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NEURO PSYCHIATRIC LUPUS PATIENTS

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CERTIFICATE

This to certify that dissertation entitled, "**A STUDY ON NEUROPSYCHIATRIC LUPUS PATIENTS"**, submitted by **Dr.K.SEERALA BOOPATHY,** in partial fulfillment for the award of the degree of Doctor of Medicine in Rheumatology by The Dr.M.G.R. Medical University, Chennai is a bonafide record of the work done by him in the Department of Rheumatology, Madras Medical College, during the academic year 2005-2008.

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CONTENTS

introduction

Neuropsychiatric systemic lupus erythematosus (NPSLE) could be defined as the neurologic syndromes of the central, peripheral and autonomic nervous system and the psychiatric syndromes observed in patients with SLE in which other causes have been excluded.

Hebra and Kaposi in 1875[1] were the first to note central nervous involvement in lupus and while writing on the erythema group of skin diseases in 1885, Osler[2] discussed cerebral changes in SLE and reported a patient with SLE and hemiplegia.

Since the first description of SLE in the nineteenth century by Kaposi and Osler, it soon became obvious that the plethora of NPSLE manifestations were not easy to handle in a uniform and reproducible way. Symptoms and signs could be focal, diffuse, central, peripheral, psychiatric, isolated, complex, simultaneous and sequential, representing both active and inactive disease states. Attribution of any manifestations to SLE, whether it be to make a clinical diagnosis or to study the condition, is a problem since concomitant drugs, infections, metabolic disorders or atherosclerotic disease can cause neuropsychiatric manifestations and make it extremely difficult to separate these from genuine lupus manifestations. Kassan and Lockshin were one of the first to draw attention to the complexity of nervous system manifestations of SLE and the need for a more organized and more easily translatable classification. In addition to recognizing specific manifestations, they stressed the importance of confounding variables and assessing the chronological course and functional impact of NP events.

How et al. developed a classification of NP-SLE for their studies of antineuronal antibodies. They identified major and minor neurologic and psychiatric manifestations. An individual patient was deemed to have NP-SLE if they had one major criterion alone or one minor criterion plus an abnormality on electroencephalography, nuclear brain scanning, cerebrospinal fluid (CSF) examination or cerebral angiography. Other potential etiologic features such as uremia, hypertension, infection and corticosteroids were considered and excluded prior to attributing the NP event to SLE. However, non-SLE controls were not included in the study and this classification scheme for NP-SLE remains unvalidated.

Potential involvement of the nervous system by systemic lupus erythematosus (SLE) has been recognized ever since the multisystem nature of the disease first was appreciated. Clinical features include both neurologic (N) and psychiatric (P) manifestations, which may involve both the central and peripheral nervous systems. Although there have been significant advances in understanding some aspects of neuropsychiatric (NP) SLE in recent years, nervous system disease continues to pose diagnostic, therapeutic, and scientific challenges for physicians and researchers alike.

Classification of neuropsychiatric systemic lupus erythematosus

It is generally accepted that the NP manifestations of SLE include a much broader spectrum of disease than the two features included in the current American College of Rheumatology (ACR) classification criteria [3,4], namely seizures and psychosis. Central nervous system (CNS) involvement predominates over peripheral nervous system disease and may take the form of diffuse disease (e.g., psychosis and depression) or focal disease (e.g., stroke and transverse myelitis) depend upon the anatomic location of pathology. Over time, several classifications have been developed for NP-SLE [5–7], none of which has received universal acceptance. A deficiency in many of the classifications of NP-SLE has been the lack of definition of individual manifestations and lack of standardization for investigation and diagnosis.

In 1999, the ACR research committee produced a standard nomenclature and set of case definitions for NP-SLE [8]. Using a consensus approach and drawing on a pool of experts from several subspecialties including rheumatology, neurology, immunology, psychiatry, and neuropsychology, 19 NP syndromes (Box 1) were defined, and diagnostic criteria were developed [8]. For each NP syndrome, potential etiologies other than SLE were identified for either exclusion, or recognition as an association, acknowledging that in some clinical presentations it is not possible to be definitive about attribution.

The issue of the identification of other potential causes for NP events in SLE patients is critical and was not addressed adequately in previous studies of NP-SLE.

Box: 1 Neuropsychiatric syndromes in systemic lupus erythematosus as defined by the American College of Rheumatology:

Central nervous system:

Aseptic meningitis

Cerebrovascular disease

Demyelinating syndrome

Headache

Movement disorder

Myelopathy

Seizure disorders

Acute confusional state

Anxiety disorder

Cognitive dysfunction

Mood disorder

Psychosis

Peripheral nervous system

Guillain-Barre syndrome

Autonomic neuropathy

Mononeuropathy

Myasthenia gravis

Cranial neuropathy

Plexopathy

Polyneuropathy

Epidemiology

The ACR nomenclature and case definitions for NP-SLE have been validated in a cross-sectional, population-based study by Ainiala et al [9]. Forty-six SLE patients were compared with 46 individuals randomly selected from the Finnish population register and matched by age, gender, education, and residence. At least one NP manifestation was identified in 91% of the 46 Finnish patients compared with 54% of controls. This provided an odds ratio of 9.5 (95% confidence interval (CI) 2.21 to 40.8) for the occurrence of an NP event and specificity of 46%.

By excluding headache, anxiety, mild depression, mild cognitive impairment, and polyneuropathy without electrophysiological confirmation, the prevalence of NP disease fell from 91% to 46% in SLE patients and from 54% to 7% in controls. This provided an odds ratio of 7.0 (95% CI 2.09 to 23.47) and specificity of 93%. In addition to the study of Ainiala et al, at least four other groups [10–13] have used the ACR nomenclature to classify their SLE cohorts for NP-SLE manifestations.

The overall prevalence of NP disease in these patient populations has varied between 37% and 95%.Of interest, the range in the prevalence of NP-SLE in these studies was as wide as that reported before the introduction of the ACR nomenclature. In previous studies, NP disease was reported in 14% to 75% of

SLE patients [14–16]. The attribution of individual NP events to SLE or to an alternative etiology remains a challenge. In the absence of a diagnostic gold standard for most of the NP-SLE syndromes, attribution is determined on the basis of exclusion using the best available clinical, laboratory, and imaging data.

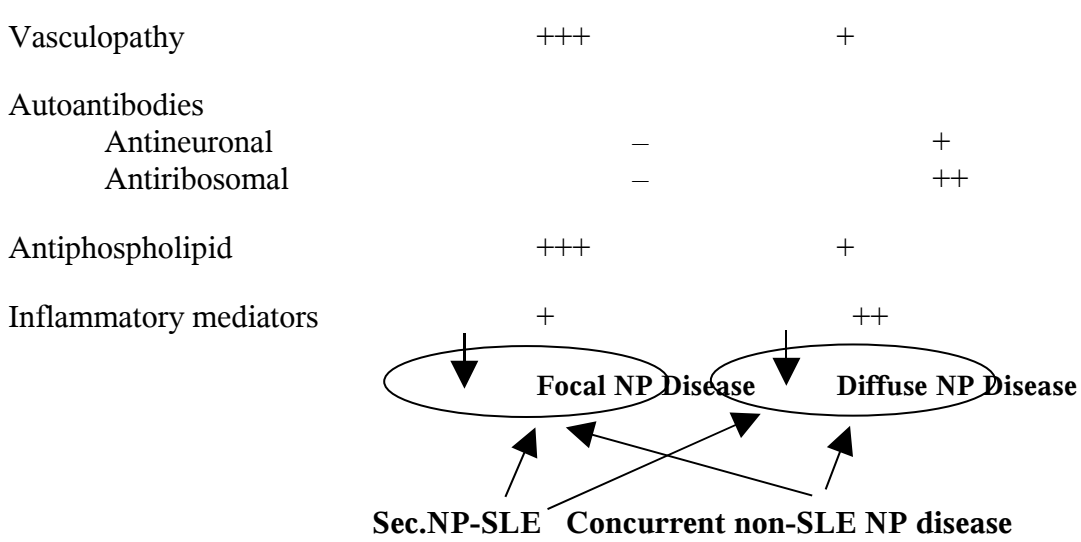
The ACR nomenclature [8] provide a basis for addressing this issue in a systematic manner, because for each NP syndrome there is a comprehensive list of exclusions and associations, the presence of which may indicate an alternative etiology. Using this approach and taking into consideration the temporal relationship between the NP event and the diagnosis of SLE, a recent study has determined that up to 41% of all NP events in SLE patients may be attributed to factors other than lupus. [11]Despite the improved definitions for individual NP syndromes, there continues to be substantial variability in the overall prevalence of NP disease between different populations. Whether this represents inherent differences between study cohorts or a bias in data acquisition remains to be determined. None of the individual NP manifestations are unique to lupus, and indeed some occur with considerable frequency in the general population.

Thus, the inclusion of control groups is critical to determine whether the prevalence of NP disease in SLE patients is in excess of that found in the normal population and in other chronic disease groups. Because many of the NP syndromes are quite rare (less than 1%), multicenter efforts will be required to assemble sufficient numbers of patients for study. Attribution of NP disease in individual patients remains a challenge, particularly in the absence of a diagnostic gold standard. Nevertheless, current evidence suggests that non-SLE factors likely contribute to a substantial proportion of NP disease in SLE patients, particularly the softer NP manifestations such as headache, anxiety, and some mood disorders.

Etiology of neuropsychiatric systemic lupus erythematosus

Given the plethora of NP manifestations reported in SLE patients, it is unlikely that there is a single pathogenic mechanism. NP events in SLE may be caused by a primary manifestation of the disease, secondary complications of the disease or therapy such as hypertension or infection, or a coincidental problem unrelated to lupus (Fig. 1).

Fig 1 Contributing factors



Box 2. Pathogenesis of neuropsychiatric systemic lupus erythematosus

Vascular abnormalities

Noninflammatory vasculopathy

Vasculitis

Thrombosis

Auto antibodies

Anti neuronal antibodies

Antiribosomal P antibodies

Antiphospholipid antibodies

Inflammatory mediators

IL-2, 6, 8, and 10

Interferon-alpha

Tumor necrosis factor–alpha

Matrix metalloproteinase (MMP)–9

Vasculopathy

Evidence in support of vascular abnormalities in NP-SLE may be found in neuropathologic studies [17–18]. A bland, noninflammatory vasculopathy involving small vessels was the predominant finding in these studies. In contrast, inflammatory disease of small or large vessels was rare. Brain micro infarcts occurred in association with, and were attributed to the microangiopathy [17]. Although instructive, there are significant limitations to using brain pathology as a means of advancing understanding of NP-SLE. First, patients who come to autopsy, which has been the most frequent source of brain tissue, represent a subset of patients with the most severe disease. Second, there is frequently a temporal disconnect between the NP event and tissue sampling. Third, this approach is restricted to the detection of structural abnormalities. Finally, confounding factors such as infection, hypertension, or corticosteroids may modify the original pathology that occurs as a consequence of the disease. The solution to these problems may come from advances in imaging technology that can act as a surrogate for brain biopsy.

Auto antibodies

A humoral immune response directed against several families of auto antigens on neurons, ribosomes, and phospholipid-associated proteins has been implicated to a varying extent in the pathogenesis of NP-SLE. The data from human studies implicating antineuronal antibodies is largely circumstantial. This includes the temporal relationship between clinical events and serologic findings [19], the presence of auto antibodies in the cerebrospinal fluid (CSF) [20], and, to a very limited extent, their identification in neuronal tissues from patients succumbing to the disease [21]. The presence of auto antibodies in the CSF of SLE patients is likely because of passive transfer from the circulation through a permeabilized blood–brain barrier [22,23], and, independently, to direct intrathecal production [19,22].

More direct evidence for the pathogenic potential of antineuronal antibodies is derived from animal

studies in which the intracranial injection of auto antibodies reactive with neuronal tissues has been shown to induce memory deficits, seizures, and neuropathologic changes. Considerable effort has gone into identifying the fine specificity of this family of auto antibodies. For example, Hanson et al [24] described reactivity to a 50-kd neuronal membrane protein in SLE patients. These auto antibodies bound to the surface of cultured rat neuroblastoma cells, and on Western blotting identified a protein of comparable size in human fetal brain and bovine adult brain. Although there was a significant association between these auto antibodies and NP-SLE, this was not restricted to any particular clinical subset of NP disease.

Auto-antibodies to gangliosides, which are a family of acid glycolipids predominantly located on neuronal and myelin membranes in the central and peripheral nervous system, have been studied extensively in SLE and in neurologic disorders such as multiple sclerosis. Although present in serum and CSF of SLE patients, there has not been a consistent association with NP manifestations of the disease.

Anti-lymphocyte antibodies are not specific for SLE and can occur in other illnesses, including infections, malignancy, inflammatory bowel disease, and multiple sclerosis. A subset of antilymphocyte antibodies, however, cross-react with neurons. Fever, neuropsychiatric symptoms, skin lesions, and hematologic abnormalities are the most common manifestations in patients with SLE and serum lymphocytotoxic antibodies. Denburg et al. has related cognitive dysfunction to the presence of serum IgM lymphocytotoxic antibodies in over 445 patients evaluated. This may reflect the presence of the antineuronal subset of antilymphocyte antibodies.

Most recently, attention has been focused on anti-NR2 glutamate receptor antibodies as a potentially novel system that could explain some of the complexities of NP-SLE. The NMDA (N-methyl-d-aspartate) receptors NR2a and NR2b bind the neurotransmitter glutamate and are present on neurons throughout the forebrain [25]. The hippocampus, which is the anatomical structure closely linked to learning and memory, has the highest density of brain NMDA receptors. In addition to their putative role in learning and memory [26], these receptors display altered expression in major psychoses, and if engaged by receptor antagonists, they cause hallucinations and paranoia.

A recent study [27] has shown that a subset of anti-DNA antibodies, derived from both murine models of SLE and from four human subjects with the disease, cross-react with a pentapeptide consensus sequence that is present in the extracellular, ligand binding domain of NR2 receptors. Moreover, these antibodies induced apoptotic cell death of neurons in vitro and in vivo and were present in the CSF of one SLE patient with progressive cognitive decline.

Thus, in contrast to the previously described antineuronal antibodies in SLE, the anti-NR2 glutamate receptor antibodies appear to have a functional consequence leading to neuronal injury in a manner similar to that seen in excitatory amino acid toxicity. In this model, excessive stimulation of the receptor is followed by increased entry of calcium into the cell and subsequent cell death. Although of interest in elucidating a novel pathway for neuronal injury in SLE, these findings are preliminary, largely derived from animal studies, and require confirmation in human subjects with NP-SLE.

Antiribosomal (anti-P) antibodies first were described in SLE patients in 1985 and are quite specific for SLE, with a prevalence of 13% to 20% depending upon the ethnic group [28]. In 1987, these auto antibodies were linked to NP-SLE, in particular psychosis [29]. Subsequent work has either supported, refuted, or extended this initial observation to include depression [30, 31]. Potential explanations for the differences is study outcomes include different diagnostic criteria for psychiatric disease, variance in the temporal relationship between clinical events and serologic testing, and differences in assay technique, particularly antigen preparation and purity.

One of the largest studies [30] examined 394 SLE patients, 63 (16%) of whom had anti-P antibodies. There was a significant association with psychosis and depression, with odds ratios between 4 and 10. Because of the low prevalence of clinical events, however, the positive predictive value was only 13% and 16% for psychosis and depression, respectively. This has important implications for the application

of this serologic test in decision-making for individual patients. In contrast, a more recent study of 149 patients [31], 12% of whom had anti-P antibodies, did not find an association with any of the NP syndromes as defined by the ACR nomenclature [8]. Additional observations on anti-P antibodies are of interest and may provide insight into their pathogenic mechanisms.

In a study of 87 SLE patients, Isshi et al [32] found a significant elevation in circulating anti-P antibodies in 34 patients who had lupus psychosis, but there was no increase in the level of serum antineuronal antibodies. In contrast, examination of the CSF from the same patients revealed a significant elevation in antineuronal antibodies but not in anti-P antibody levels. These data suggest potential interaction between these two families of auto antibodies in the pathogenesis of NP-SLE.

Autoimmune antiphospholipid antibodies, which are directed against phospholipid-binding proteins such as beta 2 -glycoprotein I and prothrombin, are associated with predominately focal manifestations of NP-SLE.

The most common neurologic disorders are those of vascular origin such as transient cerebral ischemia or stroke, but other associations include seizures, chorea, transverse myelitis, and cognitive dysfunction. In a review of over 1000 SLE patients, Love and Santoro reported neuropsychiatric manifestations in 38% of patients who had lupus anticoagulant compared with 21% of patients who did not have these antiphospholipid antibodies [33]. The favored pathogenic mechanism for this subset of auto antibodies in NP-SLE is thrombosis within vessels of different caliber and subsequent cerebral ischemia. A procoagulant state may be induced through acquired resistance to protein C and protein S, platelet aggregation, and direct activation of endothelial cells. However, the intrathecal production of antiphospholipid antibodies in NP-SLE patients [22], their association with diffuse cognitive impairment [34], and in vitro evidence indicating modulation of neuronal cell function raise the possibility of an alternative pathogenic mechanism.

Inflammatory mediators

The potential role of proinflammatory cytokines in neuropsychiatric lupus has received increasing attention in recent years. Studies in Japan were the first to report an association between enhanced intracranial production of interleukin (IL-6) with seizures [35] and interferon alpha with lupus psychosis [36]. Subsequent studies have provided further evidence for the intrathecal production of IL-6 [37, 38] and have identified other potential candidate cytokines such as IL-10 [39], IL-2 [40], IL-8 and tumor necrosis factor alpha [38]. Potential sources for the intrathecal production of these cytokines include neuronal and glial cells [36, 37].

Other potentially important inflammatory mediators are MMPs, a family of endoperoxidases that can degrade extracellular matrix components. MMP-9 is a gelatinase and is secreted by a variety of cells in the vessel wall, including macrophages, T lymphocytes, and endothelial and smooth muscle cells. Implicated in the pathogenesis of plaque rupture, elevated levels also have been associated with other conditions, including multiple sclerosis, Guillain-Barre syndrome, rheumatoid arthritis, and SLE. A recent study [40] examined the association between circulating levels of MMP-9 and NP-SLE. Although there was no difference in the levels of MMP-9 between SLE patients and healthy population controls, elevated levels of MMP-9 were associated with NP-SLE, and in particular with cognitive impairment. There was a positive correlation between circulating MMP-9 levels and both T1 and T2 lesions on brain MRI. It is also of interest that increased expression of MMP-9 is found in the disrupted blood–brain barrier following cerebral ischemia and may facilitate lymphocyte migration into and possibly through the arterial wall [41].

As with other organ involvement in SLE, nervous system disease may occur at any time in the disease course. Nevertheless, it is of interest that NP-SLE frequently presents early in the disease course, either before or following the diagnosis of lupus [42]. NP events in patients who have active multiorgan disease from lupus is well recognized [17], and when it occurs, it provides support for the notion that lupus is the most likely cause of the NP manifestation. NP-SLE, however, may also occur in the setting

of globally quiescent lupus.
Cognitive dysfunction, assessed using neuropsychologic assessment techniques, has been reported in up to 80% of SLE patients. These tests evaluate the functional integrity of the CNS through systematic assessment of performance on specific tasks. The tests are administered and scored in a standardized manner and assess multiple areas of cognitive function, including simple and complex attention, memory, visual–spatial processing, language, reasoning, psychomotor speed, and executive functions. Results can be expressed in relation to normative data or in terms of the estimated premorbid level of function or competence.
As most SLE patients who have cognitive impairment have relatively mild deficits, the careful selection and assessment of cognitive performance in control groups is of critical importance to define expected levels of function in healthy individuals and those with other chronic diseases. Although cognitive impairment may be viewed as a distinct subset of NP-SLE, it also can serve as a surrogate of overall brain health in SLE patients, which may be affected by several factors including other NP syndromes. The range in prevalence of cognitive impairment in SLE [14, 43] is most likely because of differences in selection of patients for study and lack of uniform definitions for cognitive impairment. There is no specific or unique pattern of cognitive impairment in SLE, and many individual patients have subclinical deficits.

Clinical impact and prognosis of neuropsychiatric systemic lupus erythematosus

The clinical impact of NP events in SLE has been determined by examining the association with several clinical indicators including quality of life. The NP events in SLE patients, regardless of their etiology and attribution, have a negative impact on quality of life. Although the overall clinical impact of NP-SLE may be detrimental, it is likely that individual NP manifestations differ in their prognostic implications. For example, the subtle cognitive deficits detected by formal neuropsychologic testing have not been associated with a negative impact on quality of life, at least as determined by self-report questionnaires.

Diagnostic imaging and neuropsychiatric systemic lupus erythematosus

When considering neuroimaging in NP-SLE it is helpful to incorporate an assessment of brain structure and brain function. Although CT scanning is the preferred technique for the diagnosis of acute intracranial hemorrhage, it largely has been replaced by MRI for detecting other abnormalities because of its increased sensitivity. Abnormalities on MRI scanning may be found in 19% [51] to 70% [52] of SLE patients. T2weighted MRI images identify pathologic processes that cause edema and are more sensitive than T1 -weighted images for detecting abnormalities in NP-SLE patients.
Applying the technique of fluid-attenuating inversion recovery (FLAIR), to dampen the CSF signal and highlight areas of edema, further enhances the utility of T2-weighted images [53]. Focal neurologic disease is associated with predominately fixed lesions in the periventricular and subcortical white matter usually in the territory of a major cerebral blood vessel. These multiple white matter lesions are quite nonspecific, however, and more commonly are attributed to hypertension, disease duration, and age-related small vessel disease than to the presence of NP-SLE [54]. If the lesions are larger, occur in the corpus collosum, and are seen on T1 -weighted images, then the diagnosis of multiple sclerosis has to be considered.
Diffuse NP clinical presentations are associated with transient subcortical white matter lesions and patchy hyper intensities in the gray matter that usually are not confined to the territories of major cerebral blood flow. Other abnormalities detected on MRI scanning in SLE patients include cerebral infarction, venous sinus thrombosis, and increased signal in the spinal cord accompanying the clinical presentation of myelopathy. MRI also provides quantitative volumetric analysis of brain atrophy.

The most objective neuroimaging study of brain function is positron emission tomography (PET) scanning, but practical considerations limit its applicability. Single photon emission computed

tomography (SPECT) scanning often is regarded as the poor man's PET [55]. This provides semi quantitative analysis of regional cerebral blood flow and metabolism. It is exquisitely sensitive, and in studies of SLE patients [56, 57], SPECT imaging has identified diffuse and focal deficits that may be fixed or reversible. The findings are not specific for SLE, however, and do not always correlate with clinical NP manifestations.

The interpretation of what these imaging abnormalities indicate is not always clear. The most common explanation is that they reflect a primary or secondary reduction in blood flow. In the brain, however, there is sometimes disassociation between metabolism and blood flow. Changes in blood flow and metabolism can occur in sites distant from those of the pathologic lesion, a phenomenon known as diaschisis. A study [58] of concurrent SPECT and PET imaging in 25 SLE patients, 13 of whom had a history of NP-SLE, indicated the superiority of PET scanning.

Furthermore, the abnormalities in glucose metabolism detected by PET scanning are reversible with the institution of antiinflammatory and immunosuppressive therapies [59] but may also progress to structural changes within the brain as detected by subsequent MRI.The application of several technologies to MRI scanning has provided additional opportunities to assess brain metabolism and function.

Magnetic resonance angiography (MRA) permits a noninvasive visualization of cerebral blood flow, although it is probably not optimal for visualization of flow in small caliber vessels, which are the ones primarily involved in NP-SLE. Magnetic resonance spectroscopy (MRS) allows the identification and quantification of brain metabolites, thereby providing indirect evidence of cellular changes. Thus, the amount of N-acetyl (NA) compounds, which reflect the quantity and integrity of neuronal cells, is reduced in lupus brains.

Studies of SLE patients have found an association between reduced NA brain levels with neurocognitive dysfunction [60] and independently with elevated IgG antiphospholipid antibodies [61]. Brain lactate levels also are elevated, indicating ischemia and inflammation, while choline compounds are increased, reflecting damaged cell membranes and myelin destruction.

Magnetization transfer imaging (MTI) is particularly suited to the detection and quantification of diffuse brain damage. This technique quantifies the exchange of protons between water within a macromolecule such as myelin and protons in free water. Either the loss of myelin or the accumulation of edema will alter the transfer, which is expressed as the magnetization transfer ratio (MTR) [62]. Studies have revealed a lower MTR in patients who have NP-SLE and multiple sclerosis, while there was no difference between healthy controls and SLE patients who did not have NP disease [52, 63]. The findings in SLE patients correlated with the results of cognitive assessment and psychiatric functioning. As both MRS and MTI identified abnormalities in SLE patients who have normal MRI scans, these techniques provide a means for detecting and quantifying brain injury in NP-SLE patients that is not apparent with other imaging modalities.

Diffusion weighted imaging (DWI) is highly effective for detecting hyperacute brain injury, in particular acute ischemia following stroke when the diffusion of water is highly restricted because of the acute shift of fluid into the intracellular compartment and cytotoxic edema [62]. Such abnormalities are not seen in multiple sclerosis. In a study of 20 SLE patients by Moritani et al [64], DWI abnormalities were detected in four cases. Functional MRI measures cerebral blood flow and neuronal activity by measuring oxygenation status of hemoglobin, and studies of SLE patients using this technique are awaited with interest. Although none of these techniques identify abnormalities that are

unique to NP-SLE patients it will be of considerable interest to examine their clinical significance and evolution over time and to determine the potential for reversibility.

BIOLOGIC MARKERS OF NERVOUS SYSTEM DAMAGE

Nonspecific abnormalities may be found in the CSF of 33% of patients who have NP disease [65]. They include pleocytosis and elevated protein levels. The elevated levels of CSF neurofilament triplet protein (NFL), which reflects neuronal and in particular axonal damage, were increased in SLE patients who have NP-SLE compared with SLE patients who do not have NP disease and healthy controls (66). The sensitivity was 74% and specificity 65%. Likewise, the level of CSF glial fibrillary acidic protein (GFAP), which indicates astrogliosis or scarring, was increased in the same patient population, with a sensitivity of 48% and specificity of 87%.

Moreover, the levels of both NFL and GFAP were associated with abnormalities on MRI scanning and were reduced following the successful treatment of several NP manifestations with cyclophosphamide. Although elevated levels of NFL and GFAP are not restricted to SLE, these data indicate a potentially objective, biologic indicator of nervous system disease in lupus patients.

Diagnosis and management of neuropsychiatric systemic lupus erythematosus

The first step in the management of a patient with SLE who presents with a NP event is to determine whether the event can be convincingly attributed to SLE, a complication of the disease or its therapy, or whether it reflects a coincidental disease process. This is achieved largely by a process of exclusion, given the absence of a diagnostic gold standard for most of the NP manifestations that occur in SLE. Thus, the correct diagnosis is derived from a careful analysis of the clinical, laboratory, and imaging data on a case-by-case basis. The spectrum of diagnostic tests available is listed in Box 3, and these may be used to a varying extent depending upon the clinical circumstances.

Examination of the CSF should be considered primarily to exclude infection. Analysis of CSF autoantibodies, cytokines, and biomarkers of neurologic damage is still in the research arena. In considering autoantibodies, those that are most likely to provide the greatest diagnostic yield are antiphospholipid antibodies. The value of measuring anti-P antibodies remains uncertain given the conflicting results to date, while the role of anti-NR2 antibodies in NP-SLE is unknown.

Neuroimaging should include a modality to assess brain structure and another to assess brain function. Neuropsychologic testing only should be done to address specific concerns about cognitive ability, as the detection of isolated subclinical deficits appears to have little clinical significance.

The spectrum of investigations in the assessment of systemic lupus erythematosus patients for neuropsychiatric disease is listed in (BOX 3) Management will need to be tailored according to the individual patient's needs (Box 4), and there remains a paucity of controlled studies to guide treatment decisions. Once a diagnosis of NP-SLE is established, the first step is to identify and treat potential aggravating factors such as hypertension, infection, and metabolic abnormalities.

BOX 3 INVESTIGATIONS

Cerebrospinal fluid

Exclude infection

Autoantibodies

Cytokines

Autoantibodies

Antiphospholipid

Antineuronal

Antiribosomal P

Neuroimaging

Brain structure (CT, MRI)

Brain function (PET, SPECT, MRI, MRA, MRS, MTI, DWI, FMRI) Neuropsychologic assessment

Symptomatic therapy with, for example, anti- convulsants, antidepressants, and antipsychotic medications, should be considered if appropriate. Immunosuppressive therapy with high dose corticosteroids, cyclophosphamide, and azathioprine has been used to treat many NP-SLE manifestations. With the exception of one study [67], there are no placebo- controlled studies examining the benefit of oral or intravenous corticosteroids in NP lupus. Similarly, pulse intravenous cyclophosphamide therapy [68-70], akin to that which has been used in the treatment of lupus nephritis, has been reported to be beneficial in NP-SLE, although no controlled studies have been performed. A recent open-label study of 13 patients who had lupus psychosis reported a favorable outcome in all patients treated with oral cyclophosphamide for 6 months followed by maintenance therapy with azathioprine [71]. In virtually all of these studies, immunosuppressive therapy has been used in conjunction with corticosteroids in addition to symptomatic therapies, such as antipsychotic medications.

BOX 4 MANAGEMENT

Establish diagnosis of NP-SLE

Identify aggravating factors

Hypertension

Infection

Metabolic abnormalities

Symptomatic therapy

Anticonvulsants

Psychotropics

Anxiolytics

Immunosuppression

Corticosteroids

Azathioprine

Cyclophosphamide

B-lymphocyte depletion

Anticoagulation

Heparin

Warfarin

More targeted immunosuppressive therapies, for example B lymphocyte depletion with anti-CD20 used

alone or in combination with cyclophosphamide [72], is promising but requires further study. Anticoagulation is indicated strongly for focal disease when antiphospholipid antibodies are implicated, and such therapy usually will be lifelong [73]. There are several opportunities for novel or improved therapies in the future. The optimal management of intracranial thrombosis should become clearer following the completion of controlled studies of anticoagulation therapy in patients who have primary antiphospholipid antibody syndrome, although studies to date have yielded conflicting results.

Due to the lack of controlled randomized trials there is a desperate need to assess the efficacy of various therapeutic interventions in CNS lupus, where the treatment is still empirical and based on clinical experience. Before deciding to treat and how to treat, the major points that need to be considered are: i) accurate diagnosis; ii) identification and treatment of contributing causes of CNS disease; iii) assessment of the severity; and iv) identification of the probable underlying pathogenic mechanism(s).

In this context, a better approach to management of CNS lupus may be achieved by: i) the recognition of the APS (a common thrombotic disease) and its treatment with anticoagulants; ii) a more conservative use of steroids, especially in patients with mild manifestations; and iii) the use of pulse cyclophosphamide in diffuse/nonthrombotic CNS lupus. Patients with mild manifestations (e.g., headache or depression) may need symptomatic treatment only, with analgesics, antidepressants and psychological support. In more severe CNS manifestations it is vitally important to distinguish between thrombotic and nonthrombotic mechanisms.

Focal CNS manifestations, generally due to an underlying thrombotic mechanism, are more often associated with the presence of aPL, and long-term anticoagulation is the therapeutic choice in these cases. Heparin is indicated during the acute phase, followed by long-term warfarin in order to prevent recurrences. Other focal CNS manifestations, such as demyelinating syndrome, transverse myelitis, chorea, migraine and seizures, when associated with aPL, may also benefit from anticoagulation.

Severe diffuse CNS manifestations, such as acute confusional states, generalized seizures, anxiety, mood disorders and psychosis generally require corticosteroids in the first instance. High dose of corticosteroids may only be used in severe cases and, preferably for short periods. Pulse intravenous cyclophosphamide therapy may help when more severe manifestations are refractory to corticosteroids and other immunosuppressive agents, generally when response is not seen in three to five days.

Plasmapheresis, intrathecal methotrexate and dexamethasone, iloprost, azathioprine and mycophenolate mofetil deserve further studies to confirm their usefulness in the treatment of NPSLE. It is imperative to enroll homogeneous groups of patients in the design of multicentre randomized controlled trials with good sample sizes and accurate power calculations to give an answer to the many questions currently remaining in the treatment of NPSLE, ultimately yielding to more effective treatments for this serious and potentially life-threatening manifestation of SLE.

REVIEW OF LITERATURE

The ACR nomenclature and case definitions for NP-SLE have been validated in a cross-sectional, population-based study by Ainiala et al [9]. Forty-six SLE patients were compared with 46 individuals randomly selected from the Finnish population register and matched by age, gender, education, and municipality of residence. At least one NP manifestation was identified in 91% of the 46 Finnish patients compared with 54% of controls. This provided an odds ratio of 9.5 (95% confidence interval (CI) 2.21 to 40.8) for the occurrence of an NP event and specificity of 46%. In view of the high prevalence of NP disease in both SLE and controls, the authors suggested several modifications to how the criteria should be used. Thus, by excluding headache, anxiety, mild depression, mild cognitive impairment and polyneuropathy without electro physiologic confirmation, the prevalence of NP disease fell from 91% to 46% in SLE patients and from 54% to 7% in controls. This provided an odds ratio of 7.0 (95% CI 2.09 to 23.47) and specificity of 93%.

In addition to the study of Ainiala et al, at least four other groups [10–13] have used the ACR nomenclature to classify their SLE cohorts for NP-SLE the overall prevalence of NP disease in these patient populations has varied between 37% and 95%. The most common 4 of the 19 NP syndromes in each of these five SLE cohorts are cognitive dysfunction, headache, mood disorder and cerebrovascular disease. Most of the other NP syndromes were infrequent, with a prevalence of less than 1% in most cases. Of interest, the range in the prevalence of NP-SLE in these studies was as wide as that reported before the introduction of the ACR nomenclature. In previous studies, NP disease was reported in 14% to 75% of SLE patients [14–16].

Cognitive function

Cognitive dysfunction, assessed using neuropsychologic assessment techniques, has been reported in up to 80% of SLE patients [9], although most studies have found prevalence between 17% and 66% [14, 43]. These tests evaluate the functional integrity of the CNS through systematic assessment of performance on specific tasks. The range in prevalence of cognitive impairment in SLE [14, 43] is most likely because of differences in selection of patients for study and lack of uniform definitions for cognitive impairment. There is no specific or unique pattern of cognitive impairment in SLE, and many individual patients have subclinical deficits.

For example, a review of 14 cross-sectional studies of cognitive function in SLE revealed subclinical cognitive impairment in 11% to 54% of patients (43). The outcome of cognitive impairment in SLE patients has been examined in several studies. For example, in a 5-year prospective study of 70 SLE patients using a standardized panel of neuropsychologic tests [44], the prevalence of overall cognitive impairment in SLE patients fell from 21% to 13% over the period of study. Five patterns of cognitive performance were observed over the 5-year period. Eighty-three percent of patients were either never impaired or had resolution of cognitive impairment without specific therapeutic interventions. An additional 13% of patients demonstrated an emerging or fluctuating pattern of impairment, and only 4% (two patients) showed persisting deficits that were stable over time.

Similar benign changes in cognitive performance over time have been reported by Waterloo et al [74] in 28 patients over 5 years, by Hay et al [75] in a 2-year prospective study, and by Carlomagno et al [76]. Predictors of cognitive decline over time also have been examined. In a study by Hanly et al [44], when patients who were cognitively impaired at the initial assessment were compared with those who were not impaired, the differences between groups in tests of recent memory and delayed free recall decreased over 5 years. A similar result was reported by Waterloo et al [74].

Patients who had clinically overt NP-SLE at any time in their disease course, however, had a statistically significant decline in memory performance over 5 years when compared with patients who

did not have a history of clinically overt NP-SLE [44]. The association between cognitive function and anticardiolipin (aCL) antibodies has been examined in several cross-sectional and prospective studies. In a study, 51 SLE patients were divided into those who were persistently aCL antibody positive or negative on the basis of up to seven antibody determinations over a 5-year period [34]. The relative change in performance on individual neuropsychologic tests then was compared between patients who were antibody positive and negative. Those who were persistently IgG aCL antibody positive demonstrated a greater reduction in psychomotor speed compared with those who were antibody negative. In contrast, patients who were persistently IgA aCL antibody positive had significantly poorer performance in conceptual reasoning and executive ability. These data suggest that IgG and IgA aCL may be responsible for long-term subtle deterioration in cognitive function in SLE patients.

Headache

The association between SLE and headache is controversial. The reported prevalence of headache has varied widely between 24% and 72% [9–13], but the prevalence of headache in the general population is also high, with up to 40% of individuals reporting a severe headache at least once per year. Two of the most recent studies [77, 78], which were methodologically more robust than earlier work showed no increase in the prevalence of headache in SLE. Although headache may be a component of active SLE in individual patients, particularly in patients who have active systemic disease, it is more likely that most headaches in SLE patients are unrelated to SLE [79].

Psychosis, mood disorders, and anxiety

Psychosis is reported in up to 8% of SLE patients [9–13], and it is characterized by either the presence of delusions (false belief despite evidence to the contrary) or hallucinations (perceptual experiences occurring in the absence of external stimuli). The latter are most frequently auditory. Psychosis is a rare but dramatic manifestation of NP-SLE, and when present it must be distinguished from other causes, including drug abuse, schizophrenia, and depression. Depression and anxiety are common symptoms in lupus patients and occur in 24% to 57% of patients [9–13, 31]. As there are no features of these syndromes that are unique to SLE patients, however, there is often uncertainty about the etiology and attribution in individual cases. The association between psychosis, depression, and anti-P antibodies in SLE is supported by some but not all studies [29-31].

Cerebrovascular disease

The many forms of cerebrovascular disease are reported in 5% to 18% of SLE patients [9–13] and are likely multifactorial in etiology. Accelerated atherosclerosis is recognized in SLE, particularly in relation to coronary heart disease, where there is a 5 to 10 times higher rate of events compared with control populations. This also contributes to the increased rate of cerebrovascular events in SLE. An additional etiologic factor is the prothrombotic state as a consequence of antiphospholipid antibodies, which provides a rationale for therapeutic intervention with anticoagulants in selected cases.

Seizures

Generalized and focal seizures are reported in 6% to 51% [9–13] of patients and may occur either in the setting of active generalized multisystem lupus or as isolated neurologic events. Their occurrence frequently is associated with the presence of antiphospholipid antibodies [12], which are associated with microangiopathy, arterial thrombosis, and subsequent cerebral infarction.

Uncommon presentations

The rare manifestations of nervous system disease in SLE that occur no more frequently than in 1% to 3% of patients are movement disorder, demyelinating syndromes, myelopathy, myasthenia gravis, Guillain-barre syndrome, autonomic disorder, Plexopathy and aseptic meningitis[9–13, 16]. Clinical and neuroimaging evidence of demyelination has been described and may be indistinguishable from multiple sclerosis. This may represent a concordance or overlap of two autoimmune conditions. Transverse myelopathy [80] and chorea [81] present acutely and frequently are associated with antiphospholipid antibodies. Although an arterial thrombotic event is a likely mechanism for transverse

myelopathy, the cause of chorea is less clear, and there has been speculation that it may be a consequence of a direct interaction of antiphospholipid antibodies with neuronal structures in the basal ganglia.

Neuropathy

A sensorimotor neuropathy has been reported in up to 28% [9–13] of SLE patients and frequently occurs independently of other disease characteristics [82]. The abnormalities are persistent, but in one study, 67% of patients had no change in their neuropathy over a 7-year period [90]. A controlled immunohistologic study of skin biopsies in SLE patients has demonstrated involvement of small nerve fibers [83].

Clinical impact and prognosis of neuropsychiatric systemic lupus erythematosus

The clinical impact of NP events in SLE has been determined by examining the association with several clinical indicators including quality of life. In a recent study [11], NP events were associated with significantly lower scores on most subscales of the SF-36, a generic self-report measure of quality of life, and with higher fatigue scores. These associations were present regardless of the attribution of the NP event to SLE or an alternative etiology, but they did not occur in patients who have a history of renal disease.

The data indicate that NP events in SLE patients, regardless of their etiology and attribution, have a negative impact on quality of life. In a study [45] 70% of patients who have cognitive difficulties were able to maintain their work capacity, and 86% had no change in their social functioning. Relatively few studies have examined the course of NP-SLE over time. Karassa et al [46] examined the prognosis of NP disease in 32 patients who had been hospitalized for NP-SLE and followed for 2 years. The outcome was generally favorable, with either substantial improvement (69%) or stabilization (19%) accounting for most cases. A high number of prior NP events and the occurrence of the antiphospholipid syndrome were predictors of an unfavorable clinical outcome at 2 years.

There is no consensus in the literature on the asso ciation between NP-SLE and mortality. Some studies report increased mortality [47, 48] in SLE patients who have NP disease, and others report no such association [42, 49]. One cause of mortality in SLE is suicide, which has been reported in association with NP manifestations in a recent study involving a small number of patients [50].

NP_pSLE

The prevalence of neuropsychiatric disease within different pSLE cohorts has been reported to vary from a low of 20% to a high of 95% of patients. [84, 85, 87]

HEADACHE

In children with NP-pSLE headache is the most common symptom occurring in 50–75% of patients. [84, 87] In contrast, only 6–22% would meet the criteria for ‘lupus headache’. In Toronto NP-pSLE cohort 75% of children had headache, however in the majority of patients the headache was associated with other CNS disease and 25% had a headache as the sole CNS manifestation. In all patients with severe headache, cerebral vein thrombosis, CNS infection, inflammation of the cerebral arteries and other intracranial pathologies associated with SLE should be ruled out prior to accepting the diagnosis of isolated lupus headache.

Psychiatric manifestations

Following headache, psychiatric manifestations of pSLE are the most common manifestation. About 12–40% of NP-pSLE children develop psychosis [86].The hallmarks of pSLE-associated psychosis are visual hallucinations. The presence of this type of hallucination helps to differentiate the organic psychosis associated with SLE from idiopathic schizophrenia of childhood. Visual hallucinations may be accompanied by auditory hallucinations and frequently the hallucinations are of threatening nature. The most common mood disorder seen in pSLE is depression.[85] Depression may be an organic depression secondary to NP-SLE or a more reactive depression secondary to chronic disease, and rarely

to corticosteroid use. Mania and bipolar disorder are uncommon.
Cognitive dysfunction is found in about 30% of NP-pSLE patients. The diagnosis is confirmed when the child has a documented impairment in at least one of the cognitive domains of simple or complex attention, memory, visual-spatial processing, language, reasoning/problem solving, psychomotor speed and executive functions. Although there have been many studies in adults using standardized neuropsychiatric tests at diagnosis and in follow-up, few studies have been performed in pSLE.

Cerebrovascular disease

The category of cerebrovascular disease (CVD) includes a spectrum of SLE- associated cerebral blood vessel abnormalities, ranging from involvement of inflammation of small arteries to cerebral vein thrombosis, which is seen in about 25% of NP-pSLE patients. More frequently pSLE patients present with multifocal enhancing MRI lesions suggestive of small vessel inflammation, with a normal angiogram. These patients may have diverse clinical presentation and findings include cognitive defects and headaches. Cerebral vein thrombosis, found in 15–25% of pSLE patients, is almost universally associated with antiphospholipid antibodies (aPL) and in particular with lupus anticoagulant (LAC). [89] Most patients with CVD present with a severe headache, and they may have associated seizures.

Seizures

Seizures are found in approximately 20% of NP-pSLE patients. In Toronto cohort experience, seizures are frequently associated with CVD and/or cognitive dysfunction.[91] One study has suggested an association of aPL and seizures, but further studies are required to confirm this observation.[90]Long-term anticonvulsive therapy is frequently required as EEG abnormalities often persist.

Chorea

Chorea is present in approximately 5% of patients, although one study suggested that up to 20% of patients may have chorea. Chorea is almost universally associated with the presence of aPL, and with the decline of rheumatic fever in Western countries chorea is more likely to be secondary to the presence of aPL rather than to rheumatic fever. As PAPS (primary antiphospholipid syndrome) is infrequently seen in children and adolescents, chorea is most likely secondary to SLE even in the absence of other overt symptoms. Interestingly, despite a higher prevalence of APS in adults, chorea is more commonly seen in pSLE than in adult patients. [85-87] Most patients only have one episode of chorea, and unilateral chorea is seen more commonly than bilateral. [87]

Uncommon presentations

Less common CNS symptoms include diabetes insipidus, Parkinson's syndrome, cranial nerve involvement and leuko encephalopathy.[84] Ocular involvement has been reported to occur in up to 25% of cases, with pseudotumour cerebri,papilledema and visual disturbances being the most common findings.[84,87] Retinal vascular disease, consisting of arterial or venous occlusion, cotton wool spots, optic disc edema, retinal hemorrhages or ischemic optic neuropathy can be found in up to 10% of patients. The majority of these patients have detectable aPL.

Peripheral nervous system

Peripheral nervous system (PNS) involvement occurs in 5–15% of all patients with pSLE. [85, 86] It may occur with or without concomitant CNS involvement. Peripheral nerve involvement frequently involves both sensory and motor neurons and may be either a polyneuropathy or mononeuritis. Transverse myelitis was the most common PNS disease. Overall transverse myelitis, peripheral neuropathy and aseptic meningitis each occur in approximately 1–5% of patients.[86].Less commonly, PNS involvement includes polyneuropathy, mononeuritis, myasthenia gravis, cranial neuropathy, demyelinating disease, and Guillain Barre syndrome.[84] Unlike in adults with SLE, autonomic dysfunction has been only rarely reported in pediatric patients.

INDIAN STUDIES

In a study of 334 SLE patients by Chandrasekran AN and Porkodi R et al, the NPSLE manifestations

were seen in 32.4% of patients. The most common features were headache in 46(43.6%), seizures in 33(31.1%),psychosis in 23(21.7%) and depression in 24(22.6%).[94]Another study by Bichile LS et al showed the incidence of NPSLE was in 26(20.96%) out of 124 patients. The common manifestations are seizures in 14(53.84%), psychosis in (42.3%) and CVA in 3(11%).[95]In a review of 329 cases of SLE from Northern india by Malaviya AN et al showed that the occurrence of NPSLE was 63% and the incidence of NPSLE was 23.2% in a study by Amen SN et al from Western india.[96,97]

AIM OF THE STUDY

1) To study the various neurological manifestations in patients with systemic lupus erythematosus.

2) To study the various psychiatric manifestations in patients with systemic lupus erythematosus.

3) To compare the neuropsychiatric manifestations between childhood and adult SLE patients

MATERIALS AND METHODS

One hundred consecutive patients (7 males, 93 females) with systemic lupus erythematosus who attended the Department of Rheumatology, Madras Medical College, Chennai were included as the study population. This is a prospective study done during November 2005-March2008.

INCLUSION CRITERIA

Patients who fulfilled 1997 Revised ACR Classification Criteria for systemic lupus erythematosus were included.

EXCLUSION CRITERIA

1) Patients with overlap syndrome were excluded.

2) Patients with history of head injury.

3) Patients with chronic renal failure.

4) Patients with alcoholism.

All the selected patients were subjected to clinical examination including detailed neurological evaluation. The psychiatric evaluation was done with the help from Institute of Mental health, Madras Medical College.

Psychiatric Assessment

1) Mini Mental State Examination (MMSE), which evaluates cognitive abnormalities and was considered pathologic when the score was lower than 24/30.
2) General Health Questionnaire, a 20 item questionnaire to detect the psychopathology by means of four independent subscales: somatic symptoms of psychological nature, anxiety, depression and social disability.
3) Hospital Anxiety Scale (HAS), which evaluates symptoms of anxiety.
4) Hospital Scale for Depression (HDS), which evaluates symptoms of depression.

Assessment of SLE Activity

The disease activity was measured using the SLE Disease Activity Index (SLEDAI).It consists of 24 variables, grouped according to nine organ systems (including some immunological tests), and the range possible SLEDAI scores is 0-105

Patients with neuropsychiatric manifestation were classified according to 1999 Case definitions for 19 NPSLE syndromes.

LIMITATIONS OF THIS STUDY

1) Imaging studies for brain function like SPECT, PET or MRS are not done.
2) Tests for Antineuronal and Antiribosomal antibodies are not done.

LABORATORY TESTS

Hematological evaluation including complete hemogram and peripheral smear study and biochemical parameters including blood glucose, urea, serum creatinine, liver function tests and fasting lipid profile were done for all patients. CRP was done by latex agglutination method.

ANA

ANA was done by indirect immunofluorescence using mouse liver substrate and Hep2 cells if negative by mouse liver substrate.

Anti-dsDNA

The detection of Immunoglobin IgG antibodies to dsDNA was done by CALBIOTECH INC dsDNA Ig ELISA test system. The method being as follows; Diluted patient serum is added to wells coated with purified dsDNA antigen. All unbound materials are washed away and the conjugate is added to bind to the antigen-antibody, if present. Excess conjugate is washed off and substrate is added. The plate is allowed to the hydrolysis of substrate by the enzyme. After addition of stop solution, OD reading is measured by BIORAD ELISA reader. The intensity of the color generated is proportional to the amount of specific antibody in the sample and is given in OD values. The antibody index is calculated from the OD values according to instructions in the kit. The test is positive if the antibody index is >1.1 and negative if it is <0.9.

COMPLEMENT

The complement levels were measured using by Single Radial Immune Diffusion plates. The procedure consists of immunoprecipitation in agarose gel between an antigen and its homologous antibody. It is performed by incorporating the anti C3 and anti C4 antibodies uniformly throughout a layer of agarose gel and antigen is added into the wells duly punched in the gel. Antigen diffuses radially out of the well into the surrounding gel and a visible ring of sharp precipitation forms where the antigen and antibody reacted in the zone of equivalence. A quantitative relationship does exist between ring diameters and complement concentration. The reference value for C3 is 80-160mg/dl and for C4 is 20-40mg/dl.

Cryoglobulin was tested by preparing the centrifuged serum and keeping it at 4 degree C and reading it after 72 hours for the gel precipitate at the bottom of conical tube.

Lupus Anticoagulant Study including activated partial prothrombin time, dilute Russel viper venom test and Kaolin clotting time were done. Coombs test including both direct and indirect was done.

aCL IgG and IgM by ELISA

It was done using commercial ELISA kit (CAL BIOTECH, INC). Diluted patient serum is added to wells coated with purified aCL antigen.aCL specific Ig G or IgM antibody, if present, binds to the antigen. All unbound materials are washed away and the enzyme conjugate is added to bind to the antibody-antigen complex, if present. Excess enzyme conjugate is washed off and substrate is added. The plate is incubated to allow the hydrolysis of the substrate by the enzyme. The intensity of the color generated is proportional to the amount of specific antibody in the sample. The OD values are recorded and the antibody index is calculated as per the instructions in the kit. The optical densities were read by an ELISA reader (Tecan, Austria) at 450 nm. GPL and MPL units of a serum sample were read against the standard curve. A value of 10 -15 GPLwas taken as low positive, 15 -80 GPL as medium and above 80 GPL as high positive.

Electroencephalogram [EEG] and cerebrospinal fluid examination were done if necessary and patient's

consent was available. Radiological evaluation like X-ray chest, Ultrasound Abdomen and Echocardiogram were done for all patients. HRCT chest was done if necessary.12 lead standard resting electrocardiogram was recorded in all 100 patients

RESULTS

The clinical, laboratory and imaging profile of 100 patients who satisfied the 1997 revised ACR classification criteria for SLE were analyzed. The 100 patients were divided into as to whether they belong to childhood SLE or adult SLE.

TABLE 1: AGE-WISE DISTRIBUTION

	No of patients	*Mean age ±SD*	*t-test*
SLE	69	26.75±8.65	5.81
pSLE	31	12.84±3.38	P<0.001
NPSLE	41	28.05±10.39	3.20
NPpSLE	15	13.33±3.48	P<0.01

The age range was 3 years to 55 years. The maximum number of cases occurred in 20 to 35 years. The mean age of study group is 22.44 years and the mean age in patients with NPSLE is 24.10 years. The female to male ratio was 14:1.The mean duration of illness in patients with NPSLE is 3.74 years.

Table-2: SEX-WISE DISTRIBUTION

Group	*Male*		*Female*	
	No.	*%*	*No.*	*%*
SLE	4	5.78	65	94.22
pSLE	3	9.68	28	90.32
NPSLE	1	2.44	40	97.56
NPpSLE	1	6.67	14	93.33

TABLE-3: CLINICAL PROFILE OF STUDY PATIENTS

PARAMETERS	N=100
Age (mean) in yrs	22.44
Female: Male	14:1
Duration of the disease (mean) in yrs	2.10
Mean SLEDAI	12.57
Constitutional features	82
Mucocutaneous features	96
Musculoskeletal features	74

Pulmonary involvement	10
Cardiac involvement	16
Renal involvement	30
NPSLE	56

Out of 56 patients with NP-SLE manifestations, 41 patients belong to adult group and 15 patients are children (Table3, 4, 5). The most common manifestations in adults are seizures (39%), headache and CVA (26.8%). In childhood group, the most common manifestations are seizures (80%), headache(26.6%)and psychosis(26.6%).The analysis of the other manifestations showed that the renal involvement was seen in 23(41%) NP-SLE patients.

TABLE-4: PROFILE OF PEADIATRIC SLE CASES WITH NEUROPSYCHIATRIC FEATURES

PARAMETERS	CNS N=14	PNS N=1	PSY. INVOLEMENT N=8
Duration of the disease (mean) in yrs	3.02	4	1.7
Constitutional features	14	1	4
Mucocutaneous features	10	1	6
Pulmonary involvement	-	-	-
Cardiac involvement	6	-	3
Renal involvement	10	1	4

TABLE-5: PROFILE OF ADULT SLE WITH NEUROPSYCHIATRIC FEATURES

PARAMETERS	CNS N=40	PNS N=1	PSY.INVOLMENT N=35
Duration of the disease (mean) in yrs	4.09	0.2	2.67
Constitutional features	24	-	22
Mucocutaneous features	32	1	32
Pulmonary involvement	2	-	2
Cardiac involvement	6	-	4
Renal involvement	12	-	8

TABLE-6: NEUROPSYCHIATRIC MANIFESTATIONS IN SLE PATIENTS

NP-SLE	Total no. pts N=56	pSLE N=15	SLE N=41
CNS	54(96.4%)	14(93.3%)	40(97.5%)
PNS	2(3.5%)	1	1
Aseptic meningitis	-	-	-
CVA	14(25%)	3 (20%)	11(26.8%)
Demyelinating syndrome	-	-	-
Headache	15(26.7%)	4(26.6%)	11(26.8%)
Movement disorder	-	-	-
Myelopathy	2(3.5%)		2(4.8%)
Seizure disorders	28(50%)	12(80%)	16(39%)
GBS	-	-	-
Autonomic disorder	-	-	-
Mononeuropathy	-	-	-
Myasthenia gravis	-	-	-
Cranial neuropathy	2(3.5%)	1	1
Plexopathy	-	-	-
A/c confusion state	-	-	-
Anxiety disorder	11(19.6%)	2(13.3%)	9(21.9%)
Cognitive dysfunction	12(21.4%)	2(13.3%)	10(24.3%)
Mood disorder	12(21.4%)	1	11(26.6%)
Psychosis	10(17.8%)	4(26.6%)	6(14.6%)

TABLE 7 OCULAR INVOLVEMENT

TYPE OF LESION	NP-SLE	NPpSLE	ADULT NPSLE

	N=56	n=15	n=41
Abnormal findings	10(17.8%)	6(40%)	4(9.7%)
Optic neuritis	2	2	-
Cotton wool exudates	3	2	1
Retinal vasculitis	3	1	2
Papilledema	1	-	1
Cortical blindness	1	1	-

TABLE 8 RENAL INVOLVEMENT

LUPUS NEPHRITIS	SLE n=100	NPSLE n=56
Abnormal biopsy findings	30(30%)	23(41%)
Class 2	3	2
Class 3	6	4
Class 4	16	14
Class 5	5	3
Class 6	-	-

TABLE-9: LABORATORY PROFILE OF STUDY PATIENTS

Tests	Total pts N=100	pSLE N=31	SLE N=69
Low Haemoglobin(<10G)	53	19	34
Low platelets(<1lakh)	16	6	10
High ESR	23	10	13
CRP	15	9	6
dsDNA	51	18	23
Sm Ab	35	15	20
APA positivity(aCL IgG,M,LAC)	34	10	24
Low c3,c4	19	6	13
Positive Coombs test	6	2	4
Cryoglobulins	9	1	8
Abnormal Lipid profile	32	8	24

TABLE-10: LABORATORY PROFILE OF NP-SLE PATIENTS

Tests	Total pts N=56	pSLE N=15	Adult SLE N=41
Low Hb(<10g)	37(66%)	12(80%)	25(60.9%)
Low platelets(<1lakh)	8(21.6%)	3(20%)	5(12.1%)
High ESR	19(33.3%)	7(46.6%)	12(29.2%)
CRP	9(16%)	5(33.3%0	4(9.7%)
dsDNA	29(51.7%)	9(60%)	20(48.7%)
Sm Ab	20(35.7%)	6(40%)	14(34.1%)
APA positivity(aCL IgG,M,LAC)	26(46%)	8(53.3%)	18(43.9%)
Low c3,C4	14(28%)	4(26.6%)	10(24.3%)
Positive Coombs test	5(8.9%)	2(13%)	3(7.3%0
Cryoglobulin	7(12.5%)	1	6(14.6%)
High LDL	12(21.4%)	2(13%)	10(24.3%)

Laboratory analysis of NP-SLE patients showed anemia in 37patients (66%), thrombocytopenia in 8(21.6%), elevated CRP in 9(16%) and dsDNA was positive in 29(51.7%).LAC was positive in 9 patients (16%), aCL IgG in 24(42.8%) and aCL IgM was positive in 9(16%).Low complement levels were detected in 14(25%).

TABLE-11: NP-SYNDROMES IN APA POSITIVE PATIENTS

TYPE OF LESION	APA POSITIVE PATIENTS	
	NPpSLE n=8	NPSLE n=18
CVA	2	10
Seizures	3	6
Cranial Neuropathy	1	1
Psychosis	-	3

TABLE 12 EEG FINDINGS

Abnormality	NPSLE with seizures n=28	NPSLE without seizures n=28
Diffuse slow waves	8(28.5%)	4(14.2%)
Focal epileptic activity	4(14.2%)	-
Normal	16(57.1%)	24(85%)

Out of 56 patients with NPSLE manifestations, Cerebro spinal fluid examination was done in 15 patients. The analysis reveals pleocytosis in three patients and high protein concentration in four patients.

TABLE-13: MRI FINDINGS

TYPE OF LESION	NP-SLE N=56	NPpSLE n=15	NPSLE N=41
Abnormal findings	25 (44.6%)	3(20%)	22(53.6%)
Ischemic lesion	14 (25%)	3(20%)	11(26.8%)
Small high-density lesion	4 (7%)	-	4(9.7%)
Cortical atrophy	5(8.9%)	-	5(12.1%)

High intense lesion in spinal cord	**2(3.5%)**		**2(4.8%)**

DISCUSSION

Neuropsychiatric manifestation in SLE is one of the major organ involvement which was reported frequently in the literature. This study was undertaken to assess the neuropsychiatric complications in both paediatric and adult onset SLE.The incidence of NP-SLE in our study population of 100 patients is 56%.The incidence reported in previous studies varies from 37% and 97% [9, 10-13]. 93% of our patients were females as the disease occurs predominantly in females. Of the 56 patients with NPSLE only two were males.

The age of the study population ranges from 2.5 years to 55 years.31% of patients belongs to paediatric onset SLE. 84% of the study group was below the age of 30 years and only 3 were above 50 years so that the neurological problems due to aging are minimized. The mean age of patients with neuropsychiatric manifestation was 24.10 years (range 12 to 53 years) and mean latency of NPSLE from initial systemic involvement was 3.74 years (range 0-6years).

In a study by Ainiala et al 2001[9], the four common neuropsychiatric SLE syndromes as defined by ACR Nomenclature committee were cognitive dysfunction (80%), headache (54%), polyneuropathy (28%) and cerebrovascular disease (15%). In a study by Brey et al 2002 [10], the four common syndromes were cognitive dysfunction (69%), headache (57%), mood disorder (40%) and anxiety (24%). In Sanna et al study, the common syndromes were headache (24%), cerebrovascular disease (18%), seizures (8%) and psychosis (8%). In Hanley et al study, the common syndromes were headache (28%), mood disorder (14%), cerebrovascular disease (5%) and seizures (6%). In our study population of 69 adult patients, the four common syndromes were seizures, headache, cerebrovascular disease and mood disorder. The common syndromes among 31 paediatric patients were seizures, headache, cerebrovascular disease and psychosis.

Neurological manifestations as initial presenting feature of SLE occurred in 7 patients. The ACR criteria for SLE require at least four characteristic features occur at anytime during the course, not necessarily simultaneously. Although the criteria were not fulfilled at early stage, the later emergence of more typical features of the disease confirmed the diagnosis in each case. Out of seven patients, four had seizures, two had cerebrovascular disease and one had paraplegia.

Out of 14 patients with cerebrovascular disease, 11 belong to adult group and three belongs to paediatric onset group. The majority presented with persistent hemiparesis and facial nerve weakness. There were no other relevant risk factors like hypertension, diabetes mellitus, hypercholesterolemia or smoking in any of these patients. The cerebrovascular disease was reported in 5% to 18% of SLE patients [9-13]. Isolated LMN type of cranial nerve involvement was seen in two patients.

Seizures are already known to occur in 6% to 51 % of lupus patients [9-13] compared with 0.5% to 1% in the general population. They are usually primary generalized, but partial episodes also occur. In our study the most common NP-SLE syndrome is seizure in both NPpSLE group (80%) and in adult NPSLE patients (39%). Seizure was the first SLE symptom in four patients.

The analysis of psychiatric involvement showed that the prevalence of cognitive dysfunction ranged between 17% and 66%. [14, 44-45], psychosis (8%) and depression and anxiety(24%-57%)[9-13] .In our 56 NPSLE patients , cognitive dysfunction and mood disorders occurred in twelve patients, anxiety in eleven and psychosis in ten patients. In four patients, psychosis was present as isolated feature of NP-SLE.

In our study, ocular involvement was seen in ten patients. The various manifestations were optic neuritis in two, bilateral cortical blindness in one, papilledema in one, cotton wool exudates in three, bilateral retinal vasculitis in three patients. Four patients showed APA positivity. Ocular involvement had been reported to occur in up to 25% of cases. [84, 87] The most commonly observed systemic

features in our study population were constitutional (82%), skin and mucosal involvement (96%), joints (74%) and renal involvement (30%). Skin, joint and renal involvements were most frequently observed features that preceded CNS complications.

The classical finding of a low CRP but elevated ESR was seen in 15 patients. In our study APA positivity was present in 26(46%) patients with neuropsychiatric manifestations. In a review of 1000 SLE patients, Love and Santoro reported neuropsychiatric manifestations in 38% of patients who had antiphospholipid antibodies compared with 21% of patients who did not have this antibodies [33-3].The prevalence of APA positivity in patients with various neuropsychiatric syndromes were 57%(8) in cerebrovascular disease, 25%(7) in seizure and 40%(4) in psychosis. These results were similar to the earlier reports regarding the association of APA positivity and NPSLE [92-93].

Electro encephalogram (EEG) was abnormal in 16 out of 56 patients with NPSLE. EEG was normal in 16 patients with seizures. The most common abnormality of diffuse slow wave was seen in 12 patients. Many studies suggest that EEG was rarely helpful in diffuse CNS disease and were usually abnormal only when seizures were present.

MRI and CT brain scans were done in 56 patients. Abnormalities on T2-weighted MRI images were found in 19% [51] to 70% [52] of SLE patients. The application of fluid attenuating inversion recovery (FLAIR) to dampen the CSF signal highlights the areas of edema enhancing the utility ofT2 weighted images. In our study thirty two percent of CT brain and 44.6% of MRI brain scans were abnormal. The analysis of CT results showed that it is very useful for identifying large infarcts and haemorhages. Perisulcal cortical atrophy was seen in four patients.

MRI features were often non specific. Abnormal scans were associated focal neurological deficits, normal scans with more diffuse phenomena such as headache and seizure. Diffuse presentations were associated with subcortical, small, multifocal and bilateral white matter hyper intensity lesions and patchy hyper intensities in the gray matter that usually not confined to the territories of major cerebral arteries.

CONCLUSION

There was a female predominance in the patients with neuropsychiatric manifestations due to systemic lupus erythematosus.

The Neuropsychiatric manifestations were present in 56% of our study population. The CNS involvement was seen in 96.4% of patients with neuropsychiatric manifestations.

The four common NP-SLE syndromes in adult patients were seizures, headache, mood disorder and cerebrovascular disease and in paediatric patients seizures, headache, cerebrovascular disease and psychosis. Out of 30 patients with renal involvement, 23 patients had neuropsychiatric manifestations.

The APA positivity was seen in 46% of patients with NP-SLE syndromes. It was associated with cerebrovascular disease in twelve out of fourteen patients.

Out of 28 patients with seizures, nine had APA positivity and six had abnormal MRI findings. The most common MRI finding was focal ischemic lesion in both adult and paediatric patients.

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APPENDIX-1 ABBREVIATION CODE

NPSLE	Neuropsychiatric Systemic Lupus Erythematosus
NPpSLE	Paediatric Neuropsychiatric Systemic lupus erythematosus
ACR	American college of Rheumatology
CRP	C-reactive protein
dsDNA	Double stranded DNA
Sm Ab	Anti –smith antibody
aCL IgM, G	Anticardiolipin antibody
LAC	Lupus anticoagulant
aPL	Antiphospholipid antibody
C3,C4	Compliment
MRI	Magnetic resonance imaging
DWI	diffusion weighted imaging
FMRI	functional MRI
MRA	magnetic resonance angiography
MRS	magnetic resonance spectroscopy
MTI	magnetization transverse imaging
PET	positron emission tomography
SPECT	Single photon emission computed tomography.

APPENDIX- 2 PATIENT CONSENT FORM

Study title : A STUDY ON NEUROPSYCHIATRIC LUPUS PATIENTS

Study Centre : Department of Rheumatology,Government General Hospital,Chennai.

Patient's Name : _____

Patinet's Age : _____

Identification Number : _____

Patients may check (✓) these Boxes

I confirm that I have understood the purpose and procedure of the above study. I have the opportunity to ask the question and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving any reason, without my legal rights being affected. ☐

I understand that the investigator, the ethics committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current tsudy and any further research that may be conducted in relation to it, even if I withdraw from the study. I agree to this access. However, I understand that my identify will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and to faithfully co-operate with the study team, and to immediately inform the study staff if I suffer from any detorieration in my health or well being or any unexpected or unusual symptoms. ☐

I hereby agree to allow the investigator to take around 30ml of blood from me for the laboratory investigations until the completion of study. ☐

I hereby give permission to undergo complete physical examination, and diagnostic tests including hematological, Biochemical, Radiological and urine examination. ☐

Signature / Thumb Impression of the patient. _____ Place _____ Date

Patient's Name&Address : _____

_____

Signature of the Investigator : _____ Place _____ Date

Study Investigator's Name : _____

APPENDIX-3

CASE RECORD FORM

Name Age Sex RCCNO DURATION

HISTORY

PRESENTING FEATURES

AT ONSET

DURING COURSE

PAST

PERSONAL

PHYSICAL EXAMINATION

VITAL SIGNS PULSE BP TEMP RR

CONSTITUTIONAL FEATURES

MUCOCUTANEOUS FEATURES

RENAL/GIT

CARDIOPULMONARY/PERIPHERALVASCULATURE

CNS

HIGHERFUNCTION **CRANIALNERVES**

SPINOMOTOR SYSTEM **SENSORYSYS**

CEREBELLAR FUNC **GAIT/SPINE**

PSYCHIATRIC ASSESSMENT

MINIMENTALSCORE (<24/30)

ANXIETY/MOOD DISORDER / PSYCHOSIS / COGNITIVE DYSFUNCTION ACUTE CONFUSIONAL STATE.

INVESTIGATION

BASIC

HB TC DC ESR CRP PLO. NA K HCO3

CREAT SUGAR UREA

LIPID PROFILE

IMMUNOLOGICAL

ANA dsDNA ENA aCL LAC C3, C4 LEVELS COOMBS TEST

SPECIAL INVESTIGATION

EMG/NCS EEG CSF

HPE

IMAGING

CT BRAIN MRI/MRA/MRV

ASSESSMENT

SLEDAI

SLICC

APPENDIX – 4

The Mini-Mental Status Examination

Orientation	Points
Name: season/date/day/month/year	5 (1 for each name)
Name: hospital/floor/town/state/country	5 (1 for each name)
Registration	
Identify three objects by name and ask patient to repeat	3 (1 for each object)
Attention and calculation	
Serial 7s; subtract from 100 (e.g., 93–86–79–72–65)	5 (1 for each subtraction)
Recall	
Recall the three objects presented earlier	3 (1 for each object)
Language	
Name pencil and watch	2 (1 for each object)
Repeat "No ifs, ands, or buts"	1
Follow a 3-step command (e.g., "Take this paper, fold it in half, and place it on the table")	3 (1 for each command)
Write "close your eyes" and ask patient to obey written command	1
Ask patient to write a sentence	1
Ask patient to copy a design (e.g., intersecting pentagons)	1
TOTAL	**30**

APPENDIX –5 THE GENERAL HEALTH QUESTIONNAIRE

(20 ITEM VERSION)

1. Been able to concentrate on whatever you are doing?
   a) Better than usual
   b) Same as usual
   c) Less than usual
   d) Much less than usual

2. Lost much sleep over worry?
   a) Not at all
   b) No more than usual
   c) Rather more than usual
   d) Much more than usual

3. Felt that you are playing a useful part in things?
   a) More than usual
   b) Same as usual
   c) Less than usual
   d) Much less useful

4. Felt capable of making decision about things?
   a) More than usual
   b) Same as usual
   c) Less useful than usual
   d) Much less useful

5. Felt constantly under strain?
   a) Not at all
   b) No more than usual
   c) Rather more than usual
   d) Much more than usual

6. Felt that you could overcome your difficulties?
   a) Not at all
   b) No more than usual
   c) Rather more than usual
   d) Much more than usual

7. Been able to enjoy your normal day to day activities?
   a) More than usual
   b) Same as usual
   c) Less useful than usual
   d) Much less useful

8. Been able to face up to your problems?
   a) More than usual
   b) Same as usual

c) Less useful than usual
d) Much less useful

9. Been feeling unhappy and depressed?
   a) Not at all
   b) No more than usual
   c) Rather more than usual
   d) Much more than usual

10. Been losing confidence in yourself?
    a) Not at all
    b) No more than usual
    c) Rather more than usual
    d) Much more than usual

11. Been thinking of yourself as a worthless person?
    a) Not at all
    b) No more than usual
    c) Rather more than usual
    d) Much more than usual

12. Been feeling reasonably happy, all things considered?
    a) More than usual
    b) Same as usual
    c) Less useful than usual
    d) Much less useful

13. Been managing to keep yourself busy and occupied?
    a) More than usual
    b) Same as usual
    c) Less useful than usual
    d) Much less useful

14. Been getting out of the home as much as usual?
    a) More than usual
    b) Same as usual
    c) Less useful than usual
    d) Much less useful

15. Felt on the whole you were doing things well?
    a) Better than usual
    b) About the same
    c) Less well than usual
    d) Much less well

16. Been satisfied with the way you are carried out your task?
    a) More satisfied
    b) About the same as usual
    c) Much less satisfied
    d) Less satisfied than usual

17. Been taking things hard?

a) Not at all
b) No more than usual
c) Rather more than usual
d) Much more than usual

18. Found everything getting on top of you?

a) Not at all
b) No more than usual
c) Rather more than usual
d) Much more than usual

19. Been feeling nervous and strung up all the time?

a) Not at all
b) No more than usual
c) Rather more than usual
d) Much more than usual

20. Found at times you could not do anything because your nerves were too bad?

a) Not at all
b) No more than usual
c) Rather more than usual
d) Much more than usual

APPENDIX –6 DEPRESSION SCALE

PLEASE "√ "THE APPROPRIATE COLUMN FOR EACH QUESTION
(GIVE ONLY 1 ANSWER PER ROW)

I still enjoy the things I used to enjoy	Definitely as much	Not quite as much	Only a little	Hardly at all
	0	1	2	3
I can laugh and see the funny side of things	As much as I always could	Not quite so much now	Definitely not so much now	Not at all
	0	1	2	3
I feel cheerful	Not at all	Not often	Sometimes	A lot
	3	2	1	0
I feel as it I have slowed down	Nearly all the time	very often	Sometimes	Not at all
	3	2	1	0
I have lost interest in my appearance	Definitely	I don't take so much care as I should	I may not take as much care	I take just as much care as ever
	3	2	1	0
I look forward with enjoyment to things	As much as ever	Rather less than I used to	Definitely less than before	Hardly at all
	0	1	2	3
I can enjoy a good book or radio or TV programme	often	Sometimes	Not often	Very selection
	0	1	2	3

Depression Sub score

APPENDIX – 7 ANXIETY SCALE

PLEASE " √"THE APPROPRIATE COLUMN FOR EACH QUESTION
(GIVE ONLY 1 ANSWER PER ROW)

I feel tense	Most of time	A lot of time	Occasionally	Not at all
	3	2	1	0
I get frightened feelings, that something bad is going to happen	Quite badly	Not too badly	A little	Not at all
	3	2	1	0
I worry a lot	A great deal of time	A lot of time	From time to time	Only occasionally
	3	2	1	0
I can sit at ease and feel relaxed	Definitely	Usually	Not often	Not at all
	0	1	2	3
I get frightened feelings, like butterflies in stomach	Not at all	Occasionally	Quite often	Not at all
	0	1	2	3
I feel restless	Very much	Quite a lot	Not very much	Not at all
	3	2	1	0
I get sudden feelings of panic	Very often	Quite often	Not often	Not at all
	3	2	1	0

Anxiety Sub score: Name of the Doctor:

Name of Patient: Diagnosis:

Age: Sex: Location:

APPENDIX – 8

SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY INDEX
SELENA MODIFICATION

Physicians Global Assessment _____

0 None | 1 Mild | 2 Med | 3 Severe

SLEDAI SCORE

Check box: If descriptor is present at the time of visit or in the proceeding 10 days

Wt	Present	Descriptor	Definition
8	☐	Seizure	Recent onset. Exclude metabolic, infectious or drug cause
8	☐	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Excluded uremia and drug causes.
8	☐	Organic Brain Syndrome	Altered mental function with impaired orientation, memory or other intelligent function, with rapid onset fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.
8	☐	Visual Disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serious exodate or hemorrhages in the choroids, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	☐	Cranial Nerve Disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	☐	Lupus Headache	Severe persistent headache: may be migrainous, but must be non-responsive to narcotic analgesia.
8	☐	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis
8	☐	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual, infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis
4	☐	Arthritis	More than 2 joints with pain and signs of inflammation (i.e. tenderness, swelling, or effusion).
4	☐	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/adolase or electromyogram changes or a biopsy showing myositis.
4	☐	Urinary Casts	Heme-granular or red blood cell casts
4	☐	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	☐	Proteinuria	>0.5 gm/24 hours. New onset or recent increase of more than 0.5 gm/24 hours.
4	☐	Pyuria	>5 white blood cells/high power field. Exclude infection.
2	☐	New Rash	New onset or recurrence of inflammatory type rash.
2	☐	Alopecia	New onset or recurrence of abnormal, patchy or diffuse loss of hair.
2	☐	Mucosal Ulcers	New onset or recurrence of oral or nasal ulcerations

2	□	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	□	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram confirmation.
2	□	Low Complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.
2	□	Increased DNA binding	>25% binding by Farr assay or above normal range for testing laboratory.
1	□	Fever	>38°C. Exclude infectious cause
1	□	Thrombocytopenia	<100,000 platelets/mm3
1	□	Leukopenia	<3,000 White blood cell/mm3. Exclude drug causes.

____ TOTAL SCORE (Sum of weights next to descriptors marked present)

Mild or Moderate Flare □	**Severe Flare** □
□ Change in SLEDAI > 3 points	□ Change in SLEDAI > 12
□ New/worse discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus Nasopharyngeal ulcers Pleuritis Pericarditis Arthritis Fever (SLE)	□ New/worse CNS-SLE Vasculius Nephritis Myositis Pk < 60.000 Home anemia: Hb <7% or decrease in Hb > 3% **Requiring:** double prednisone Prednisone>0.5 mg/kg/day hospitalization
□ Increase in Prednisone, but not to >0.5 mg/kg/day	□ Prednisone >0.5 mg/kg/day
□ Added NSAID or Plaquenil	□ New Cytoxan, Azathioprine, Methotrexate, Hospitalization (SLE)
□ ≥1.0 Increase in PGA, but not to more than 2.5	□ Increase in PGA to > 2.5

INSTITUTIONAL ETHICAL COMMITTEE

GOVERNMENT GENERAL HOSPITAL & MADRAS MEDICAL COLLEGE
CHENNAI.600 003

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FAX : 044 - 2530 5115

K.Dis.No.25406/P&D3/Ethics/Dean/GGH/07 **Dated: 22.11.2007**

Title of the work : Study on Neuropsychiatric Manifestation of LUPUS patients

Principal investigator : Dr. K. Seerala Boopathy M.D.

Department : Dept. of Rheumatology,

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 22.11.2007 at the Conference Hall of the Dean, Tower Block I, Government General Hospital, Chennai.3.

The members of the Committee, the Secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The principal investigator and their team are directed to adhere the guidelines given below:

1. You should get detailed informed consent from the patients/participants and maintain confidentiality.
2. You should carry out the work without detrimental to regular activities as well as without extra expenditure to the Institution or Government.
3. You should inform the IEC in case of any change of study procedure, site and investigation or guide.
4. You should not deviate form the area of the work for which I applied for ethical clearance.
5. You should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
6. You should abide to the rules and regulations of the institution(s).
7. You should complete the work within the specific period and if any extension of time is required, you should apply for permission again and do the work.
8. You should submit the summary of the work to the ethical committee on completion of the work.
9. You should not claim funds from the Institution while doing the work or on completion.
10. You should understand that the members of IEC have the right to monitor the work with prior intimation.

SECRETARY	CHAIRMAN	DEAN
IEC, GGH, Chennai.	IEC, GGH, Chennai.	GGH&MMC, Chennai.