Original Article

Central Nervous System Manifestation in Patients with SLE: A 12-Year Retrospective Chart Review at a Tertiary Center

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ABSTRACT

Background: Central nervous system manifestation of systemic lupus erythematosus (CNS-SLE) is a common complication, which is clinically associated with patient morbidity and mortality.

Objective: To determine the CNS-SLE manifestations and to determine the predictors of death among the studied cohort.

Design: Retrospective

Setting: King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia

Subjects: All patients diagnosed with SLE were identified, using a computerized retrieval system, for the period January 1, 2000 to May 31, 2012.

Intervention(s): Data pertaining to demographics, risk factors for cerebrovascular accident and CNS manifestations were collected from the patients’ medical charts.

Main Outcome Measure(s): CNS-SLE and the predictors of death among the studied cohort.

Results: The study included 307 patients (91% females) with a mean (M ± SD) age of 35.6 ±13 years and mean disease duration of 9 ± 5 years. CNS manifestations were found in 70 patients (23%). The commonest was stroke in 25 patients (35%) and aseptic meningitis, cerebritis, recurrent stroke and cavernous sinus thrombosis occurred only in one patient each (1.4%). The most significant predictors for CNS involvement were hyperlipidemia (OR = 5.48) followed by positive Antiphospholipid antibodies (OR = 2.74). By univariate analysis CNS involvement, negative anti-nuclear antibody (ANA) and combined low complements were found to be predictors of death.

Conclusions: Clinical studies have shown varying results with respect to the prevalence of CNS involvement in SLE. Antiphospholipid antibodies (APA) is a known risk factor whereas the role played by hyperlipidemia in escalating the risk of CNS involvement in SLE warrants further clinical evaluation.

KEYWORDS: central nervous system, neuropsychiatric, systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem disease. Involvement of the nervous system is a common complication of SLE. It predominantly involves the central nervous system (CNS) and is also known to affect the peripheral nervous system to a lesser extent.

CNS manifestations of SLE (CNS-SLE) affect patients’ physical and mental activity, and subsequently lower their life quality[1]. The prevalence of neuropsychiatric systemic lupus erythematosus (NPSLE) ranges from 14% to over 80%[2].

Although CNS-SLE is a serious complication of SLE, it is a possibly treatable illness[3]. CNS SLE manifestations can occur in isolation without the involvement of other body systems[9].

CNS-SLE manifestations range from serious manifestation like acute confusional state, seizure disorder, and stroke to subtle deficits such as mild cognitive dysfunction[4][5]. The differentiation between primary NPSLE and secondary NPSLE continues to remain one of the crucial challenges in the management of SLE patients[6]. Currently, there is a dearth of scientific data pertaining to the clinical predictors of CNS-SLE[7]. However, clinical research has established the association between specific autoantibodies and CNS-SLE. In this context, the role played by antiphospholipid antibodies (APA)
in the occurrence of cerebrovascular disease (CVD) and the association of psychosis and depression with anti ribosomal P antibodies has been documented in scientific literature[2-4]. The objectives of the current study were to determine the CNS manifestations of SLE and to determine the predictors of death among the studied cohort.

PATIENTS AND METHODS

Patient selection and data retrieval

This retrospective descriptive study was conducted at the King Abdulaziz university hospital (KAUH), located at Jeddah, Kingdom of Saudi Arabia (KSA). Patients with a diagnosis of SLE were identified using the computerized databases of KAUH from 01 January 2000 to 31 May 2012. Medical records of both in and out patients, coded for the diagnosis of SLE, were reviewed to ensure that patients met the criteria for the diagnosis of SLE[9]. Patients with autoimmune diseases other than SLE were excluded. The study was approved by the Biomedical Ethics Research Committee at KAUH.

Clinical and laboratory evaluation

The following data were recorded: demographic data (age, gender, nationality), duration of disease at the time of study, major risk factors for CVD were included in our patient check list in the form of diabetes mellitus, hypertension, hyperlipidemia and smoking. CNS-SLE syndromes were reviewed based on medical records data. Given below is an explanation of the diagnostic criteria and definitions of CNS-SLE included in the current study.

All past NPSLE syndromes were listed and classified according to the standardized American College of Rheumatology (ACR) nomenclature and case definitions[9,10]. Demyelinating syndrome was defined as acute or relapsing demyelinating encephalomyelitis with evidence of discrete neurologic lesions distributed in place and time[8].

The term ‘lupoid sclerosis’ has been used to describe SLE with demyelinating syndromes resembling multiple sclerosis which are a rare manifestation of SLE and are a diagnostic challenge. Whether this entity actually exist is not clear. The committee therefore, changed the definition to demyelinating syndrome with the appropriate description to enhance further research on this rare condition[9].

The diagnostic criteria for diabetes mellitus (DM) were based upon the guidelines of the American Diabetes Association (ADA)[10]. The definition of hypertension (HTN) suggested in 2003 by the seventh report of the Joint National Committee (JNC 7)[11] was applied in the current study. Diagnosis of hyperlipidemia was based upon the reference values followed in the United States for the ninetieth percentile for total cholesterol, low density lipoprotein (LDL) cholesterol and triglycerides and for the tenth percentile for high density lipoprotein (HDL) cholesterol[12].

APA syndrome was diagnosed based on the modified Sapporo criteria[13]. Anti-double-stranded DNA autoantibodies (anti-dsDNA) test was performed using the enzyme linked immunosorbent assay (ELISA) technique (Quanta LiteTM dsDNA Kit, INOVA Diagnostic Inc, CA, USA), and it was measured in IU/ml. Based on the manufacturer’s instructions, results of anti-dsDNA tests were classified as follows: 1) Negative: If the level was between 0 - 200 IU/ml; 2) Equivocal: If the level was between 201 - 300 IU/ml; 3) Moderately positive: If the level was between 301 - 800 IU/ml; and 4) Strongly positive If the level was > 801 IU/ml. Complement components 3 and 4 (C3 and C4) were measured by nephelometry; hypocomplementemia was defined as a level below the lower normal value (C3 < 0.75 mg/l and C4 < 0.2 mg/l). There were no specific diagnostic criteria to differentiate between delirium, confusional states and encephalopathy.

Acute confusional state (ACS) was diagnosed and defined as per American Psychiatric Association’s Diagnostic and Statistical Manual, 4th edition (DSM-IV), which lists four key features that characterize delirium as follows; 1) Disturbance of consciousness with reduced ability to focus, sustain, or shift attention. 2) A change in cognition or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established, or evolving dementia. 3) Disturbances that develop over a short period of time (usually hours to days) and tend to fluctuate during the course of the day. 4) Evidence from the history, physical examination or laboratory findings suggestive of the fact that the disturbance is caused by a medical condition, substance intoxication, or medication side effect[14]. Any possible secondary cause of ACS was considered including infection, electrolyte abnormalities, renal failure, drug effects, etc[15]. Cognitive dysfunction was defined as any combination of the following; difficulty in short or long-term memory, impaired judgment and abstract thinking, aphasia, apraxia, agnosia, and personality changes[16]. Psychosis was defined as impaired and bizarre thinking that often includes delusions and hallucinations[17]. Mood disorders such as depressive syndromes are defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)[18]. A major depressive syndrome or episode was defined as five or more of the following symptoms, for most of the day nearly every day for a minimum of two consecutive weeks; depressed mood, loss of interest or pleasure in most or all activities, insomnia or hypersomnia, change
in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, thoughts of worthlessness or guilt, recurrent thoughts about death or suicide (at least one symptom being either depressed mood or loss of interest or pleasure). Diagnostic criteria from the DSM-IV for anxiety disorder include excessive anxiety and worry about a number of events or activities, occurring more days than not for at least six months that are out of proportion to the likelihood or impact of feared events\(^{19}\).

Cerebrovascular disease (CVD) included ischemic stroke, transient ischemic attack (TIA), hemorrhagic stroke, chronic multifocal disease (recurrent or progressive neurologic deterioration attributable to CVD) and sinus thrombosis\(^{20}\). Only radiologically confirmed hemorrhagic and ischemic stroke were included. The definition of TIA was endorsed from the 2009 guidelines from the American Heart Association and American Stroke Association (AHA/ASA) which included: a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction\(^{21}\).

The current study included any reported attack of seizure whether single or repeated. Epileptic seizures were defined as seizures caused by electrical hypersynchronization of neuronal networks in the cerebral cortex while epilepsy was defined as recurrent epileptic seizures due to a genetically determined or acquired brain disorder\(^{22}\). Any movement disorders and their subtypes were included in this study; chorea, ataxia, choreoathetosis, dystonia, and hemiballismus\(^{23}\). Transverse myelitis (TM) is defined as an acute inflammatory process affecting a focal area of the spinal cord and characterized clinically by acutely or sub acutely developing symptoms and signs of neurological dysfunction in motor, sensory and autonomic nerves and nerve tracts of the spinal cord\(^{24}\). The study included any documented history of headache regardless of the type or the severity. The study included the diagnosis of aseptic meningitis if it presented with symptoms, signs and laboratory evidence for meningeal inflammation with negative bacterial cultures\(^{25}\).

Lupus nephritis was defined by the presence of any of the following: proteinurea, red blood cell casts, serum creatinine >120 mmol/l or estimated glomerular filtration rate (GFR) <89 ml/min per 1.73 m\(^2\) of body surface area\(^{26}\). We excluded all patients who were on dialysis. Pulmonary manifestations were either: pleurisy, pleural effusion and pericardial effusion, pneumonia, pneumonitis, pulmonary hypertension, interstitial lung disease, bronchiectasis, diaphragmatic dysfunction, pulmonary tuberculosis (TB), pulmonary embolism (PE), adult respiratory distress syndrome (ARDS), diffuse alveolar hemorrhage (DAH), cryptogenic organizing pneumonia (COP) and pulmonary edema\(^{27}\). Skin manifestations were identified as the presence of any of the following: malar rash or photosensitivity or discoid rash\(^{28}\).

Statistical analysis

Statistical analysis was done using statistical package for social science (SPSS software version 18). The qualitative data were presented in the form of numbers and percentages. Chi-square test was used to compare qualitative data of two groups. Yates correction was used when appropriate. Odds ratio (OR) and 95% confidence intervals (CI) were calculated to estimate the risk. The quantitative data were presented in the form of mean and standard deviation (SD). Student t test was used to compare quantitative data of two groups. Logistic regression was done to determine the predictors of death. Results with p-value less than 0.05 were considered statistically significant.

RESULTS

The study included 307 patients with SLE from 01 January 2000 to 31 May 2012. The study population mainly comprised of females (91%) with a mean (± SD) age of 35.6 ± 13 years and mean disease duration of 9 ± 5 years at the time of diagnosis. CNS manifestations were found in 70 patients (23%). Stroke was the commonest manifestation, observed in 25 patients (35%). Out of these, 16 patients (64%) were cases of ischemic stroke whereas nine (36%) experienced hemorrhagic stroke. Aseptic meningitis, cerebritis, recurrent stroke and cavernous sinus thrombosis comprised the least common manifestations seen only in one patient each (1.4%) each. Table 1 summarizes the CNS manifestation in the studied population.

We tried to analyze if the presence of stroke risk factors in SLE patient with stroke have any statistical

<table>
<thead>
<tr>
<th>CNS Neuropsychiatric manifestations</th>
<th>Number of cases</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic Stroke</td>
<td>16</td>
<td>64</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>9</td>
<td>36</td>
</tr>
<tr>
<td>Headache</td>
<td>24</td>
<td>34</td>
</tr>
<tr>
<td>Seizure</td>
<td>17</td>
<td>24.2</td>
</tr>
<tr>
<td>Acute confusional state</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Psychiatric symptoms</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Abnormal movement</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Transverse myelitis</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Aseptic meningitis</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>Cavernous sinus Thrombosis</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>Memory disturbance</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Several features may co-exist with the same patient
significance in our study. As mentioned previously 25 patients had stroke, 19 out of 25 patients (76%) had no co-morbid illnesses. Only six patients (23%) had co-morbid illnesses which were not statistically significant risk factors for stroke development. All of the co-morbid patients were hypertensive, while three were diabetics, two were hyperlipidemic and none were smokers.

On examining the different clinical and laboratory variables for the risk of the development of any CNS manifestation, the most significant predictors were hyperlipidemia (OR = 5.48, p = 0.001) followed by positive APA (OR = 2.74, p = 0.001). Table 2 summarizes the association between different variables and the CNS manifestations. Other co-morbidities due to SLE did not show any statistical significance as predictors for the development of CNS-SLE apart from pulmonary involvement (p-value = 0.045, Table 4).

During the study period, a total of 28 patients died (9%). Out of these, 10 patients (36%) had CNS manifestations. As per univariate analysis, certain predictors of death were noted among the study patients, namely: negative ANA, low C3, CNS manifestations and combined low C3 and C4. However, as per multiple logistic regression analysis, the only significant predictor was negative ANA, CNS manifestations and low C3. On the other hand combined low C3 and C4 were found to be non-significant (Table 3). Positive APA and anti-dsDNA did not represent a significant risk for mortality.

Table 2: Characteristics of 307 patients with SLE with and without central nervous system manifestations

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>With CNS n = 70 (%)</th>
<th>Without CNS n = 237 (%)</th>
<th>p-value b</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (Mean ± SD)</td>
<td>34.84 ± 13.1</td>
<td>35.84 ± 13.66</td>
<td>0.5</td>
<td>0.5</td>
<td>(0.55-1.66)</td>
</tr>
<tr>
<td>Less than 30 (n = 124)</td>
<td>28 (40)</td>
<td>97 (41)</td>
<td>0.99</td>
<td>0.96</td>
<td>(0.6-1.79)</td>
</tr>
<tr>
<td>More than 30 (n = 182)</td>
<td>42(60)</td>
<td>140(59)</td>
<td>1.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (n = 276)</td>
<td>64 (91)</td>
<td>212 (89)</td>
<td>1.26</td>
<td>0.46</td>
<td>(0.46-3.59)</td>
</tr>
<tr>
<td>Male (n = 31)</td>
<td>6(9)</td>
<td>25 (11)</td>
<td>0.079</td>
<td>0.8</td>
<td>(0.28-2.16)</td>
</tr>
<tr>
<td>Nationality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saudi n = 170</td>
<td>27 (39)</td>
<td>143 (60)</td>
<td>0.41</td>
<td>0.23</td>
<td>(0.23-0.69)</td>
</tr>
<tr>
<td>Non Saudi n = 137</td>
<td>43 (61)</td>
<td>94 (49)</td>
<td>0.002*</td>
<td>2.42</td>
<td>(1.35-4.35)</td>
</tr>
<tr>
<td>Duration of disease (Mean ± SD) Years</td>
<td>9.25 ± 6.16</td>
<td>9.36 ± 5.24</td>
<td>0.89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-morbid illness (n = 58)</td>
<td>14(20)</td>
<td>44 (18.6)</td>
<td>0.92</td>
<td>1.1</td>
<td>(0.56-2.15)</td>
</tr>
<tr>
<td>Diabetes Mellitus (n = 16)</td>
<td>4 (6)</td>
<td>12 (5)</td>
<td>0.76</td>
<td>1.14</td>
<td>(0.35-3.64)</td>
</tr>
<tr>
<td>Hypertension (n = 39)</td>
<td>14(20)</td>
<td>35 (15)</td>
<td>0.38</td>
<td>1.44</td>
<td>(0.73-2.86)</td>
</tr>
<tr>
<td>Hyperlipidemia (n = 17)</td>
<td>10 (14)</td>
<td>7 (3)</td>
<td>0.001*</td>
<td>5.48</td>
<td>(1.82-16.76)</td>
</tr>
<tr>
<td>Smoking (n = 5)</td>
<td>1(1.4)</td>
<td>4 (1.7)</td>
<td>0.67</td>
<td>0.84</td>
<td>(1.7-7.7)</td>
</tr>
<tr>
<td>APA – positive (n = 65)</td>
<td>25(37)</td>
<td>40(21)</td>
<td>0.001*</td>
<td>2.74</td>
<td>(1.45-5.17)</td>
</tr>
<tr>
<td>Anti-dsDNA IU/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative 0 - 200 (n = 82)</td>
<td>17(24)</td>
<td>65(27.4)</td>
<td>RC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equivocal 201-300 (n = 45)</td>
<td>9(12)</td>
<td>36(15.2)</td>
<td>0.89</td>
<td>0.96</td>
<td>(0.35-2.57)</td>
</tr>
<tr>
<td>Moderately positive 301-800 (n = 50)</td>
<td>9(12)</td>
<td>41(17)</td>
<td>0.87</td>
<td>0.84</td>
<td>(0.31-2.23)</td>
</tr>
<tr>
<td>Strongly positive &gt; 800 (n = 130)</td>
<td>38(50)</td>
<td>95(40)</td>
<td>0.39</td>
<td>1.41</td>
<td>(0.69-2.85)</td>
</tr>
<tr>
<td>Hypocomplementemia mg/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3 (n = 88)</td>
<td>23(34)</td>
<td>65(30)</td>
<td>0.46</td>
<td>1.29</td>
<td>(0.7-2.39)</td>
</tr>
<tr>
<td>C4 (n = 155)</td>
<td>37(55)</td>
<td>118(55)</td>
<td>0.54</td>
<td>1.15</td>
<td>(0.69-2.03)</td>
</tr>
<tr>
<td>C3 &amp; C4 Combined (n=73)</td>
<td>21(33)</td>
<td>52(25)</td>
<td>0.21</td>
<td>1.52</td>
<td>(0.8-2.88)</td>
</tr>
</tbody>
</table>

SLE: systemic lupus erythematosus, CNS = central nervous system manifestation, APA = antiphospholipid, C = complement, RC = reference category for other variables is the negative group, OR = odds ratio, CI = confidence interval

a Data were presented as frequencies (number and percentages) unless otherwise stated
b p-value was estimated by Chi-square, *significant association p < 0.05

Table 3: Univariate and multivariate analysis of the death predictors among the studied patients with SLE (n = 307)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adjusted odds ratio 95% confidence interval</th>
<th>p-value</th>
<th>Unadjusted odds ratio 95% confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS manifestations</td>
<td>2.39 (1.85-6.69)</td>
<td>0.075</td>
<td>2.02 (0.85-4.62)</td>
<td>0.069</td>
</tr>
<tr>
<td>Low C3</td>
<td>1.96 (0.71-16.7)</td>
<td>0.04*</td>
<td>2.229 (1-4.96)</td>
<td>0.71</td>
</tr>
<tr>
<td>Combined low C3 and C4</td>
<td>2.33 (0.21-25.71)</td>
<td>0.029*</td>
<td>2.42 (1.07-5.46)</td>
<td>0.48</td>
</tr>
<tr>
<td>Negative ANA</td>
<td>15.47 (7.6-71.36)</td>
<td>0.001*</td>
<td>17.47 (7.6-71.36)</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

CNS: central nervous system manifestation, ANA: antinuclear antibody, C: complement, * = statistically significant
The calculated mean of duration between the central nervous system insult in SLE patients and the time of death was 16 ± 4.4 months.

DISCUSSION

The three most important findings elicited through this study are as follows: The prevalence of CNS-SLE was determined to be 23%, the most common manifestation was stroke occurring in 35% of the patients and a significant association was noted between the occurrence of these manifestation and positive APA as well as hyperlipidemia. The presence of CNS involvement combined with low complement and negative ANA were found to be crucial predictors of CNS-SLE related mortality.

The current study is quite similar to a previous study conducted by Kasitanon et al which showed the frequency of NPSLE to be 18%[10, 28]. Previous studies by Piyawan et al and Mok et al revealed a much lower frequency of CNS-NP-SLE than our study (11.3% and 13.5% retrospectively)[7, 29]. The current study reported a lower prevalence than the studies conducted by Ainala et al and Brey et al which showed a frequency of 54% and 55.4% respectively[6, 20]. Stroke showed the highest frequency among other CNS manifestations (35%), followed by headache (34%) and seizure (24.2%).

In the current scientific literature review, a recent study by Piyawan et al[7] showed high prevalence of seizure (32%), CVA (23%) and Psychosis (23%). In contrast, the results of some previous SLE cohort studies[6,9,31,32] showed that the CNS-SLE most commonly involved cognitive function (55 - 80%), followed by headache (24 - 72%), and psychosis (0 -8%).

In the current study, the prevalence of the ischemic subtype of stroke was found to be much higher than the hemorrhagic subtype (64% versus 36% respectively). In comparison, previous similar studies have reported only one case as recurrent ischemic stroke[33, 34]. The pathogenesis of CVD in SLE is related to multifactorial processes such as accelerated atherosclerosis and a hypercoagulable state as a consequence of APA[35]. Both, large or small cerebral vessels are a target for SLE[36].

Headache was reported in a total of 24 out of 70 patients. However, it is noteworthy in this regard, that the causes of headache can be multifactorial. Also, it is practically difficult in a retrospective study, to prove if all cases of headache were directly related to SLE disease or not. Therefore, establishing a direct causal relationship seems difficult in this scenario[37]. We could not find details about types of headache for most patients. This is a limitation of our study due to its retrospective design.

Two cases out of 70 were diagnosed as transverse myelitis, which is a well-known neurological association with SLE and may be its initial feature[38].

We had one case of aseptic meningitis which may not be directly related to SLE but to the medications used in treatment, including Ibuprofen (and less commonly other non steroidal anti inflammatory drugs - NSAIDs, excluding aspirin) and azathioprine[39]. ACS was reported in a total of 10 out of 70 patients (14.2%).

A high prevalence of seizures was noted in the study (24.2%). Seizures can be primarily caused by lupus or secondary to brain infection, drugs, or metabolic disturbances and hypertension[40]. We had 17 / 70 patients with seizure presentation. Nine cases were generalized tonic clonic seizures, one case was a simple partial seizure, one case was partial seizure with secondary generalization, one case was complex partial seizure and one case had both types of seizures (myoclonus and generalized tonic clonic). Data was missing in five cases. Psychiatric symptoms were reported in eight patients (11%). Five cases were reported as psychosis, one case had an anxiety disorder and depression was reported in two cases.

Similar to the study conducted by Piyawan et al[7], this study too, did not report any case of cognitive dysfunction. Also, this study did not find any documented case of demyelinating syndrome. A variation can be seen in the prevalence of different CNS manifestations between different clinical studies. This can be attributable to multiple factors including the age of SLE onset, race, ethnicity and socio-economic status and the method of study[7], and can also be related to ACR nomenclature system[9].
The current study tried to elicit significant predictors for the occurrence of CNS-SLE. The findings of this study showed that the presence of ANA and antibodies to dsDNA did not correlate with CNS manifestations. The risk of CNS-SLE in APA positive patients was found to be statistically significant (p = 0.001). Although hyperlipidemia showed significant association with the development of CNS-SLE, the small number of hyperlipidemic patients in this study, limits the robustness of this result.

With respect to the prediction for stroke or other CNS-SLE, the data gathered in the current study, could not differentiate whether or not these predictors are secondary to SLE. This study did not include the control status of these diseases. However, it should be included in future studies.

The European League against Rheumatism (EULAR) recommendation suggests treatment for NPSLE with steroids, immunosuppressants, antiplatelet and anticoagulation agents[40]. However, clear guidelines for its prevention are unavailable. Since APA and hyperlipidemia play a strong role in prediction, a physician could treat every SLE patient with an agent that may affect both. For example, the antimalarial agent hydroxychloroquine, as recent studies suggested, may act as a seroconverter of APA and may lower the lipid level[42,43].

The strength of this study is that it included a large number of SLE patients. On the other hand, the limitation of the study is its retrospective nature which might have resulted in the underestimation of some of the manifestations, specifically cognitive impairment, although it was included in the classification criteria. In addition, the onset of DM and HTN in relation to SLE onset, were not recorded. This makes it unclear whether these were a primary or secondary to SLE. The control status of the different risk factors for CVD could not be documented in this study. Hence, a prospective study has been initiated, in order to evaluate SLE patients for cognitive impairment alone, to better understand whether or not this problem has been underestimated.

CONCLUSION
Clinical studies have shown varying results with respect to the prevalence of CNS involvement in SLE. APA is a known risk factor whereas the role played by hyperlipidemia in escalating the risk of CNS involvement in SLE warrants further clinical evaluation.

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REFERENCES