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ORIGINAL ARTICLE

Neuropsychiatric Lupus in Singapore: Disease Characteristics and Outcomes

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Abstract

Introduction: The aim of this study is to describe the clinical characteristics and outcomes of Systemic lupus erythematosus (SLE) patients with central nervous system (CNS) involvement in our population.

Methods: We conducted a retrospective review of the medical records of patients diagnosed with neuropsychiatric lupus (NPSLE) in Singapore General Hospital between Jan 2007 and Oct 2017.

Results: The records of eighteen patients were analysed retrospectively. The median age of diagnosis of NPSLE was 33.5 years. The median duration of SLE at the time of the neuropsychiatric manifestations was 4.5 months. Thirty-three percent had NPSLE as the first presentation of SLE. The most frequent clinical presentation was acute confusional state (30.8%) followed by cerebrovascular disease (23.1%) and seizures (19.2%). Seven patients (38.9%) had more than one neuropsychiatric syndrome. The commonest Magnetic Resonance Imaging (MRI) brain abnormality was white matter hyperintensities (61.1%), followed by acute infarcts (33.3%) and cerebral hemorrhage (22.2%). Multi-vessel involvement (3 or more vessels) (55.6%) was observed on magnetic resonance angiography (MRA). Majority of the patients (72.2%) received intravenous methylprednisolone, 66.7% had intravenous cyclophosphamide and 22.2% had rituximab. Twelve patients (66.7%) had clinical improvement and three patients (16.7%) had relapsing courses. There were three deaths from diffuse alveolar hemorrhage and ischaemic heart disease.

Conclusion: Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) manifests in a variety of clinical presentations, with NPSLE syndromes being the first presentation of SLE in one third of the patients. Prompt diagnosis and management is essential to improve clinical outcomes.

Keywords

Central nervous system, Neuropsychiatric lupus, Lupus, SLE

Introduction

Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) is a diagnostic challenge. In 1999, the American College of Rheumatology (ACR) established the nomenclature and case definitions of NPSLE, including 12 syndromes of central nervous system (CNS) diseases and 7 of peripheral nervous system (PNS) diseases [1].

The reported prevalence of NPSLE varies widely from 12-56%, depending on the populations studied [2-5]. A patient may present with one or more non-specific syndromes of NPSLE described. Therefore, a high index of clinical suspicion is required for the physician to make the diagnosis. The diagnosis of NPSLE is based on clinical symptoms and signs, together with further tests to assess if the symptoms are attributable to SLE. Tests include the use of Magnetic Resonance Imaging (MRI) of brain to look for features of NPSLE and exclude other differentials. The importance of diagnosing NPSLE promptly lies in the fact that it is potentially life-threatening, with a mortality rate of up to 19% [6]. Patients with NPSLE undergo more aggressive treatment and experience higher morbidity and hours loss in working capacity [2,7,8].

In Singapore, data published in 1998 showed a

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prevalence of CNS involvement of 16.7% [9]. An older study in 1987 found CNS disease to be the 2nd highest cause of death among SLE patients, accounting for 18% of the deaths [10]. This study aims to provide updated local data in regards to clinical characteristics, treatment and outcomes of our patients with CNS involvement in SLE.

Methods

Study population

A retrospective analysis of medical records between January 2007 and October 2017 was performed. We included all patients with NPSLE diagnosed in Singapore General Hospital who fulfilled the revised 1997 American College of Rheumatology (ACR) criteria for diagnosis of SLE and the 1999 ACR nomenclature and case definitions for neuropsychiatric lupus syndromes [1,11]. The study was approved by the Sing Health centralized institutional review board (Ref no: 2017/3070) and waiver of informed consent was obtained. Patients in this study were identified through the hospital database using physician-reported diagnoses that were coded as 'Lupus encephalopathy', 'Systemic lupus erythematosus encephalitis', 'Cerebral systemic lupus erythematosus', 'Cerebral lupus' or 'Cerebral vasculitis'. Neuropsychiatric symptoms were attributed to SLE by the managing rheumatologists after the exclusion of alternative etiologies like infection, metabolic abnormalities and drug causes [12]. Patients with peripheral nervous system involvement by SLE were excluded in this study. A final list of 18 patients was obtained. Patient demographics (including age, sex and duration of SLE at the time of NPSLE presentation), clinical presentations, cumulative organ involvement, biochemical and immunological laboratory tests, cerebrospinal fluid (CSF) analysis, brain MRI findings, SLE disease activity index-2K (SLEDAI-2K) at the time of NPSLE presentation, treatment received, and outcomes were analysed retrospectively based on medical records [13].

Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 25.0 was used for data processing and analysis. Descriptive statistical analysis was carried out. Continuous variables were expressed as medians and means with interquartile range (IQR) and standard deviation (SD), respectively. Categorical data was expressed as percentages.

Results

Patient characteristics

Table 1 lists the baseline characteristics of all patients. Of the 18 patients included in this study, there were 15 females. Majority of the patients were of Chinese ethnicity (83.3%), while the rest were Malay (5.6%), Indian (5.6%) and Vietnamese (5.6%). The median age of diagnosis of NPSLE was 33.5 years with a range between 18-73 years. The median disease duration from SLE onset to neuropsychiatric event was 4.5 months, with a range from 0-217 months. Six patients (33.3%) had NPSLE as their first presentation of SLE. Two patients had previous clinical stroke. None had pre-existing epilepsy or psychiatric conditions. Majority of the SLE patients had hematological manifestations (83.3%), followed by lupus nephritis (77.8%), mucocutaneous (61.1%) and arthritis (44.4%). The median SLEDAI-2K score at diagnosis of NPSLE was 24.

Table 1: Clinical characteristics of SLE patients.

Clinical characteristics of SLE patient	n (%)
Gender	
Female	15(83.3)
Male	3(16.7)
Ethnicity	
Chinese	15(83.3)
Malay	1(5.6)
Indian	1(5.6)
Other (Vietnamese)	1(5.6)
Age at diagnosis, years*	33.5(27-47)
Duration of disease at diagnosis of NPSLE, months*	4.5(0-48)
NPSLE as first presentation of SLE	6(33.3)
History of cerebrovascular accident	2(9.5)
Hematological	15(83.3)
Lymphopenia	13(86.7)
Leukopenia	10(55.6)
Thrombocytopenia	10(55.6)
Autoimmune Hemolytic anemia	9(50)
Lupus nephritis	14(77.8)
Class III	2(14.3)
Class IV	4(28.6)
Class V	1(7.1)
Class IV/V	3(21.4)
Mucocutaneous	11(61.1)
Arthritis	8(44.4)
Pulmonary	3(16.7)
Gastrointestinal	1(5.6)
Anti-phospholipid Syndrome	2(11.1)
SLEDAI-2K score at diagnosis of NPSLE*	24(19-29)

*Median (interquartile range)

Neuropsychiatric manifestations

A total of 26 neuropsychiatric events occurred in 18 patients as shown in Table 2. All patients had central nervous system manifestations and 7 patients (38.9%) had more than one neuropsychiatric syndrome at presentation. The most frequent clinical presentation

Table 2: Clinical features of NPSLE.

Clinical Features of NPSLE	n(%)
Acute confusional state	8(30.8)
Cerebrovascular disease	6(23.1)
Seizure disorder	5(19.2)
Mood disorder	2(7.7)
Psychosis	2(7.7)
Anxiety disorder	2(7.7)
Cognitive dysfunction	1(3.8)

Table 3: Laboratory indices.

Laboratory indices	n(%)
Hemoglobin, g/dL*	9.6(7.9-10.3)
Platelet, x10^9/L*	139.5(91-267)
White blood cell count, x10^9/L*	4.5(2.6-10.2)
Erythrocyte Sedimentation Rate, mm/hour*	54(17-106)
Low C3 complement, n(%)	14(77.8)
Low C4 complement, n(%)	14(77.8)
Positive Antinuclear antibody	17(94.4)
Homogeneous	13(76.5)
Speckled	6(35.3)
Nucleolar	1(5.9)
Positive Anti-dsDNA antibody	15(83.3)
Anti-RNP antibody	7(38.9)
Anti-Ro antibody	6(33.3)
Anti-Sm antibody	5(27.8)
Anti-La antibody	3(16.7)
Anti-cardiolipin IgM	3(16.7)
Anti-cardiolipin IgG	2(11.1)
Lupus anticoagulant	1(5.6)

*Median (interquartile range)

was acute confusional state (30.8%) followed by cerebrovascular disease (23.1%) and seizures (19.2%). The rest of the NPSLE manifestations were mood disorders (7.7%), psychosis (7.7%), anxiety disorder (7.7%) and cognitive dysfunction (3.8%).

Laboratory indices & CSF analysis

The median hemoglobin was 9.6 (7.9-10.3) g/dL, platelet 139.5 (91-267) × 10^9/L, white blood cell counts 4.5 (2.6-10.2) × 10^9/L and erythrocyte sedimentation rate 54 (17-106) mm/hour. Fourteen patients (77.8%) had low complements. Serologically, seventeen patients (94.4%) had positive antinuclear antibodies and majority were of homogeneous pattern as illustrated in Table 3. Fifteen patients (83.3%) had positive anti-dsDNA antibodies, 27.8% (5/18) had positive anti-Smith antibodies, 16.7% (3/18) had positive anticardiolipin IgM antibodies, 11.1% (2/18) had positive anticardiolipin IgG antibodies and 5.6% (1/18) had positive lupus anticoagulant.

Table 4: MRI brain findings.

MRI Brain findings at diagnosis of NPSLE	**n(%)**
Normal	2(11.1)
More than one abnormality	6(33.3)
Abnormal MRI	16(88.9)
White matter hyperintensities	11(61.1)
Acute infarcts	6(33.3)
Cerebral haemorrhage	4(22.2)
Cerebral atrophy	3(16.7)
Cerebral oedema	1(5.6)
Magnetic Resonance Angiography (MRA)	
No irregularities	9(50)
Arterial territories affected	9(50)
posterior cerebral artery	6(33.3)
middle cerebral artery	5(27.8)
anterior cerebral artery	4(22.2)
internal carotid artery	4(22.2
Magnetic resonance Venogram; n = 9	
Venous thrombosis	0(0)

Lumbar puncture was carried out on 9 patients to exclude CNS infections. All CSF cultures were negative for bacterial, viral, fungal and parasitic infections. These microbiological tests include cytomegalovirus, herpes simplex virus, varicella zoster virus, toxoplasma gondii, measles, mumps, acid-fast bacilli (AFB), tuberculosis, cryptococcus, aspergillosis and histoplasmosis.

Radiological features

All 18 patients had MRI and magnetic resonance angiography (MRA) of the brain performed as part of the evaluation. All except two patients (11.1%) had abnormal MRI brain and six patients (33.3%) had more than one abnormal MRI finding. As shown in Table 4, the commonest abnormality seen was white matter hyperintensities (61.1%) followed by cerebral infarction (33.3%), cerebral hemorrhage (22.2%), generalized cerebral atrophy (16.7%) and cerebral edema (5.6%).

Only half of the patients had abnormal MRA findings. MRA abnormalities reported include luminal irregularities, beading, narrowing, stenosis, occlusion and stuttering flow signals along the vessels. Among the 9 patients who had MRA abnormalities, the posterior cerebral artery (PCA) was the most commonly affected (33.3%), followed by the middle cerebral arteries (MCA) (27.8%), the anterior cerebral artery (ACA) (22.2%) and internal carotid artery (ICA) (22.2%). More than half of the patients (55.6%) had multi-vessel (3 or more vessels) involvement. Two patients had dual-vessel involvement and the remaining two patients had single-vessel involvement. Nine patients had magnetic resonance venogram performed and none of them had venous thrombosis.

Treatment and outcomes

Thirteen patients (72.2%) received intravenous methylprednisolone as part of their initial therapy. Three patients (16.7%) received intravenous hydrocortisone at a prednisolone daily dose equivalent of at least 1 milligram per kilogram body weight. The remaining two patients (11.1%) were on moderate doses of oral prednisolone of at least 0.5 milligram per kilogram body weight.

Ten patients (66.7%) were treated with intravenous cyclophosphamide as induction therapy and four had intravenous rituximab (22.2%). Other treatments used were mycophenolate mofetil (27.8%) and intravenous immunoglobulin (11.1%). One patient underwent plasmapheresis due to concurrent diffuse alveolar hemorrhage. The other treatments used were antiplatelet, anticoagulation and anti-convulsant. Psychiatric treatment included anti-psychotic, anti-depressants, anxiolytics and electroconvulsive therapy (as per Table 5).

Twelve patients (66.7%) showed clinical improvement with treatment of NPSLE. Three patients (16.7%) had relapsing disease who later presented with paranoid delusions, bipolar disease, anxiety disorder and seizures. There were three deaths (16.7%) which include deaths from diffuse alveolar hemorrhage and ischaemic heart disease. The cause of death of the third patient was unknown.

Discussion

Neuropsychiatric systemic lupus erythematosus (NPSLE) is one of the most severe presentations of SLE with high mortality rates of up to 19% [6,14]. The prevalence of NPSLE ranges from 12-56% and this wide variation can be explained by differences in study design, inclusion and exclusion criteria [2-5,7]. Locally, a retrospective study of SLE patients from the period of 1980 to 1992 reported a prevalence rate of 8.6% [15]. In this study, we describe the clinical characteristics, imaging features, treatment and outcomes of SLE patients with CNS involvement.

Table 5: Treatment and outcomes.

Treatment of NPSLE	n (%)
Intravenous methyl prednisolone	13(72.2)
Cyclophosphamide	10(66.7)
Mycophenolate mofetil	5(27.8)
Rituximab	4(22.2)
Intravenous Immunoglobulin	2(11.1)
Plasmapheresis	1(5.6)
Antiplatelet	3(16.7)
Anticoagulant	2(11.1)
Anticonvulsant	5(27.8)
Psychiatric treatment	3(16.7)
Outcomes	**n(%)**
Clinical improvement	12(66.7)
Relapsing NPSLE	3(16.7)
Death	3(16.7)
Diffuse alveolar hemorrhage	1(5.6)
Ischaemic heart disease	1(5.6)
Unknown	1(5.6)

Our study showed one third of patients had NPSLE as their first presentation of SLE, slightly higher compared to a systematic review by Zhang, et al. which reported 22.8% of patients who had NPSLE as an initial presentation [16]. Therefore, physician should remain cognizant of SLE patients who present with non-specific neuropsychiatric symptoms. Similar to other cohort studies, our patients had severe SLE disease with concomitant cytopenia, lupus nephritis, mucocutaneous and skeletal involvement at presentation.

Neuropsychiatric manifestations are classified into focal and diffuse syndromes. Focal neurological manifestations are thought to reflect localized CNS involvement and is attributable to structural abnormalities which may be a result of arterial ischaemia or venous thromboses. Examples are strokes, seizures and demyelinating syndromes. Diffuse neuropsychiatric manifestations are not associated with structural pathology and typically do not reflect disease activity in the CNS [17-19]. Examples are acute confusional state, mood disorder and psychosis. Among the twelve CNS syndromes, eight were present in our patients. Overall, the number of focal neurological syndromes and diffuse neuropsychiatric syndromes were almost the same. There were 14 focal neurological syndromes and 12 diffuse neuropsychiatric syndromes. Acute confusional state (27.5%) was the commonest, followed by cerebrovascular disease (20.7%) and seizure disorders (17.2%). These findings were similar to the inception cohort studied by Hanly, et al. and a retrospective study by Feng, et al. in 1982. The latter reported organic brain syndrome (characterized by impairment of orientation, perception, memory or intellectual function) being the commonest manifestation (47%), followed by seizures (24%) [20]. However, studies in China reported headache as the most frequent NPSLE manifestation [3,21].

Cerebrovascular disease was consistently among the top five neuropsychiatric manifestations in many studies and it is believed that antiphospholipid antibodies play a role in its pathogenesis [22]. However, this association was not observed in our cohort as among the patients with cerebrovascular disease, only one had antiphospholipid syndrome, while the rest were negative for anti-cardiolipin IgM, anti-cardiolipin IgG and lupus anticoagulant. Of note, beta-2 glycoprotein antibodies results were not available for our patients.

This would be helpful to better study the relationship between antiphospholipid antibodies and strokes.

The lack of specific laboratory marker, histopathology findings (CSF analysis and biopsy) and specific imaging tool often makes diagnosis of NPSLE difficult. Hence, it is prudent to rule out secondary causes as patients with cerebrovascular accident or CNS infections such as encephalitis or meningitis can present in a manner similar to NPSLE. Often, lumbar puncture is performed for CSF examination and culture to exclude infection. In our cohort, 9 patients had lumbar puncture and none had CNS infections.

Neuroimaging such as MRI brain is useful in excluding other causes of neuropsychiatric symptoms such as infections, abscesses, strokes or tumor, despite its subpar specificity of 60-82% [23]. Almost 90% of our patients had abnormal MRI brain, higher than the 53% reported by Steup-Beekman [24]. The relative order of frequencies of MRI abnormalities is similar in our current study and in the cohort described by Steup-Beekman's. Both cohorts report white matter hyperintensities as the commonest, followed by infarcts. Less common findings include cerebral hemorrhage and cerebral atrophy.

The underlying pathology of white matter hyperintensities are not fully understood. They are thought to possibly be multifactorial in etiology-small vessel angiopathy, microthromboemboli, vasculitis and demyelination [23,25]. In SLE patients, the presence of white matter hyperintensities has shown to be associated with older age, positive antiphospholipid antibodies, presence of disease damage, higher SLEDAI score, NPSLE, and presence of cerebral infarcts [23]. Further studies would be helpful to further delineate how white matter hyperintensities may be associated with inflammatory or ischaemic phenotypes of NPSLE [26,27]. It must also be remembered that white matter hyperintensities are not specific for NPSLE, and has been demonstrated in non-NPSLE patients [28].

MRA abnormalities were seen in 50% of patients. The posterior cerebral artery was the most commonly affected arterial territory, and 77.8% had more than a single vessel involvement. Only 44.4% of patients with arterial involvement had clinical stroke. As it is known that posterior cerebral artery supplies the thalamus, this may potentially cause a decline in cognitive function such as memory and inattention later in life. More studies are needed to correlate these findings with the disease course and its impact on neuropsychological outcomes.

The challenges in the management of NPSLE is contributed by the fact that patients frequently have more than 1 neuropsychiatric manifestation, as shown in 7 patients (38.9%) in our study. This affects treatment decisions as the rheumatologist needs to make a judgement of whether the patient's NPSLE has an inflammatory or ischaemic phenotype, or if both phenotypes co-exist.

Patients with inflammatory phenotypes of NPSLE are treated with immunosuppressants like intravenous pulsed methylprednisolone, cyclophosphamide and rituximab [29]. Currently, the available evidence for the use of glucocorticoids and cyclophosphamide come from several non-controlled trials, and randomized controlled trials respectively [30]. Based on this, majority of the patients in this cohort received intravenous pulsed methylprednisolone (72.2%) and cyclophosphamide (66.7%).

Three patients received antiplatelet, and another two were on warfarin for antiphospholipid syndrome (APS). Of note, the NPSLE manifestation in one of the patients with APS was not directly due to the hypercoagulable state. The wide range of treatment in our group of 18 patients, ranging from the varying glucocorticoid doses to the differing choices of steroid-sparers, is reflective of the diverse array of patient factors to consider in the management of NPSLE. Frequently, NPSLE is part of a multi-organ involvement by SLE. The rheumatologist also takes into consideration the patients' multiple co-morbidities such as infections or bleeding complications. As such, the choice of treatment -be it immunosuppressants, antiplatelet and/or anticoagulation- is affected by patient's concurrent medical issues at the time of management.

Apart from immunosuppressive therapies, appropriate symptomatic intervention also plays an important role in improving outcomes [29]. Co-management with the Neurologists and Psychiatrists were crucial as they provided specialist input on anti-convulsants (27.8%) and psychiatric interventions (16.7%). It is worth noting that three patients in our study that had a relapsing course of the NPSLE had predominantly psychiatric manifestations. As such, the management of NPSLE requires close collaboration with psychiatrists so that immunosuppressive therapy and psychiatric intervention can be titrated based on each individual patient's unique NPSLE manifestation to avoid over-treatment with immunosuppressants.

NPSLE has been associated with higher mortality. Zirkzee, et al. demonstrated that the hazard ratios were highest in patients with acute confusional state (HR 3.4) and older age at diagnosis of NPSLE. The causes of death varied from NPSLE itself (16%), SLE (non-NPSLE) (13%), infection (22%), cancer (13%) and others. In our study, two of the three who died had acute confusional state and seizures at presentation. NPSLE itself, however, was not the direct cause of death. Due to the small sample size, it is hard to postulate if early treatment contributed to a better outcome in these cases.

Our study is limited by the small number of patients identified with having NPSLE, and its retrospective

design. The reason for the small number of patients is contributed by under-reporting of neuropsychiatric diagnoses in the electronic medical records. This under-reporting has also affected the proper identification of patients with peripheral nervous system involvement of SLE from the medical records. As such, we have excluded patients with peripheral nervous system involvement in this study. Improved awareness and diagnosis of NPSLE and its 19 syndromes will allow us to better study this heterogenous condition.

The attribution of patients' symptoms to SLE remains a challenge. The ACR case definitions have been found to have low specificity for NPSLE [1,31,32]. In our study, we encountered patients who were initially documented as having headaches as a manifestation on SLE. These patients were later excluded from the analyses as they do not fit the description of 'Lupus headache', which SLEDAI-2K defines as a severe, persistent headache that may be migrainous, but must be nonresponsive to narcotic analgesia [32]. In this retrospective study, the diagnoses of NPSLE were made by the managing rheumatologist with the help of the available clinical and laboratory data. A prospective study will allow for the incorporation of a more standardized method of attribution that has been described by several authors [33,34]. A bigger study will provide better generalisation of the results.

This study is also not dedicated to analysing brain imagings. All our patients underwent conventional MRI brain with MRA as part of their evaluations. Although all the scans are performed in the same institution, they are reported by several different radiologists who were provided with the patient's history as part of clinical care. It would have been better if there was a designated radiologist who is blinded to patients' clinical background. In addition, advanced MRI techniques will be helpful to identify abnormalities not detected on conventional MRI.

Conclusion

Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) manifests in a variety of clinical presentations, and is the first manifestation of SLE in one third of our local NPSLE patients. Prompt diagnosis and management is essential to improve clinical outcomes.

Author Contribution

Both authors acknowledge they have contributed significantly, and were involved in the conceptualization and methodology of the study. The authors analysed the data and take responsibility for the accuracy of the data analysis. Both authors drafted, critically revised and approved the final manuscript.

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