have mild disease, which is comparable with study by C Magro-Checa et al.[8] It contradicts the study by Kakaki et al in which most of the cases had severe disease activity. This is because of higher number of other organ involvement in their study. SLEDAI was significantly higher in CNS as compared to PNS disease in our study. Study by Kampylafka et al showed statistically significant correlation between high disease activity index and CNS manifestation.

In our study majority of cases improved and only 5% expired due to intercurrent illness. We compared SLEDAI between expired and survived and found that disease activity was significantly higher in cases who expired as compared to who survived. Previous studies refer that higher the score more severe is the manifestations.[19,20] On follow up, we found significant decrement in values of SLEDAI, SLICC/ACR damage index and Likart scale at 6 months, suggestive of improvement. A study by C Magro-Checa et al[8] showed better clinical outcome and a meaningful improvement in NPSLE than non-NPSLE events which is similar to our study. We propose that these findings may be related to reversibility of brain inflammation/dysfunction after starting immunosuppressive therapy as well as to spontaneous decrease of disease activity

CONCLUSION

Neurological manifestations are not uncommon in SLE and can affect different neuroaxis. It can occur in the absence of either serologic activity or other systemic disease manifestations. They correlate with disease activity, and results in high morbidity if not diagnosed early. Studies attempting to link NPSLE to underlying SLE-specific pathophysiological processes are ongoing. It is necessary to detect subclinical NPSLE by having a high index of suspicion, and evaluation by clinical, immunological, neuroimaging and neurophysiological tests.

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Ethical clearance: Taken.

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