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Original Article

Internal Medicine Section

Neurological Manifestations in Systemic Lupus Erythematosus: A Single Centre Study from North East India

SANJEEB KAKATI[1], BHUPEN BARMAN[2], SOBUR U AHMED[3], MASARAF HUSSAIN[4]

ABSTRACT

Introduction: Neurological manifestations although common in Systemic Lupus Erythematosus (SLE), are often not recognized due to their diversed and varied presentation. Therefore, the study was planned to highlight the pattern of neurological involvement in SLE to help in early recognition.

Aim: To study the pattern of neurological involvement in SLE and its correlation with disease activity and different investigation.

Materials and Methods: This hospital based prospective observational study was carried out from August 2009 to July 2010. Diagnosed cases of SLE [based upon American Rheumatism Association (ARA) criteria] who presented with neurological manifestations at the time of diagnosis or develop during the course of the disease were included in the study. They were assessed clinically and investigated with neuroimaging and neurophysiological tests as applicable.

Results: In total, 52 consecutive patients with SLE were evaluated, 92% were female. The most common age group was 21 to 25 years. Nervous system involvement was found in 19 (36.54%) patients. Cognitive impairment was the most frequent manifestation, present in 11 (57.89%) patients followed by seizure disorder in eight patients (42.1%). Peripheral neuropathy was diagnosed in eight (42.1%), acute confusional state in six (31.57%) and headache and depression was diagnosed in five (26.31%) patients each. Less common manifestations were psychosis, movement disorder and aseptic meningitis. Percentage of neurological manifestations directly correlated with disease activity. A significant difference was found in Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score between the patients with Neuro Psychiatric Systemic Lupus Erythematosus (NPSLE) and those without NPSLE (32.42±16.34 Vs 17.3±10.6).

Conclusion: Neurological involvement in SLE is seen relatively early in the course of the disease with cognitive impairment being the most common manifestation and correlate with disease activity.

Keywords: Acute confusional state, Cognitive impairment, Neurolupus, Seizure

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a prototypic autoimmune disease characterized by production of autoantibodies against cell nucleus giving rise to diverse clinical manifestations encompassing almost all the organ systems of the body. Nervous system involvement is frequently reported in 75% of patients in SLE and that varied from mild subtle signs like headache and mood disturbance to life threatening conditions like acute confusional state, stroke and myelopathy [1]. The wide range of presentations and differential diagnosis often pose a very difficult diagnostic challenge for clinicians [2].

The American College of Rheumatology (ACR) described case definition and classification criteria for 19 Central Nervous System (CNS) and Peripheral Nervous System (PNS) syndromes that have been observed in SLE, which collectively are referred to as NPSLE [3].

Approximately 40% of NPSLE manifestation develops before the onset of SLE or at the time of diagnosis; 63% develop it during the first year of diagnosis [4]. Exact cause of neurological manifestations of SLE is not known. It may be a primary manifestation of the disease, secondary complications of the disease or therapy, or it may be a coincidental finding unrelated to SLE. Vascular abnormality, autoantibody and inflammation play important role in development of NPSLE. The risk factors for neurological manifestation in SLE are high tire of antiphospholipid (aPL) antibody, anticardiolipid (aCL) antibody, cutaneous vasculitis, arterial thrombosis [5]. An early diagnosis and treatment will definitely help in reducing morbidity and mortality of patients suffering from SLE.

The aim of the present study was to evaulate the various neurological manifestations in SLE and to assess the role of neuroimaging, electrophysiological studies in the diagnosis of subclinical neurological manifestations and to correlate neurological manifestations with disease activity.

MATERIALS AND METHODS

The present hospital based prospective observational study was undertaken in the Department of Medicine, Assam Medical College, Dibrugarh, North Eastern part of India during the period from August 2009 to July 2010. Patients fulfilling the American Rheumatism Association (ARA); now called the Americans Collage of Rheumatology (ACR), published criteria for SLE (update in 1997 and revised in 1982) were included in the study [6,7]. Total 52 patients were included in this study and each was followed up for a period of six months. Patients below 12 years were excluded from the study. Approval of the hospital ethics committee was taken. Informed consent was taken from every patient.

As the main objective of the study was to see the pattern of neurological involvement in patients with SLE in a definite time period, consecutive numbers of patients during that period of the study were included in the study group.

Disease Activity Index: For disease activity index the SLEDAI was used which include 20 variables representing nine organ system. Patients were categorized according to their disease activity score into three groups: mild (<10), moderate (10-20), severe (20) [8].

Antinuclear Antibody (ANA) was assayed by Immunofluorescence Assay (IFA) in standard NABL accredited Indian laboratories. A titre

>1:20 was taken as positive. Anti ds DNA test was performed by radioimmunoassay (Farr assay) in standard NABL accredited Indian laboratories with a normal value of < 35 IU/ml. Complement level (C3) was assessed by immunoturbimetry with a normal value of 90-180 mg/dl. Anti-phospholipid (aPL) antibody was assessed by enzyme immunoassay in standard NABL accredited Indian laboratories includes following:

a) Anti cardiolipin (aCL) antibody was assessed by enzyme immunoassay and a level of >15 U/ml was taken to be positive.

b) Lupus Anticoagulant (LA) was done by enzyme immunoassay by both Partial Thromboplastin Time/Activated Partial Thromboplastin Time (PTT/APTT), PTT–LA, and diluted Russels Viper Venom Time (dRVVT).

Magnetic Resonance Imaging (MRI) brain was done in the Department of Radiology, using Siemens Magnitom Avanto (1.5 Tesla) machine. MR spectroscopy, Diffusion Weighted (DW) imaging, and MR angiography was done whenever indicated.

Nerve conduction velocity was performed in the Department of Neurology, using Medicaid's "Neuro Perfect 4-channel EMG, NCV, EP System". Both sensory and motor nerve conduction study was done. Interpretation was done on the basis of conduction velocity of action potential in meter per second.

Skin biopsy was done by dermatologist and results were interpreted on the basis of nerve fiber density per square centimeter of biopsied skin.

Cerebrospinal Fluid (CSF) analysis was done for physical, chemical, cytological analysis and culture was also done to rule out CNS infection.

Electro Encephalography (EEG) was performed in the Department of Neurology, using Medicaid's "Neuro Perfect 4-channel EMG, NCV, EP System".

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

RESULTS

A total of 52 patients were included in the study. The age of the patients ranged from 14 to 45 years with most of the patients (28.85%) were in the age group of 21 to 25 years. Mean age of our patient was 25.59±7.86 years of the 52 patients studied, only four (7.7%) were male and rest 48 (92.3%) were female with a male: female ratio of 1:12.

Manifestation	Frequency	Percentage (%)
Aseptic Meningitis	1	5.26
Headache	5	26.31
Seizure Disorder	8	42.1
Acute Confusional State	6	31.57
Anxiety Disorder	2	10.52
Cognitive Dysfunction	11	57.89
Movement disorder	1	5.26
Psychosis	4	21.05
Depression	5	26.31
Autonomic disorder	2	10.52
Neuropathy Cranial	3	15.78
Mononeuritis Multiplex	1	5.26
Polyneuropathy	4	21.05

[Table/Fig-1]: Frequency of the observed neurological manifestations of SLE in studied patients.
One patient had multiple manifestation

Nervous system was involved in 19 of 52 patients (36.54%). CNS was involved in 16 (30.76%) while PNS was involved in eight (15.38%) patients. Both CNS and PNS were involved in five (26.31) patients. The most common feature was cognitive impairment (57.89%) followed by seizure disorder (42.1%). Six patients (31.57%) presented with acute confusional state with altered sensorium. Mild depression was present in five (26.31%) out of 19 patients with clinical NPSLE. Persistent headache, not relieved by narcotics was present in five (26.31%) patients. Frank psychosis was present in four (21.05%) patients. One of them was admitted initially in the department of psychiatry and subsequently was diagnosed to have SLE. This patient also had rheumatoid arthritis and was on long term steroid therapy. Two (10.52%) patients had anxiety disorder, while one (5.26%) patient had aseptic meningitis. One patient had movement in the form of abnormal facial chewing movement [Table/Fig-1].

Among the PNS manifestations, the most common was polyneuropathy present in four (21.05%) patients. Two patients presented with symptoms both motor and sensory neuropathy of which one presented with weakness both upper and lower limbs with paraesthesia. On examination, there were diminished deep tendon reflexes of all four limbs. The other had paraesthesia but no motor weakness was there; and on examination there was absent bilateral ankle jerk and diminished sensation. The other two patients presented sensory symptoms of paraesthesia without motor symptoms. Cranial neuropathy was present in three (15.78%) patients. Out of these, two had second cranial nerve disorder (optic neuritis), the other had seventh nerve palsy. Two patients had autonomic neuropathy in the form of postural hypotension and decreased sweating of lower limbs. One patient had mononeuritis multiplex involving the ulnar nerve and common peronial nerve and posterior tibial nerve. Most of the patients with PNS manifestation also had concomitant CNS manifestation, but three patients had purely PNS manifestations, out of which one had seventh cranial nerve palsy, one had second cranial nerve palsy and the one had mononeuritis multiplex (peroneal, posterior tibial, ulnar).

The most common type of seizure (87.5%) was Generalized Tonic Clonic Seizure (GTCS). One patient had partial seizure in the form of epilepsia partialis continua involving the facial muscles.

Out of 52 patients studied, 43 (82.69%) had normal cognitive function with an Mini-Mental State Examination (MMSE) score between 24 and 30. Three patients (5.76%) had mild cognitive impairment with a score between 18 and 23 while six (11.53%) had severe cognitive impairments with a score between 0 and 17 [Table/Fig-2]. The mean score of the patients with NPSLE was 20.89±5.91 while that of patients without NPSLE was 28.42±2.06.

Disease activity of the patients was calculated using SLEDAI scoring. Most of the patients (46.14%) had an SLEDAI score between less than 20. Almost 25% percent patients had a score between 21 and 29. Two patients (3.84%) had a score above 50. According to SLEDAI score, 12 patients had mild disease (SLEDAI <10), another 12 had moderate disease (SLEDAI 10-20) and rest 28 had severe disease (SLEDAI >20). The minimum score was 2 and the maximum score was 65. The mean score was 22.44±14.97 [Table/Fig-3]. Among the patients with NPSLE the mean score was 32.42±16.34, while among the patients without NPSLE, mean score was 17.3±10.6. The patients with highest score (i.e., 65) died within two weeks of presentation. This was one of the patients who presented with NPSLE before diagnosis of SLE.

Score	No. of Patients	Percentage (%)
24-30	43	82.69
18-23	3	5.76
0-17	6	11.53

[Table/Fig-2]: MMSE score.

Score	No of patients	Percentage
<10	12	23.07
10-19	12	23.07
20-29	13	25
30-39	07	13.46
40-49	06	11.53
50-59	01	1.92
60-69	01	1.92

[Table/Fig-3]: SLEDAI score.

SLEDAI Score	No. of Patients	NPSLE present in	Percentage (%)
<10	12	2	16.66
10-19	12	2	16.66
20-29	13	4	30.77
30-39	7	4	57.14
40-49	6	5	83.33
50-59	1	1	100
60-69	1	1	100

[Table/Fig-4]: Correlation of disease activity with neurological manifestation.

Findings		No. of Patients	Percentage (%)	
ANA		48	92.3	
Anti ds DNA		46	88.46	
Low complement		35	67.3	
aPL (done in 32 patients)	aCL	9	28.12	34.37
	Lupus anticoagulant	7	21.87	
	Both	4	12.5	

[Table/Fig-5]: Immunological observation.

Clinical NPSLE	Positive APLA		
Yes = 19	YES	No. of Patients	Percentage (%)
		9	47.37
	NO	No. of Patients	Percentage (%)
		10	52.63
NO = 13	YES	No. of Patients	Percentage (%)
		2	15.4
	NO	No. of Patients	Percentage (%)
		11	84.6

[Table/Fig-6]: Correlation of clinical CNS features with positive aPL.

Investigation	Total number of patients	Abnormal results	Percentage
MRI Brain	32	17	53.12%
EEG	32	12	37.5%
NCV study	32	7	22.58%
CSF analysis	32	15	46.87%

[Table/Fig-7]: Investigation results of different parameters.

Percentage of neurological manifestations directly correlated with disease activity. Out of 24 patients having disease activity less than 20, only four (16.66%) had neurological manifestations; while eight (40%) of the 20 patients having a score between 20 and 39 had neurological manifestations. Of the six patients having a score between 40 and 49, five (83.33%) had neurological manifestations [Table/Fig-4]. Both the patients having a score above 50 had neurological manifestations (100%).

ANA was positive in 48 (92.3%) of 52 patients and anti-ds DNA was positive in 46 (88.46%) patients. A low complement level was found in 35 (67.3%) patients. The aCL was positive in 9 (28.12%) out of 32 patients. It was observed that higher the titer of anti ds DNA, more was the disease activity [Table/Fig-5,6].

Clinical NPSLE	Abnormal MRI		
Yes = 19	Yes	No of patients	Percentage (%)
		14	73.68
	No	No of patients	Percentage (%)
		5	26.31
No = 13	Yes	No of patients	Percentage (%)
		3	27.27
	No	No of patients	Percentage (%)
		10	76.92%

[Table/Fig-8]: Correlation of Clinical CNS features with positive MRI finding.

Lesion	Number of cases	Percentage (%)
Subcortical white matter lesions	11	64.7%
Cortical atrophy	8	47.05%
Periventricular white matter lesion	6	35.29%
Discrete grey matter lesion	3	17.64%
Cerebral oedema	3	17.64

[Table/Fig-9]: MRI findings.

MRI was performed in 32 of total 52 patients which included 19 with clinical neurological manifestations and 13 without clinical neurological manifestations but having high disease activity (SLEDAI ≥ 20). Out of 32 patients in whom MRI was performed, 17 (53.12%) had abnormal finding while 15 (46.88%) had normal findings [Table/Fig-7]. The commonest MRI finding was subcortical white matter lesions found in 11 (64.7%) patients followed by cortical atrophy in eight (47.05%), periventricular white matter lesion in 6 (35.29%), discrete grey matter lesion in 3 (17.64%) and cerebral oedema was found in 3 (17.64%) patients. Out of 19 patients with NPSLE, MRI abnormality was found in 14 (73.68%) and of the 13 patients without clinical NPSLE where MRI was done three (27.27%) had positive findings [Table/Fig-8,9]. It indicates that subclinical neurological findings are present in SLE patients with higher disease activity without clinical neurological manifestations. In one of our patients MR angiography showed features of Posterior Reversible Encephalopathy Syndrome (PRES). This patient was on immunosuppressive medication for lupus nephritis and also had hypertension. She presented with headache, acute confusional state, seizure and psychosis. MRI brain showed diffuse subcortical white matter lesion and vasogenic oedema involving bilateral posterior cerebral artery territory.

EEG abnormality was found 12 (37.5%) out of 32 patients, the most common finding being diffuse delta wave slowing. EEG abnormality was found more commonly in patients with clinical NPSLE (42.11%) than those without clinical NPSLE (30.77%).

Abnormal result on NCV study was found in 22.58% our patients, motor neuropathy being common than sensory neuropathy.

Abnormality in CSF analysis in the form of high protein and pleocytosis was found in 15 (46.87%) out of 32 patients.

The different neurological presentations were compared with other recently published series [Table/Fig-10].

DISCUSSION

Nervous system involvement is frequent in SLE affecting both CNS and PNS. It can present in different ways like aseptic meningitis, cerebrovascular accident, headache, psychosis, seizure, cognitive impairment, depression, and various forms of peripheral neuropathies like mononeuropathy, polyneuropathy, autonomic neuropathy, plexo-

Study features	Present study	Robert M et al., [11]	Brey RL et al., [12]	Sanna G et al., [10]	Khare S et al., [13]
Number of patients included in the study	52	50	128	323	35
Nervous system involvement	19 (36.54%)	39 (78%)	102 (80%)	185(57.3%)	35(100%)
Cognitive dysfunction (%)	11(57.89%)	7(17.95%)		35(10.8%)	3(9%)
Seizure (%)	8(42.1%)	8(20.51%)	21(16%)	27(8.3%)	23(66%)
Acute confusional state (%)	6(31.57%)	6(16.2%)		12(3.7%)	7(20%)
Headache (%)	5(26.31%)	20(55.6%)	73(57%)	78(24%)	2(6%)
Depression (%)	5(26.1%)		37(28%)		
Psychosis (%)	4(21.05%)	6(16.2%)	6(5%)	25(7.7%)	3(9%)
Polyneuropathy (%)	4(21.05%)		29(22%)		2(6%)
Cerebro vascular accident (%)	NS	6(16.2%)	2(2%)	47(14.5%)	2(6%)
Movement disorder (%)	NS	8(20.51%)	1(1%)		

[Table/Fig-10]: Comparison of different neurological manifestations in SLE patients in observed study with other studies (values represent percentage of the total patients studied) [10-13].

pathy and cranial neuropathy. CNS lupus is the least understood serious but potentially treatable manifestations of the disease SLE which is found to occur much more often in the context of well established active disease.

The detailed pathogenesis of great variety of neurological manifestations in SLE is still unknown. If we go back to the history, initially it was thought to be due to fever and uraemia and later cerebral vasculitis came into the picture. In the present scenario, different mechanisms have been postulated by different authors for primary involvement of CNS in lupus: vascular occlusion or haemorrhage, cytokine effects, autoantibody mediated lesions, genetic mutation (TREX 1, HLA-DRB1*04), choroid plexus dysfunctions, abnormal hypothalamic-pituitary axis dysfunction and accelerated atherosclerosis [9].

Profile Neuro Psychiatric Systemic Lupus Erythematosus (NPSLE)

CNS was involved in 30.76% patients, while PNS was involved in 15.38% patients. Both CNS and PNS were involved in 26.31% patients. This result of our study correlates with most other studies where CNS involvement was found more frequently than PNS manifestation [10-13].

Most common finding in the present study was cognitive impairment-found in 57.89%. Cognitive and psychiatric impairment occurs in wide range of patients with SLE and this variation may be due to variations of diagnostic criteria for such disorders. One interesting observation was that many a times impairment of cognitive function were seen when their illness was apparently quiescent. Possible underlying mechanism for cognitive impairment is autoantibody mediated or indirect effect of depression and hence, there is a possibility of reversibility of cognitive impairment in SLE [14]. Affective disorders such as depression and anxiety have been seen in few numbers of patients in the present study. A lupus psychosis is also seen in four patients, although it is often very difficult to differentiate it from iatrogenic steroid induced psychosis as one of patients with psychosis also had rheumatoid arthritis and was on long term steroid therapy.

Seizure was the second most common mode of presentation found in 42.1% of patients in our study. According to available literature frequency of seizure in SLE patients has been reported from 7% to 40% with an average of 15% [15]. Most of patients had generalized tonic clonic seizure; however, some of them had simple focal and complex partial seizure. One of our patients had epilepsia partialis continua involving facial muscles. This is a rare finding reported only in few case reports [16]. Although in most of the cases seizure is often accompanied by other systemic and neurological features, sometimes it may precede SLE by many years [17].

Acute meningitis is rare in SLE although there are reports of meningeal inflammation in one fifth of cases. One (5.26%) patient had features meningitis like neck rigidity and Kerning's sign with altered sensorium. CSF analysis in this patient showed high protein and pleocytosis and CSF culture was sterile. There is a possibility of association of asceptic meningitis with the use of non steroidal anti inflammatory drugs. One of our patient had movement disorder in the form of abnormal facial chewing movement. It was a less common finding compared to most other study. Classical movement disorder described in SLE is chorea which is found in less than 4% of cases [14]. Chorea in SLE, often subtle and transient, is mostly found in women of less than 30 years of age as an acute flare. Stroke and recurrent transient ischemic attack has been reported in most of the studies, however, we have not found in any case in the present study [10-13].

PNS involvement was seen in five (26.31%) patients, four patients had perioheral neuropathy and one patient had mononeuritis multiplex. Cranial neuropathy was found in three (15.78%) patients. These findings are often in concordance with published data. Two patients (10.52%) had autonomic neuropathy. This finding has been mentioned infrequently in other studies [12,18].

One patient developed femoral dermatomal herpes zoster that was on mycophenolate mofetile therapy. This was an uncommon finding describe only in one study by Khare S et al., from Mumbai, India, in one patient that had thoracic dermatomal herpes zoster and the patient was on cyclophosphamide pulse therapy [13]. Immunosuppression due to Mycophenolic acid (MMF) was probably the reactivation of herpes in this patient.

Onset of Neuro Psychiatric Systemic Lupus Erythematosus (NPSLE)

In our study it was observed that 52.62% developed NPSLE within two years of symptoms of SLE. It holds true the fact that neurological manifestations occur quite early in course of SLE. Three (15.78%) of our patients developed their neurological features before they were diagnosed to have SLE and five (26.31%) developed it within one year of diagnosis. It has been reviewed from the available literature that 28% to 40% of adult NPSLE manifestations develop before or around the time of the diagnosis of SLE and 63% occur within the first year after diagnosis [19,20].

Disease Activity Scoring

A significant difference was found in SLEDAI score between the patients with NPSLE and those without NPSLE. Percentage of

neurological manifestations directly correlated with disease activity. It was also observed that higher the score more severe was the manifestations [10-13].

Magnetic Resonance Imaging (MRI) Brain

MRI is the neuroimaging choice of test for NPSLE in clinical practice which is often characterized by diffuse periventricular white matter lesion followed by cortical atrophy, ventricular dilatation and infarction [21,22]. Progressive hippocampal atrophy in MRI brain often associated with increased disease duration, more cognitive impairment and increasing use of corticosteroid [23]. In the present study MRI abnormality was found in 53.12 % patients with most common finding being subcortical white matter lesion. In one of our patients MR angiography showed features of Posterior Reversible Encephalopathy Syndrome (PRES). This patient was on immunosuppressive medication for lupus nephritis and also had hypertension. She presented with headache, acute confusional state, seizure and psychosis. MRI brain showed diffuse subcortical white matter lesion and vasogenic oedema involving bilateral posterior cerebral artery territory.

Electro Encephalography (EEG)

Epileptiform discharges in the form of diffuse delta and theta wave were observed in 37.5% of our patients. The EEG abnormality was mostly observed in patients with clinical NPSLE and that abnormal EEG may be an indicator for subclinical NPSLE.

Nerve Conduction Study and Skin Biopsy

Abnormal result on Nerve Conduction Velocity (NCV) study was found in 22.58% patients. Our result correlates closely with Goransson LG et al., who found it in 18% patients in the form of large diameter nerve fibre neuropathy [24]. Motor neuropathy was found more commonly than sensory neuropathy in our study. Common peronial nerve was more commonly found to be involved among the motor neuropathies followed by posterior tibial nerve. Small fiber neuropathy in skin biopsy was found in 31.25% patients of whom 40% had normal nerve conduction study indicating isolated small fiber neuropathy. Goransson LG et al., found small fiber neuropathy in 13% patients of whom 75% had normal NCV [24].

Cerebrospinal Fluid (CSF) Analysis

Mild form of abnormality in CSF is frequent with neurolupus and is characterized by slight pleocytosis and elevation of protein with normal flucose. Along with different immunological analysis of many inflammatory markers in CSF like Interferon-gamma-inducible protein (IP 10) has shown promising results [25].

LIMITATION

Small sample size, lack of detailed investigations and proper cognitive assessment are the limitations of the study.

CONCLUSION

Neurological manifestations are not uncommon in SLE. They correlate with disease activity, and result 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, neuroimaging and neurophysiological tests.

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PARTICULARS OF CONTRIBUTORS:
1. Professor, Department of Medicine, Assam Medical College, Dibrugarh, Assam, India.
2. Associate Professor, Department of Medicine, NEIGRIHMS, Shillong, Meghalaya, India.
3. Postgraduate Student, Department of Medicine, Assam Medical College, Dibrugarh, Assam, India.
4. Assistant Professor, Department of Neurology, NEIGRIHMS, Shillong, Meghalaya, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Bhupen Barman,
Quarter B-9-B, NEIGRIHMS, Mawdiangdiang, Shillong-793018, Meghalaya, India.
E-mail: drbhupenb@gmail.com

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