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NEUROPSYCHIATRIC LUPUS: A CASE SERIES

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ABSTRACT Neuropsychiatric lupus (NPSLE) is a severe complication of systemic lupus erythematous and could also be the initial manifestation of Systemic lupus erythematosus, resulting in high morbidity and mortality. The incidence of Neuropsychiatric lupus is 39-50% in lupus patients and occurs in the early stages of the disease. The manifestations of NPSLE vary, ranging from cognitive dysfunction to acute confusional states, refractory seizures, psychosis, cerebrovascular accident, myelopathy, etc. The pathogenesis of NPSLE is poorly understood, it could be inflammation mediated by autoantibodies (immune complex deposition) or thrombotic pathways (antiphospholipid antibodies). Diagnosis may be challenging due to a lack of specific markers, and it is based on clinical, immunological and neuroimaging studies. Herein the cases presented as psychosis, cerebrovascular accident, seizures as the predominant symptoms and eventually diagnosed to have systemic lupus erythematosus with Neuropsychiatric lupus.

KEYWORDS : Systemic Lupus erythematosus, Antiphospholipid syndrome, Antinuclear antibodies, Neuropsychiatric lupus

INTRODUCTION:

Systemic lupus erythematosus is an autoimmune disease results in multiple organ dysfunctions, and its pathogenesis is multifactorial1. SLE affects both the central and peripheral nervous system, resulting in various neurological, psychiatric manifestations. NPSLE have high mortality, morbidity and poor prognosis.

systemic lupus erythematosus patients presenting with neuro-psychiatric manifestations needs exclusion of other causes, such as infections and drug side effects, ahead of concluding as NPSLE. A lack of specific biomarkers for NPSLE delays in diagnosis, results in disease progression and poor quality of life, if not diagnosed early. Hence, high suspicion, appropriate investigations, early treatment and regular follow up can reverse the disease state and save patients from long term morbidity. Autoantibodies and vascular mechanisms are considered potential causes of pathogenesis of neuropsychiatric lupus. The case series presented here for their diverse neuropsychiatric symptoms, masquerading as primary neurological, psychiatric disease and later on diagnosed and treated as neuropsychiatric lupus. Eventually few patients had other systemic manifestations of SLE. Presentation of this case series will invoke the thought process of primary care physicians to include immunological profiling in the investigatory panel in young adults with neuropsychiatric symptoms.

PATIENT 1:

A Young teenage female with no known comorbidity presented with complaints of vomiting and loose stools. she had history of altered behavior with auditory hallucinations and inappropriate smiling and crying for past 3 months. On examination she was disoriented, agitated and her vitals were stable. The patient was diagnosed as acute psychosis and started on antipsychotics.

The results of the basic investigations are listed in Table 1.

She had hypothyroidism and started on tablet thyroxine sodium. Despite receiving antipsychotics, she had persistent episodes of altered behavior and hallucinations; hence immunological profiling done, which revealed positivity for ANA, antidsDNA and low complements.

She was diagnosed as Neuropsychiatric lupus presented as psychiatric manifestations, pulsed with injection methylprednisolone (1 gm IVOD) for three days and injection cyclophosphamide therapy. The patient's psychotic symptoms improved dramatically and on follow-up with immunosuppressors and steroids. In this case patient initially presented as psychiatric illness and later diagnosed to have SLE.
The clinical, radiological and immunological profiles of the patients are listed in Table2.

PATIENT 2:

A young female, presented to the emergency ward with complaints of vomiting, headache, swaying to the right side, weakness of the right upper limb and lower limb and slurring of speech of 2 days duration. clinical diagnosis of Ataxic hemiparesis made and worked up further. The basic blood profiles, chest X-ray was normal and CT of the brain showed no significant abnormalities.

The results of basic investigations are listed in Table 1.

MRI of the brain [Figure-1} revealed focal leptomeningeal enhancement in Pontomedullary, pontine junction and superior aspect of pons and T2/Flair hyperintensity with diffusion restriction involving the left medial hemi-medulla and T2/Flair hyperintensity without diffusion restriction in the pons. Further neurological workup, CSF analysis was acellular and negative for anti-aquaporin-4 and anti-NMO antibodies. Vasculitis workup revealed ANA, anti-SSA, anti-SSB-positive and anti-dsDNA-positivity. APLA profile was negative. Hence, the patient diagnosed as Neuropsychiatric lupus presenting as troke.The patient treated with injection methylprednisolone pulse and injection cyclophosphamide therapy. The patient's neurological symptoms improved and on follow-up with steroids and immunosuppressants.

The clinical, radiological and immunological profiles of the patients are listed in Table 2.

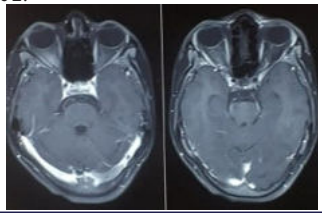

Figure 1a -Post contrast T1 weighted image- Focal leptomeningeal enhancement over pontomedullary, mesencephalic pontine junction, superior aspect of pons

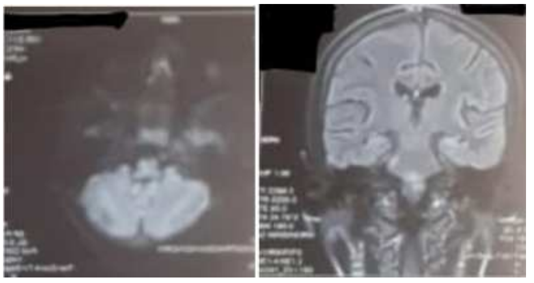

Figure- 1b- T2 /flair Hyperintensities with diffusion restriction in left medial hemi medulla

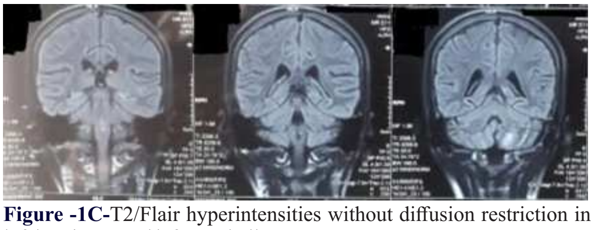

Figure -1C-T2/Flair hyperintensities without diffusion restriction in left hemipons and left cerebellum

PATIENT 3:

A young male, nonsmoker with no known co-morbidities admitted with acute onset of inability to use his left upper limb and lower limb, slurring of speech. Clinical examination showed left-sided hemiparesis. Vitals were stable with high blood pressure (150/90 mmHg). CT brain images showed acute infarcts in the right temporal, right occipital and right thalamic regions. He was diagnosed as acute CVA (hemiparesis) with newly detected diabetes mellitus, systemic hypertension and started on antiplatelets.

The results of basic investigations are listed in Table 1.

A few days later, he developed acute chest pain. ECG revealed acute anterior wall Myocardial Infarction. Echo revealed anterior wall hypokinesia and Ejection Fraction-38%. APLA profile done in view of young onset stoke and CAD revealed Lupus anticoagulant positivity and negative for anticardiolipin and beta-2 glycoprotein. His ANA and antidsDNA was strong positive. The patient started on oral anticoagulants (Tablet Acitrom).

During the course of hospitalization, he also developed one episode of generalized tonic clonic seizures, and antiepileptic therapy started. There was no change in behavior during the course of the illness. Finally diagnosed as SLE (lupus nephritis, NPSLE and secondary APLA). The patient was treated with steroids, immunosuppressants (tablet MMF) and anticoagulants, the patient improved clinically and on follow up.

The clinical, radiological and immunological profiles of the patients listed in Table 2.

PATIENT 4:

A young female attended Dermatology OPD with a complaint of skin lesion over the scalp and crusted erosive lesions over the lips and a history of photosensitivity, previously diagnosed with pediculosis capitis and treated for the same elswhere. clinical examination showed up scarring alopecia [Figure-2], acanthosis nigricans, provisionally diagnosed as cutaneous lupus treated with topical steroids. She had subclinical hypothyroidism.

Subsequently she developed sleep disturbances, decreased speech, and auditory hallucination; and diagnosed with acute psychosis and started on antipsychotics by Psychiatrist. Later developed tremors and slowness of movements, drug-induced extrapyramidal symptoms, suspected and weaned of anti-psychotics. The patient admitted for altered sensorium and fever few days later.

The results of basic investigations are listed in Table 1.

SLE was suspected in view of cutaneous, neurological and psychiatric signs, and investigated further. MRI brain showed normal signal. Diagnosed as SLE with NPSLE based on clinical condition(cutaneous, neurological, psychiatric) and immunological positivity(ANA, antids DNA, antiribosomal P). The patient treated with pulse steroids, Inj. Cyclophosphamide, Tab HCQ and antipsychotics. Her psychiatric and neurological symptoms improved, and followed up with immunosuppressants and steroids.

The clinical, radiological and immunological profiles of the patients are listed in Table 2.

PATIENT 5:

A young female in her early 20s with no known co-morbidity, admitted with fever headache, vomiting and consequently had episodes of new onset GTCS. Vital signs were stable with normal blood glucose level. The patient was drowsy, arousable, did not obey oral commands and showed no signs of meningeal irritation.

The results of basic investigations are listed in Table 1.

The patient was initially diagnosed with acute meningoencephalitis and treated with intravenous (IV) antibiotics and antiepileptics. MRI Brain and CSF analysis were normal, seizures were refractory to antiepileptic and had persistent fever.

EEG- Periodic multiple bilateral fronto-central temporal IEDs of spike and wave morphology. Fever profile and cultures were normal, immunological profiling was done. It showed strong positivity for ANA-3+, anti-dsDNA-positive, anti-RNP, and anti-ro52, low C3 and C4, APLA profile–negative.

Hence patient diagnosed as NPSLE, treated with pulse steroids (injection methylprednisolone). Due to persistent seizures, resistant to antiepileptics, intravenous immunoglobulin 0.4 g/kg/dose and injection Rituximab (1 gm) given. Though seizure frequency reduced finally patient succumbed to illness.

The clinical, radiological and immunological profiles of the patients are listed in Table2.

PATIENT 6:

An adolescent female attended Dermatology outpatient clinic with history of rashes over the face, upper limb [Figure-3], trunk and increased hair loss ,photosensitivity. Clinical examination revealed a malar rash with sparing of the nasolabial fold, pigmented nodular crusting lesions over both ears, forehead and scarring alopecia [Figure-4]. Provisionally diagnosed as cutaneous lupus and treated with topical steroids and Tab HCQS

The results of basic investigations are listed in Table 1.

TABLE-1 Results of basic investigations .

Investigations	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
CBC	TC-6200 Hb-9.6 Platelets-2.8L	TC- 8200 Hb-10.8 Plt-2.2L	TC-12000 Hb- 11.2 Plt- 1.8L	TC-4400 Hb -8.6 Plt-1.3L	Tc-5900 Hb-9.8 Plt- 2.1L	Tc- 8800 Hb-10.3 Plt-3.2L
RFT& LFT	S.Urea-22 S. Cr-0.8 LFT WNL	S.urea-32 S.cr- 1.0 LFT WNL	FBS-214 S.Urea 32 S.cr-1.0 LFT WNL	S.Urea-28 S.cr-0.9 LFT WNL	S.Urea- 30 S.cr-1.0 LFT WNL	S.Urea 23 S.cr- 1.0 LFT WNL
URINE R/E URINE PCR	Normal	Normal	Sugar-nil, albumin-2+, RBCs- 1+, UPCR-3.2	Normal	Normal	Normal
ESR CRP	40mm/hr negative	80mm/hr positive	100mm/hr positive	70mm/hr negative	60mm/hr positive	70mm/hr Negative
APLA & ANA PROFILE	ANA- +VE 3+, Anti dsDNA- Positive	ANA- +ve Anti dsDNA, Anti SSA & SS B - ve APLA Negative	ANA- +ve (2+) Anti dsDNA strong positive. APLA profile – Lupus Anticoagulant +	ANA- 3+ Anti dsDNA, Histone, Nucleosome, antiribosomal P protein Ab - positive	ANA-3+ Anti-dsDNA, Anti RNP ab, Anti ro 52 ab Strong positive APLA -ve	ANA-2+ Anti-Ribosomal P ab, SS A ab strong +ve Anti dsDNA - negative
CT BRAIN MRI BRAIN	Normal MRI- diffuse cerebral atrophy	Normal MRI- T2/FLAIR Hyperintensities in left pons and left hemimedulla	CT brain-acute infarcts in right temporal, occipital and right thalamic regions	Normal Normal	Ct- cerebral edema MRI - normal	Normal Normal
C3 & C4 LEVELS	C3 50 mg/dl C4-7 mg/dl	C3 - 81 mg/dl C4- 10 mg/dl	C3 78 mg/dl C4- 7 mg/dl	C3 84 mg/dl C4- 12 mg/dl	C3 - 70 mg/dl C4-4 mg/dl	C3 75 mg/dl C4- 12 mg/dl
Other investigations	TSH - 6.82 fT4-0.7	CSF- acellular, protein elevated. Anti-Aquaporin 4 and Anti NMDA Ab – negative	Fundus- no retinopathy. 24 Hr urine protein- 1890 mg/d. Renal biopsy class V Lupus Nephritis. ECHO- Anterior wall hypokinesia with EF 38%	CSF analysis- normal. TSH- 5.6 FT4 - 0.8	CSF analysis- Protein elevated. CSF cultures- negative. S Calcium 7.9 mg/dl Autoimmune encephalitis profile - negative	CSF analysis- normal.

A few days later patient was admitted with intermittent fever, altered behavior, abnormal speech, and visual hallucinations. Also had a history of difficulty in recalling memories, such as recognizing friends. MRI brain was normal. Autoimmune workup revealed immunological positivity, revised diagnosis systemic lupus erythematosus (Neuropsychiatric &Cutaneous lupus).

The patient was treated with pulse steroids and antipsychotic and immunosuppressants (injection Cyclophosphamide). The patient clinically improved and on tab MMF (mycophenolate mofetil) maintenance therapy with steroids.

The clinical, radiological and immunological profiles of the patient are listed in Table 2.

TABLE-2 – Clinical, radiological and immunological profile of patients

Variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age	17yrs	28yrs	31 yrs	19 yrs	25yrs	14yrs
Gender	Female	Female	Male	Female	Female	Female
Comorbids	No	no	T2DM, SHTN	Hypothyorid	nil	nil
Risk factors	Absent	absent	Absent	SLE in mother+	absent	Absent
Initial presentation	Altered behaviour Self talk, Hallucinations, inappropriate smile and cry.	Headache, Vomiting, Right UL weakness, Swaying to left side	Acute CVA with left hemiparesis	scarring alopecia, Acanthosis nigricans	Fever, altered sensorium, refractory seizures	Malar rash, Nodular crusting lesion, scarring alopecia
Significant past history	Polyarthralgia+ 6months ago	Nil	Nil	Photosensitivity+/rash+	Polyarthritis 3yrs ago	nil
Neuropsychiatric manifestations	Acute psychosis	Right side hemiataxia & Hemiparesis	CVA, seizures	Acute psychosis with EPS	Refractory seizures	Acute psychosis, transient memory loss
Reasons to evaluate for SLE	Young onset psychosis, no prior psychiatric illness	Young stroke To R/o CNS vasculitis	Young stroke, Proteinuria without retinopathy	Characteristic skin lesions SLE in Mother	Young onset, refractory seizures	Cutaneous SLE
Basic investigations	Normal except ESR 60 mm/hr. CRP - negative	Normal , ESR- elevated. csf – normal.	Normal, 24 hrs urine protein- 2 gm.	Pan cytopenia	Normal. ESR- raised	Normal ESR- 70 mm/hr.
Radiological Imaging & biopsies	MRI- diffuse cerebral atrophy with small vessel ischemic changes	MRI- Focal leptomeningeal enhancement withT2/FLAIR hyper intensities in pons, left hemi medulla	Ct brain- acute infarct in Right thalamic area. Renal biopsy – CLASS V lupus nephritis	MRI - normal	CT- cerebral edema, MRI –normal. CSF virology/ CBNAAT - neg	MRI- normal
Autoimmune profile	ANA & Anti-dsDNA +ve	ANA, Anti-dsDNA, Anti SS-A,SS-B - positive, APLA- neg	ANA & Anti dsDNA positive. C3,C4 – LOW APLA- LA +ve	ANA, Anti-dsDNA, anti - Ribosomal P protein- +ve, c3, c4 -low	ANA, Anti-dsDNA , anti RNPab - +ve.Anti-NMDA- neg	ANA,Anti RNP,AntiSS-A - +VE, Anti ds DNA- negative
Other SLE manifestations	Nil at present	nil	Lupus nephritis CAD/AW MI/EF - 38%	nil	Polyarthritis+	Cutaneous SLE
Management	iv steroids, Anti – psychotics, inj. cyclophosphamide.	iv steroids and inj. cyclophosphamide, antiplatelets	iv steroids, antiplatelets, Tab.acitrom,&T.MMF	iv steroid, anti-psychotics, Inj. cyclophosphamide	iv steroids, IVIG infusion, inj. Rituximab	Iv steroids, Antipsychotics inj.cyclophosphamide
Prognosis	Good	Good	Good	Good	POOR	Good

DISCUSSION.

The diagnosis of neuropsychiatric lupus is a challenge for clinicians due to its variegated presentation. A high index of suspicion is needed when NPSLE presents as an initial manifestation of SLE. NPSLE is classified based on the 1999 American College of Rheumatology criteria and has 12 central, 7 peripheral nervous system manifestations and psychiatric manifestations2. Unterman et all3 reported in his study, the major manifestations of NPSLE are headache, mood disorders, cognitive dysfunction, and seizures.

A multicentric Turkish study which analysed 1107 of juvenile systemic lupus erythematous patients, a hundred forty-nine had NP involvement (13.5%). The most common NPSLE findings were headache (50.3%), seizure (38.3%), and acute confusional state (33.6%) in that study4. Another single centred Turkish study of juvenile SLE, neuropsychiatric manifestation was shown in 75% of the study population among the patients studied5. Kivitys etal6 have shown that neuropsychiatric manifestations could be the first symptom of SLE leading to diagnostic challenges similar to our case series.

According to a study by Zirkee et 7al, the standardized mortality ratio is 9.5, which indicates a devastating disease state. Pego-Reigosa et al.8, who studied psychotic manifestations in patients with SLE, reported that psychosis occurred in 60% of their study population, 80% of whom experienced psychosis in the first year of the disease, and that it strongly correlated with lupus disease activity.

The pathophysiology of NPSLE is very complex and is attributed predominantly to vascular thrombosis associated with APLA antibodies and autoantibody-mediated immune cytotoxicity.9 The most common antibodies associated with NPSLE, particularly in patients with psychosis, are anti-ribosomal P, and the other antibodies such as anti-dsDNA/NR2, anti-phospholipid, anti-cardiolipin, and anti-GABA

The risk factors for psychosis in NPSLE patients are cutaneous lupus, lupus nephritis and young adulthood 10as seen in two of our cases. The distinction between organic and functional psychosis is very difficult, as we had in our case series too.

The prevalence of seizures in patients with SLE varies from 2 to 8%, mostly in young adults. The most common presentation is tonic-clonic seizures (60-88%), including secondary generalized seizures. In our case series two patients had GTCS. Status epilepticus is very rare in SLE patients11 and mostly correlates with structural abnormalities. Autoantibodies such as APLA antibodies and ribosomal P antibodies are associated with seizures in patients with lupus. However, Howro et al. reported that anti-B2 glycoprotein IgG antibodies are (11 times) more commonly associated with seizures and 9 times more commonly associated with tonic clonic seizures than are seronegative IgG antibodies. In our series of patients who presented with seizures, strong anti-ribosomal P antibodies were detected.

Stroke in SLE patients may range from 2 to 19% and is closely associated with systemic inflammation, a prothrombotic state due to APLA antibodies and atherosclerosis12, as seen in one of our case, who had strong lupus anticoagulant positivity. Different mechanisms may underlie SLE-related ischemic strokes, including antiphospholipid syndrome and embolic phenomena. Despite that the frequency of embolic strokes has not been properly studied in SLE. Several risk factors are associated with increased risk of cerebral embolism, such as Libman-Sacks endocarditis and antiphospholipid antibodies. MRI often shows multiple small cortical hyperintensities on T2WI and FLAIR with diffusion restriction in more than one vascular territory13. White matter hyperintensities (WMH) lesions on T2 and FLAIR weighted images are also associated with NPSLE, and they are usually located in the subcortical and periventricular frontal and parietal lobes. A meta-analysis revealed a 3-fold increased risk of stroke in patients with white matter hyperintense lesions14, one of our patients had white matter lesions. The prevalence of headache in patients with SLE varies, ranging from 24 to 72%. The most common

type is migraines, although tension headache is common in the general population.

Cognitive impairment is highly prevalent in lupus patients and manifests as deficits in attention and memory that affect daily living and quality of life. Depression is the most common mood disorder in patients with lupus. The acute confusional state varies from mild confusion to disturbed attention to severe disorganization with hallucination and agitation[15].

Neuropsychiatric lupus patients are always diagnosed with exclusion, and other organic causes to be ruled out behead, attributing to lupus disease activity. Treatment protocols include symptomatic management, such as antipsychotic, antidepressant, and antianxiety drugs, to treat psychiatric manifestations and antiepileptics to treat seizures.

Steroids (both oral and pulse) and immunosuppressants such as injection cyclophosphamide, the tablet mycophenolate mofetil, and azathioprine can be used. In the absence of a response to these therapies, b cell-depleting agents such as Rituximab, intravenous immunoglobins and plasma exchange therapies can be used16. Anticoagulants and antiplatelets can be used if associated with APLA antibodies. Further research needs to search for and validate biomarkers for NPSLE and individual NP events, including neuroimaging findings, attribution models, and serologic markers17. This will be a fundamental step in planning randomized control trials in the treatment of NPSLE to improve outcome.

CONCLUSION

NPSLE can present with different neurological and psychiatric manifestations, and a high index of suspicion, continuous follow-up and appropriate investigations are required to diagnose NPSLE. The above case series also showed that NPSLE patients commonly present with internal organ involvement, such as cutaneous or renal involvement, with varied antibody profiles over a time period. NPSLE requires a multidisciplinary approach for both diagnosis and treatment.

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