Brain SPECT in patients with neuropsychiatric SLE: the additional value of semi–quantitative analysis

By

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Declaration

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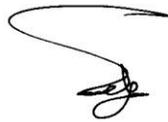
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Abstract

Introduction:

There is conflicting data on the value of single photon emission tomography (SPECT) for the diagnosis of neuropsychiatric SLE (NPSLE). Visual assessment of brain SPECT scans is the standard approach in clinical practice. However the definition and identification of significant changes may be limited by a high interobserver variability, especially in centres with limited experience. This may be reduced by a more objective semi-quantitative assessment. The objectives of this study were to determine the sensitivity and specificity of SPECT for the detection of NPSLE at our institution using visual assesment, to determine the additional value of using an objective semi-quantitative diagnostic criterion, and to investigate the correlation between abnormal perfusion pattern and clinical NPSLE classification in patients with active NPSLE.

Material and methods:

Nineteen patients with NPSLE and 19 normal controls were studied with brain SPECT. Scans were interpreted blindly by two nuclear medicine physicians using two methods; visual and semi-quantitative assessments. In the visual method, overall visual impression was recorded for each scan using a four point scale, where A=normal, B=probably normal, C=probably abnormal, and D=abnormal. In addition, each brain region was assigned a severity score from 0=normal perfusion to 3=severe hypoperfusion. In the semi-quantitative assessment, ten-band color scale was used, and perfusion deficit was quantified on the side with the lower color intensity comparing to the contralateral side. A score was given to the region with perfusion deficit according to the difference (in color bands) between the two hemispheres.

Analysis was performed for the visual assessment method (overall impression and severity scores) and the semi-quantitative assessment method using a receiver operator characteristic (ROC) curve. Optimal cut-off points were determined and the accuracy of the different techniques was also compared statistically. Finally, the correlation was determined between the SPECT perfusion pattern and the clinical pattern of disease.

Results:

An ROC curve analysis for the overall visual impression resulted in an area under the curve of 0.76. At a cut-off point of C (probably abnormal), brain SPECT had 89% sensitivity and 57% specificity for the diagnosis of NPSLE. The severity score which include the total severity score and the modified total severity score resulted in areas under the curve of 0.75 and 0.79 respectively. The semi-quantitative assessment resulted in areas under the ROC curve of 0.80. Statistically, there was no difference between the overall visual impression, visual severity scores, and the semi-quantitative assessment. Agreement analysis between the SPECT pattern and clinical pattern of disease showed agreement in 91.6% in the diffuse pattern, whereas agreement in the focal pattern was seen in only 42.8%.

Discussion and Conclusion:

In this study, we found that brain SPECT is able to diagnose active NPSLE with a high sensitivity and moderate specificity. The overall visual impression, visual severity scores, and the semi-quantitative assessment showed no significant differences between the techniques. The use of the semi-quantitative assessment described may be useful in centers with limited experience in the interpretation of brain SPECT. The correlation between the SPECT pattern and clinical disease pattern may provide some insights into the pathophysiology of NPSLE.

Opsomming

Inleiding:

Daar is teenstrydige inligting oor die waarde van brein enkelfoton emissie tomografie (EFET) vir die diagnose van neuropsigiatriese SLE (NPSLE). Visuele beoordeling van brein EFET flikkergramme is die standaard benadering in kliniese praktyk. Die definisie en identifisering van betekenisvolle veranderinge mag egter beperk word deur 'n hoë inte-waarnemer wisseling, veral in sentra met beperkte ondervinding. Dit mag verminder word deur 'n meer objektiewe semi-kwantitatiewe beoordeling. Die doel van hierdie studie was om 1. die sensitiwiteit en spesifisiteit van EFET vir die opspoor van NPSLE in ons instelling te bepaal, 2. die bykomende waarde van 'n objektiewe semi-kwantitatiewe diagnostiese kriterium vas te stel, en 3. die korrelasie tussen 'n abnormale perfusiepatroon en 'n kliniese NPSLE klassifikasie in pasiënte met aktiewe NPSLE te ondersoek.

Materiaal en Metodes:

Negentien pasiënte met NPSLE en 19 normale kontroles is met brein EFET bestudeer. Flikkergramme is blind deur twee kerngeneeskundiges geïnterpreteer, deur gebruik te maak van twee metodes, 'n visuele en semi-kwantitatiewe beoordeling. Vir elke flikkergram is 'n globale visuele indruk genoteer deur gebruik te maak van 'n 4-punt skaal, waar A=normaal, B=waarskynlik normaal, C= waarskynlik abnormaal, en D=abnormaal. Bykomend is 'n ernstigheidsgraad waarde van 0=normale perfusie tot 3=erge hipoperfusie vir elke breinstreek toegeken. Vir die semi-kwantitatiewe beoordeling is 'n telling vir streke met laer intensiteit vergeleke met die kontralaterale kant toegeken, volgens die verskille in kleurbande deur gebruik te maak van 'n tienbandskaal. Die visuele metodes vir die globale indruk, visuele ernstigheidsgraad waarde, en die semi-kwantitatiewe beoordeling is geanaliseer deur 'n relatiewe funksioneringskenmerk (receiver operator characteristic (ROC)) kurwe te gebruik en optimale afsnypunte te bepaal. Die akkuraatheid van die verskillende tegnieke

is ook statisties vergelyk. Laastens is die korrelasie tussen die EFET perfusiepatroon en die kliniese siektepatroon bepaal.

Resultate:

'n ROC kurwe analise vir die globale visuele indruk het gelei tot 'n area onder die kurwe van 0.77. By 'n afsnypunt van (C) het brein EFET 'n sensitiwiteit van 89% en 'n spesifisiteit van 57% vir die diagnose van NPSLE gehad. Die visuele ernstigheidsgraad telling, en die semi-kwantitatiewe beoordeling het onderskeidelik tot areas onder die ROC kurwe van 0.75 en 0.79 vir die visuele ernstigheidsgraad waarde, en 0.8 vir die semi-kwantitatiewe beoordeling gelei. Statisties was daar geen verskil tussen die globale visuele indruk, die visuele ernstigheidsgraad waarde, en die semi-kwantitatiewe beoordeling nie. Ooreenstemmingsanalise tussen die EFET patroon en kliniese siektepatrone het 'n ooreenstemming van 91.6% in die diffuse patroon getoon, terwyl die fokale patroon ooreenstemming van slegs 42.8% getoon het.

Bespreking en Gevolgtrekkig:

In hierdie studie is gevind dat brein EFET 'n diagnose van NPSLE kan maak met 'n hoë sensitiwiteit en gemiddelde spesifisiteit. Die globale visuele indruk, visuele ernstigheidsgraad waarde, en die semi-kwantitatiewe beoordeling wat beskryf is, het geen betekenisvolle verskille tussen die tegnieke getoon nie. Die gebruik van die semi-kwantitatiewe beoordeling wat beskryf is, mag van waarde wees in sentra met beperkte ondervinding in the interpretasie van brein EFET. Die korrelasie tussen die EFET patroon en kliniese siektepatrone mag insig gee in die patofisiologie van NPSLE.

Dedication

This thesis is dedicated to my mother.

Acknowledgment

I wish to express my gratitude to my supervisor Dr. James Warwick, whose encouragement, guidance, tremendous assistance and support from the initial to the final stage enabled me to develop an understanding of the subject.

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Lastly, I offer my regards and blessings to all of those who supported me in any respect during the completion of this project.

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Chapter 1 - Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory multi-organ disease. It is characterized by a variety of clinical features including abnormalities of the skin, joints, lungs, heart, kidneys, and the nervous system**.** The disease has a variable course marked by active and inactive periods**.**[1]

In different studies nervous system involvement in SLE has varied from 18 to 80 %[2,3,4,5]. The diagnosis of neuropsichiatric SLE (NPSLE) is based on clinical data and this variation may reflect the lack uniformity in diagnostic criteria. It occurs also in the majority of paediatric SLE patients at least as frequently as lupus glomerulonephritis. However, the actual prevalence and incidence remain uncertain.[6]

Nervous system manifestations in SLE include neurological syndromes of the central, peripheral and autonomic nervous systems, as well as psychiatric syndromes. These manifestations have been given different terms, such as CNS lupus, neuro-lupus, lupus cerebritis, and lupus vasculitis. However, all these terms are inappropriate, as they do not include the wide range of the neurological and psychiatric complications in SLE. Therefore, the term neuropsychiatric SLE is considered to be more appropriate as it encompasses these manifestations.[7]

A challenging problem in SLE is to determine whether neurological or psychiatric symptoms are due to lupus itself or due to secondary factors.[8] Moreover, it is at times not easy to distinguish focal from diffuse processes by clinical presentation,[9] and the diagnosis of CNS involvement of SLE is difficult[10] due to the absence of a reliable laboratory investigation or an ideal imaging modality, as there is no ''gold standard'' for the diagnosis of NPSLE.

Neuro-imaging methods are useful and necessary, in order to narrow the differential diagnosis, elucidate the underlying pathological mechanisms, identify anatomic foci of pathology, quantify disease activity, and determine the functional and prognostic consequence of NPSLE.[11] Functional brain imaging using SPECT provides a measure of regional cerebral blood flow (rCBF) which has been claimed to be sensitive in detecting brain involvement in SLE.[12] [13] [14] However, it has a low specificity and comparable abnormalities have been described in SLE patients without neuropsychiatric manifestations.[15] [16]

There are different methods to assess brain SPECT in SLE patients with neuropsychiatric manifestations. Currently, most nuclear medicine departments use visual assessment which provides a qualitative description of the deficit(s) seen in the images. However, the major challenge is to define and identify significant changes. This method is also limited by high interobserver variability and low reliability.[17]

Investigators have attempted to use semi-quantitative methods to reduce the inter-observer variation, and to improve the detection of non-visualized lesions. Semi-quantitative techniques based on regions of interest provide a reasonable and objective measurement of relative changes in blood flow in regions of the brain. The regions of interest can be drawn manually, which may lead to variability of results, as well it is often, time-consuming and may require several subjective interactions on the part of the operator.[18] Regions of interest can also be drawn semi-automatically after being spatially re-oriented into a standard brain space and automatically calculated and analyzed for asymmetry.[19]

Recent developments in neuro-imaging data analysis using voxel-wise analysis such as statistical parametric mapping (SPM) and brain registration and analysis of SPECT studies (BRASS) showed an improvement in classification accuracy, and have been shown to be preferable over a purely visual assessment and volumes of interest (VOI).[20] [21]

Only one study has examined a voxel-wise analysis in NPSLE, where it showed abnormalities in regions that could be missed using visual or VOI analysis.[22] However, this technique requires software which is not widely available, and it needs the creation of a template from a normal database, and requires a significant degree of technical skill. This makes these voxel-based techniques difficult to implement in an ordinary Nuclear Medicine Department. Therefore, instead of using voxel-wise analysis, this study examines the use of a simple semi-quantitative assessment by using a color scale. This approach can be available everywhere, without the problems associated with a voxel-based method.

Study objectives:

The primary aim of the study is to determine the sensitivity and specificity of SPECT for the detection of NPSLE at our institution, and to determine the optimal diagnostic criterion for interpretation, using a visual analysis.

A secondary aim is to determine the additional value of using a simple semi-quantitative analysis to improve the sensitivity and specificity of SPECT for the detection of NPSLE.

A third aim is to investigate correlations between abnormal perfusion patterns and clinical NPSLE manifestations in patients with active NPSLE.

Chapter 2 - Literature Review

2.1. Etiology and risk factors for neuropsychiatric SLE:

Neuropsychiatric events in SLE may be caused by primary manifestations of the disease itself, or be secondary to steroid drugs, or infective, hypertensive and metabolic complications, or caused by coincidental problems unrelated to lupus.[23]

Genetic factors like HLA-DR9 antigen and HLA-DR3 may result in susceptibility to the development of the neuropsychiatric features of SLE, whereas HLA-DR4 may confer protection against the development of these features.[24] CNS involvement in SLE is also strongly associated with the presence of antiphospholipid syndrome, in particular with arterial thrombosis, and with cutaneous vasculitic lesions. [25]

2.2. Pathology and pathogenesis of neuropsychiatric SLE:

The pathogenesis of neuropsychiatric SLE is likely to be multifactorial and reflects a mixture of pathogenic mechanisms, which include vascular abnormalities, auto-antibodies, and local production of inflammatory mediators.[26] Vasculopathy of large or small vessels may either be directly responsible for the clinical disease or, alternatively, exert its effect by enhancing blood brain barrier permeability for pathogenic autoantibodies.[27]

Several brain-specific and systemic auto-antibodies have been implicated to a varying extent in the pathogenesis of NPSLE.[28] Antiphospholipid antibodies have been found to be linked to focal Neuropsychiatric (NP) disease, whereas anti-ribosomal P antibodies and anti-NR2 antibodies were associated with diffuse disease. [29]

2.3. Neurological manifestations of SLE:

Since the first report of stupor and coma in SLE, a multitude of neuropsychiatric syndromes have been reported. However, the lack of uniformity in patients' diagnoses, standardization of terminology, and disease classification has resulted in inappropriate diagnosis and management.

In 1979 Kassan and Lockshin proposed a classification system for NPSLE to enable better segregation of clinical subsets and the identification of the variety of clinical presentations such as seizure, psychosis, neuropathy, movement disorders.[30] However, the proposed definition for SLE of the revised American Rheumatology Association (ARA) in 1982 accepted only seizures and psychosis,[1] and other events find no expression in the criteria. Most investigators did not agree with this definition. [31]

In 1990, an ad hoc workshop in Canada and USA proposed diagnostic criteria for NPSLE including 33 items;[31] subdivided into three primary categories; neurology, psychiatric, and laboratory. This classification system has however not been utilized widely, as details on the diagnostic and exclusion criteria were not provided.

In 1999, the ACR developed a standard nomenclature and set of case definitions for 19 NPSLE syndromes, and patients were diagnosed to have NPSLE if they meet the case definition in addition to three or more of the ACR (non NPSLE) criteria for SLE.[7] This has provided a uniform methodology for defining clinical subsets of patients with NP manifestations and suggests a shift in thinking about nervous involvement in SLE away from the concept that any nervous system involvement in patients with SLE can be categorized simply as NPSLE. The neuropsychiatric complications in SLE were classified into central nervous system involvement (diffuse or focal) and peripheral nervous system involvement.

Diffuse syndromes include psychosis, mood disorder, cognitive dysfunction and acute confusional state. These events were the most problematic, since it was difficult to determine whether these manifestations were due to SLE itself or due to psychological reaction to the stress of having chronic illness. Focal syndromes include cerebrovascular disease, demyelinating syndrome, headache, a septic meningitis, chorea, seizures, and myelopathy. Peripheral nervous system involvement includes Guillian-Barre syndrome, myasthenia gravis, autonomic disorder, mononeuropathy, plexopathy and polyneuropathy.[7]

As with other organ involvement in SLE, nervous system disease may occur at any time in the disease course, but most of the events were seen early and in 40 % of the group occurred before or at the time of SLE diagnosis,[2] and these events may present as single or multiple neurological events in the same individual. [5]

Neuropsychiatric events in SLE patients occur commonly in multi-system involvement, which provides support for the notion these events are most likely due to lupus. However, nervous system disease in SLE can occur even without multi-system involvement. [32]

The clinical outcome of SLE revealed increased disability and mortality among patients with NPSLE, [33] which is considered as being worse in South Africa than in Western countries.[34] Moreover, the outcome is significantly worse for NP events attributed to primary SLE compared to secondary causes such as steroids.[35] The outcome is also worse with focal syndromes which lead to permanent and irreversible changes, while reversible changes are common with diffuse syndromes.[36] The outcome is also worse with a complex event compared to isolated events.[8]

2.4. Diagnosis of neuropsychiatric SLE:

The management of NPSLE requires the presence of cerebral lupus to be established and its severity to be assessed, but the diagnosis of CNS involvement in SLE is difficult. In reviewing the extensive range of immuno-serological, electrophysiological, and neuro-imaging techniques that have been investigated as possible markers of CNS lupus, it is apparent that there is still no single test which is diagnostic.[10]

The detection of auto-antibodies is not routinely utilized as a diagnostic marker for NPSLE, because their association with disease remains highly contentious.[37] Cerebrospinal fluid (CSF) abnormalities are commonly found but are non-specific, as is EEG, which is of little diagnostic value in neuropsychiatric lupus.[15]

Structural imaging modalities were found to be useful in evaluating patients with focal syndromes. However, they are insensitive in non-focal presentations such as depression and cognitive disorders.[38] Magnetic resonance imaging (MRI) is more sensitive than CT in demonstrating particular morphological abnormalities, but the poor specificity of the lesions found on MRI prevents the diagnosis of NPSLE being made from radiological findings alone. Another drawback of MRI is the difficulty in differentiating active CNS manifestations from old inactive lesions.[39]

Since the first use of Oxygen-15 in 1975,[40] functional imaging using Positron emission tomography (PET) and SPECT have started to play a role in SLE patients with NP manifestations. PET is considered to be a sensitive and reliable method for evaluating SLE patients with CNS involvement. This was demonstrated by Meyer *et al*. where FDG PET showed abnormal perfusion and metabolism in all patients.[41] Similar results have been found in a study done by Weiner *et al*,[42] but the usefulness of PET is considerably reduced by its high cost,[38] and lack of availability.

2.5. Single photon emission tomography (SPECT):

Since SPECT was introduced in the early 1980s as a method for evaluating cerebral blood flow, it has continued to provide useful information and a better understanding of the clinical presentation of numerous neuropsychiatric conditions such as dementia, stroke, psychiatric disorders, epilepsy,[43] HIV dementia,[44] as well as in NPSLE.[12] [13] [14] The role of SPECT in NPSLE will be discussed in the next section.

The principle of SPECT brain imaging is governed by the brain blood barrier (BBB), which excludes many substances from entering the brain from the blood. Radiopharmaceuticals for brain imaging can be broadly grouped into two categories: diffusible tracers, which are lipophilic and readily cross the BBB and non-diffusible tracers, which are hydrophilic and cannot cross the BBB.[45] Cerebral perfusion studies are performed using the former group.

Several radiopharmaceuticals have been used for the assessment of cerebral perfusion in NPSLE patients. ^{123}I-iodoamphetamine seems to be useful to identify active CNS involvement; [46] however, it is limited by its lack of cost effectiveness and availability in many parts of the world, including South Africa.

The development of the technetium-99m-hexamethylpropylene amine oxine (^{99m}Tc HMPAO) has offered the clinical community a safe, effective and sensitive technique for evaluating regional cerebral blood flow, as it is deposition in the brain is proportional to the cerebral blood flow. However, its rapid decomposition in vitro necessitates its administration within 30 minutes of preparation. On the other hand technetium-99m-ethyl cysteinate dimer (^{99m}Tc ECD) has a better in vitro stability and brain-to-background ratio, resulting in a slightly better image quality.[47]

2.5.1. Clinical applications of SPECT in neuropsychiatric SLE patients:

The utility of SPECT for evaluation of CNS damage in SLE patients is not clearly established, and many controversies exist. This section will concentrate in the clinical value of SPECT in NPSLE.

2.5.1.1. Asymptomatic SLE patients:

Several studies have investigated SLE patients without active NPSLE or a past history of neuropsychiatric manifestations, where SPECT showed hypoperfusion in some patients.[14] These abnormalities could be explained by the transient and mild nature of some minor manifestations which may go undetected, or may be related to diffuse cerebral and extracerebral vasculopathy resulting from the clinical and inflammatory nature of SLE.[48]

Alternatively, these patients may have sub-clinical CNS involvement and may show psychiatric symptoms in the near future.[49] In addition, age and use of steroid medication may result in brain atrophy which may be another important factor that affects the interpretation of the SPECT images.[50]

2.5.1.2. Active NPSLE patients:

SPECT provides confirmation of clinically active CNS involvement in SLE patients, and it may give an objective indication of cerebral disease in patients with borderline clinical evidence, particularly if performed within the first four months after the onset of CNS involvement.[51] The sensitivity of SPECT for detecting abnormalities in children during active CNS disease has been shown to be almost 100 %. This was shown by Szer *et al.*[52] where all children had abnormal cerebral perfusion. This is similar to results found by Huang *et al.*[53]

In adult NPSLE patients, SPECT demonstrated significantly decreased cerebral perfusion in 70-88 % of patients during active NP manifestations.[13] [15] [48] [54] [55] The sensitivity for detecting these abnormalities depends on the clinical subtype of NP manifestations, as SPECT is more sensitive for diffuse and major manifestations rather than focal and minor manifestations.[12] [56]

2.5.1.3. Correlation of SPECT findings with neuropsychiatric manifestations:

Conflicting reports exist whether or not cerebral blood flow abnormalities correlate with neuropsychiatric function. Kusher *et al.* reported that the magnitude of changes in cerebral blood flow depends on the NPSLE subtype, as the greatest change occurred in patients with diffuse NP manifestations, whereas focal manifestations showed focal lesions.[46] This is in agreement with Zhang *et al.*[57] In addition to that, patients with more than one type of NP manifestation had a greater number of areas of hypoperfusion. [58]

In contrast, a correlation between the pattern of defects and clinical symptoms was not evident in the studies reported by Rubbert *et al.* and Kodama *et al.*[13] [49] Furthermore, Waterloo *et al.* reported that there was no association between dysfunction in any cognitive domain and cerebral blood flow changes except between slowed psychomotor speed and executive dysfunction, with the parietal and frontal lobes respectively.[59]

Interestingly, most patients with long standing disease showed cerebral blood flow abnormalities with a predominance of focal uptake defects, whereas most of the diffuse uptake was seen in patients with shorter disease duration.[13] However, Nossent *et al.* showed that focal and diffuse defects can occur in short or long disease duration.[54]

Correlations between SPECT findings and some immunologic parameters were also studied. An association has been found between SPECT and cumulated tissue damage and overall disease activity measured by systemic lupus activity measure (SLAM) index. However, no significant relationship was found between the presence of the auto-antibodies and SPECT imaging findings.[15]

2.5.1.4. Monitoring and guiding therapy:

Once a diagnosis of NPSLE is established, the first step is to identify and treat potential aggravating factors such as hypertension and uremia. Symptomatic therapy should be considered if appropriate. Immunosuppressive therapy has been used to treat many NPSLE manifestations, and anticoagulant is indicated strongly for focal disease.[23]

SPECT, besides helping with the diagnosis of NPSLE and starting the appropriate therapy, has been shown to be a very sensitive method in monitoring disease severity and response to treatment. Huang *et al.* showed that SPECT was consistently abnormal in children during active CNS disease, where improvement was seen after the symptoms resolved, suggesting the reversibility of the neurological disorder.[53] Moreover, SPECT as a technique could detect abnormalities long before the development of irreversible damage, and therefore is useful in guiding the clinical treatment.[57] However, Sun *et al.* thought that SPECT should be considered only as an independent parameter to help in evaluating the therapeutic effect only if the clinical and serological examinations are controversial or discrepant.[60]

2.5.1.5. Prognosis:

SPECT seems to be useful in determining the prognosis of NPSLE patients. Kodama *et al.* investigated this, and demonstrated that SPECT revealed abnormal findings during psychiatric remission, which might represent the presence of sub-clinical CNS involvement, and indicate poor prognosis.[49]

2.5.2. Sensitivity and specificity of SPECT versus other imaging modalities:

The role of different neuro-imaging modalities in the diagnosis and evaluation of NPSLE is still controversial. SPECT has been found to be useful for the identification of blood flow abnormalities in patients with NPSLE, which has seen commonly in the frontal, parietal, and temporal lobes;[14] however the sensitivity for detecting these abnormalities depends on the clinical subtype of NP manifestations. The sensitivity is very high for major CNS symptoms (90 -100 %),[13] [14] compared to minor symptoms (71% - 84.6 %).[13] [61] The sensitivity for detecting diffuse symptoms is 86 %[12] [57] while only 33 % of focal disease was identified with SPECT.[12] Using acetazolamide can reveal a marked reduction in cortical perfusion reserve, which can increase SPECT sensitivity.[62] However, SPECT lacks specificity, as similar abnormalities were seen in patients with a past history of NPSLE (66.7%),[15]SLE patients without neuropsychiatric manifestations (13 -37 %), [14] [48] and in other neurological conditions.[43]

There is some evidence to suggest that SPECT may even be more sensitive than FDG PET in NPSLE, as detecting changes in rCBF may be superior to detection of changes in glucose metabolism, which can be preserved in NPSLE. This was demonstrated by Koa *et al*. where SPECT was able to detect 69 % of NPSLE compare to 46 % for FDG-PET.[63] Another study done by Koa *et al*. showed 100 % sensitivity for SPECT and 90 % for PET.[64]

Structural imaging such as CT and MRI have been found to be less sensitive than functional modalities such as SPECT and PET which can be explained by the fact that functional impairment may occur before structural damage develops. This was demonstrated by Castellino *et al*. where SPECT showed a sensitivity of 90.9 %, while MRI detected only 62 % of the NPSLE patients.[16] A similar result was found by Zhang *et al*. where SPECT detected up to 90 %, and MRI 45 % of cases. However, MRI was found to be useful with severe or advanced changes of NPSLE, while SPECT could be more useful for prompt diagnosis of early stages of the disease.[57]

2.5.3. Image analysis methods:

Brain image analysis has been gone through many developments during the past years. Whereas visual image interpretation is still used in routine clinical practice in most centers, new techniques which allow derivation of quantitative diagnostic data may increase sensitivity and specificity. These, however are not widely available.

2.5.3.1. Visual image analysis:

The visual image interpretation using a variety of grey and color scales remains the first step for any nuclear medicine physician. Most of the observers use one of a number of color scales, which often increase an observer's sensitivity to detect small changes in activity compared to using a grey scale, however color scales can introduce false "edges" that may lead to the over interpretation of small changes as being significant. [65] Color scales can be regarded as belonging to one of two categories. The first category includes colors that have a continuous variation in color with changing intensity. The second group are color scales that give discrete color levels with changing intensity.[66]

Different approaches have been used to determine cerebral perfusion abnormalities in NPSLE patients using visual assessment. The commonest one is by identify any areas of hypoperfusion or asymmetry in the distribution of the tracer[57][58][67]. Some observers preferred to consider a scan positive only when these abnormalities were seen on at least two consecutive slices, [12][16][51] or even when abnormal defects were present in almost six slices.[15] In one study, a scan was considered abnormal if there is visible difference of at least of two colors compared to the contralateral side.[13] Another approach defined the pattern of uptake as a focal defect when it is was visible in two consecutive slices, while more than two slices was considered to be a diffuse uptake defect. [13] However Lin *et al*. defined a focal pattern when a single lesion or multiple small lesions were confined to one or two lobes, while lesions involving three or more lobes were considered to be a diffuse pattern.[14]

Whatever the choices of visual analysis, these methods are limited by a high inter observer variability and low reliability.[20] Therefore, quantitative analysis using different techniques have been investigated for a more accurate and observer – independent image interpretation.

2.5.3.2. Quantitative analysis:

The advancement of technology allows the assessment of brain perfusion in a quantitative way, resulting in lowering of the variability across the different nuclear medicine departments and enhancing the consistency of image interpretation independent of reader experience. This approach provides the best way for unbiased comparison of multiple investigations in the same patient or for the comparison of an individual investigation with normal or control studies.[68]

These quantitative analysis methods are divided mainly into two groups:

(1) Absolute quantification

(2) Semi-quantitative analysis

2.5.3.2.1. Absolute quantification:

An absolute quantification of regional cerebral blood flow should be more objective and may reduce the inter-subject or even the intra-subject variation. However, it is not practical for routine clinical use because it requires arterial blood sampling, careful correction for attenuation, complex modeling of enzyme kinetics, and in vitro measurements of blood samples.[63]

2.5.3.2.2. Semi-quantitative analysis:

Several approaches have been presented for semi-quantitative analysis comparing images of patients with a normal population. Some require creating a normal brain perfusion database, to be able to detect an abnormal perfusion pattern, by using different approaches based on (1) image standardization (2) a statistical model for evaluating significance.[69]

2.5.3.2.3. Image standardization:

This is a technique to transform the brain image of an individual subject into a standard steriotactic brain space, e.g. Talarach space. The main aim of registration is to establish an exact correspondence between the voxels of different studies across different patients, making direct comparison possible. Although manual alignment of images is possible, it is time consuming and lacks reproducibility. Therefore, automated registration is highly desirable.[70] Standardized images can be used for image averaging to decrease variation in image intensity.[71]

2.5.3.2.4. Statistical models:

Once standardized image data have been obtained, a number of programs using different statistical models exist to compare patient images with a normal brain image. These programs include regions or voxels of interest (ROI/VOI) and voxel-wise analysis.

2.5.3.2.4.1. Voxel–wise analysis:

Recent developments in neuro-imaging data analysis use voxel based analysis to reduce observer subjectivity inherent in visual analysis, by using various software packages such as SPM and BRASS. This approach has the advantage of including the rCBF information for the whole brain for statistical analysis without any a priori hypothesis regarding the regions possibly involved, which could result in a better characterization of rCBF differences in brain regions while also reducing the operator's subjectivity.[72]

SPM has been successfully applied to identify the distribution of functional abnormalities in patients with dementia and depression [73] as well as in evaluating the severity of aphasia.[74] BRASS has also been applied in some neurological disease such as Parkinson's syndrome, [75] Alzheimer's disease,[76] [77] traumatic brain injury, and in patients with cognitive impairment.[20]

A single study of SPECT using SPM was used in NPSLE patients to evaluate rCBF objectively, and the relationship between the rCBF and the psychiatric symptoms. This study showed no significant areas of decreased perfusion in SLE patients without psychiatric symptoms in comparison with a control group. On the other hand, SLE patients with major psychiatric symptoms demonstrated reduced perfusion in the posterior cingulate gyrus. Abnormalities in this region could be missed using a visual or VOI analysis.[22]

Quantified analysis of functional brain images would ideally be made on a voxel-wise basis. Although a voxel-wise comparison is theoretically relatively simple, it can present a number of challenges including unavailability of software, and normal data. In addition, skilled staffs are required to implement the software correctly.[78] This may go some way to explain why these techniques are not in more widespread use. It is therefore, worthwhile to explore methods that are widely available, and simpler to implement.

2.5.1.2.4.1. ROI and VOI analysis:

With this technique, regions of interest can be drawn manually, which may lead to variability of results, or can be drawn semi automatically after being spatially re-oriented into a standard brain space and automatically calculated and analyzed for asymmetry. Nearly all SPECT camera suppliers offer software for ROI techniques. Standard software normally offers a left-to-right hemisphere and anterior-to-posterior comparison showing maximum, minimum, and average count rates.[19]

A semi-quantitative approach based on VOI had been used to measure regional CBF in NPSLE patients. This was used by Waterloo *et al*. where the regional CBF was performed with an automated computer program, and semi-quantitatively measuring the blood perfusion in 16 symmetrical sectors of the brain. A reduction in rCBF of greater than 15 % relative to the visual cortex was considered abnormal.[59]

Nossent *et al.* defined first the region with decreased perfusion visually, and uptake in each region was divided by the uptake in the same region of the contralateral side. Ratios below 0.95 were considered as abnormal.[54] Sanna *et al.* divided the brain into six circular regions of interest (ROI), and an index of asymmetry was expressed according to a specific formula. Pathological cases had an index asymmetry of > 6, while the index asymmetry in the control group was less than 5.78.[15]

VOI based methods seem to be useful to identify areas of hypoperfusion, as well as following disease progression.[58] However, Liu *et al.* suggested that these methods are not valid for SLE patients with brain involvement, since brain lesions in SLE are always multifocal and can be symmetrical and therefore, calculating ROI relative to the contralateral side or to the cortex may not be useful.[79] In addition to that, semi-quantification based on ROI requires visual interpretation and several subjective interactions to identified regions with reduced perfusion before using this method.[18]

Whatever the choice of analysis, (visual, semi-quantitative, or absolute quantitative analysis) it is important to realize that functional imaging is influenced by the kinetics of the tracer, the energy of the gamma photon, the imaging detector system, the reconstruction algorithm and the algorithm calculating the functional parameter.[78]

A simple semi-quantitative approach based on the use of a standard color scale in a defined way may significantly enhance visual interpretation, while being available everywhere, easy to implement, and not relying on having access to a normal database.

6. Hypothesis:

Our hypothesis is that:

(1) Visual assessment of SPECT scans can discriminate between patients with clinically active NPSLE and a control group with no previous history of SLE or NPSLE.

(2) The distinction of NPSLE patients and controls using brain SPECT can be significantly enhanced using a simple semi-quantitative analysis technique.

(3) In patients with active NPSLE, correlations exist between abnormal perfusion patterns and clinical NPSLE manifestations.

Chapter 3 - Material and Methods

3.1. Study design:

This was a retrospective, controlled, descriptive and analytic study in which patients with neuropsychiatric SLE were compared to a normal control group.

3.2. Study population:

3.2.1 Neuropsychiatric SLE (NPSLE) group:

We reviewed the charts of 200 SLE patients seen by the Rheumatology Division in Tygerberg Hospital, during the period of 1995-2009, and from the electronic database of the Nuclear Medicine department, we selected 19 patients who had undergone brain SPECT and had active NPSLE disease during the time that they had the scan.

Data on gender, age, disease duration, and clinical manifestations was collected for each patient from the patient record and was reviewed with an expert Rheumatologist from the Rheumatology unit.

Patients with active NPSLE were defined by the new onset or persistence of neurological manifestations at the time of SPECT scanning. Patients were subdivided into two groups:

(A) Patients with diffuse NPSLE syndromes (acute confusional state, cognitive dysfunction, mood disorders, anxiety disorders, and psychosis)

(B) Patients with focal NPSLE syndromes (stroke, seizures, cranial nerve palsy, demyelinating syndrome, aseptic meningitis, and movement disorders). If the patient had both diffuse and focal CNS disease, that patient was designated as having diffuse disease.

3.2.1.1 Inclusion criteria:

Each patient had to fulfill certain criteria, which were:

1. American college of rheumatology (ACR) criteria for the diagnosis of SLE (four criteria or more) (Appendix 1).

2. Patients with active changes in neurological or psychiatric function in the history or physical examination as defined by the American college of rheumatology criteria.

3.2.1.2 Exclusion criteria:

Patients with any of the following criteria were excluded from the study:

1. Head neoplasm
2. History of head injury
3. Diabetes mellitus
4. History of alcohol or drug abuse
5. History of dementia

3.2.2 Control group:

The control group was made up of 19 normal healthy subjects who were selected from the electronic database at Nuclear Medicine department at Tygerberg Hospital. This group was studied by brain SPECT as part of a previous research project, where they initially underwent a physical examination and a psychiatric screening interview with the Mini International Neuropsychiatric Interview (Version 4.4). All healthy volunteers were examined by magnetic resonance imaging (MRI) scan, which had been reported by an expert radiologist to rule out any pathology. Only individuals without abnormalities on these screening tests and MRI were included in this group.

3.3. SPECT imaging:

Thirty-seven patients were injected with ^{99m}Tc-HMPAO intravenously with a dose ranging from 550 to 740 MBq. One patient was injected with ^{99m}Tc-ECD. The injection was done after establishing a lipophilic species of at least 80 %.

Imaging was performed using a dual headed gamma camera equipped with fan beam collimators. Thirty-three scans were obtained using an Elscint Helix (General Electric Medical Systems USA), while five scans were obtained using an Infinia (General Electric Medical Systems USA). Projections were acquired with three -degree intervals over 360 degree (120 projections for each head), and 20 seconds per projection.

Acquisition was acquired using a 128 × 128 matrix. Collimators were positioned as close as possible to the patient's head. The average radius of rotation was 14.7 cm. Approximately 3.5 million counts were obtained for all, but three studies the obtained counts were 1.6, 2.3 and 2.4 million counts.

Projection data were reviewed in cinematic display prior to reconstruction to ensure the absence of motion artifacts, and to ensure that the entire brain was in the field of view. In the event of those problems being present, data acquisition was repeated.

All SPECT studies were reconstructed on a Hermes system (Nuclear Diagnostic, Sweden) with an ordered subsets expectation maximization (OSEM) iterative algorithm (four iterations, 30 subsets). No scatter correction was applied to any scan. Uniform attenuation correction was performed (attenuation coefficient = 0.12 cm^{-1}). The reconstructed data were post-filtered using a Butterworth filter (order 5, cut-off 0.5 of Nyquist frequency). Images were oriented along the orbitomeatal line and along the temporal axis.

3.4. Data assessment and statistical analysis:

The two groups were combined and all studies were anonymised. The status of each scan was encoded and all identifying information was removed in the header file. Images were then assessed visually and semi-quantitatively. All the data were entered into a spreadsheet for analysis, and coding of scans was broken to reveal the NPSLE and control groups. Analysis was performed for the visual assessment method and the semi-quantitative assessment method. Statistical tests were considered significant if the p value was < 0.05.

3.4.1 Visual assessment:

Scans were reported by two Nuclear Medicine physicians who were blinded to the clinical status (NPSLE versus control) of the scans. The brain was divided into six cortical regions in each cerebral hemisphere (frontal lobe, parieto-occipital lobe and temporal lobe), and six sub-cortical regions (basal ganglia, thalamus, and cerebellum). Visual assessment was done using two different color scales (French color table and ten band color table). The ten-band color table consisted of equally spaced discrete colors with maximum counts set to the maximal intensity voxel in the brain.

Perfusion to a region was considered normal if there was homogenous perfusion with no reduced uptake compared to the contralateral side or adjacent grey matter. A region with inhomogeneous or reduced activity in at least two consecutive slices was considered as abnormal. Visual interpretation and statistical analysis were carried in the following steps:

1. Overall impression:

The overall impression for each scan was given, using the four point scale from A to D. Grade A = normal, grade B = probably normal, grade C = probably abnormal, and D = abnormal.

Receiver operator characteristic (ROC) analysis was applied to determine the cut-off point with the highest accuracy and the area under the ROC curve, considering the clinical diagnosis as the gold standard. The optimal sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated. Group differences between the NPSLE and the control group were analyzed with the Mann-Whitney U test.

2. Severity score:

Perfusion to each region was scored in a qualitative way using a scale from 0 to 3. Scored 0=normal perfusion, 1=mild hypoperfusion, 2=moderate hypoperfusion, and 3=severe hypoperfusion. Then we calculated the total severity score (TSS) for each scan as the sum of the severity scores for all 12 regions. A ROC curve was applied to determine the cut-off point with the highest accuracy, and the area under the curve. Group differences between the NPSLE and the control group were analyzed with the Mann-Whitney U test.

After that, we modified the total severity score by calculating the total score for the regions that had been scored as severity score 2 or 3. A ROC curve was applied to determine the cut-off point with the highest accuracy and the area under the curve. Group differences between the NPSLE and the control group were analyzed with the Mann-Whitney U test.

3. SPECT patterns:

The patterns of perfusion abnormality were classified into focal and diffuse using the following criteria:
○ Focal pattern if a single lesion or lesions were confined to one or two regions.
○ Diffuse pattern if lesions involved three or more regions.
A kappa test was applied to assess the degree of agreement between the SPECT pattern (diffuse/focal) and the clinical classification (diffuse/focal).

3.4.2 Semi-quantitative assessment:

The brain was divided into the same 12 regions described above. A ten-band color scale was utilized as described above. Each of these discrete colors represented a 10 % difference in the percentage of the maximal brain voxel counts. The interpretation was carried out in the following way:

The color was compared with the contralateral region. A perfusion deficit was quantified on the side with the lower color intensity. The perfusion deficit was determined using the difference (in color bands) between the two hemispheres for the region on the ten-band scale. For example a differences of one color band was given a score of 1 for the region with the lower band, two color band differences a score of 2, etc. (See Figure 3.1)
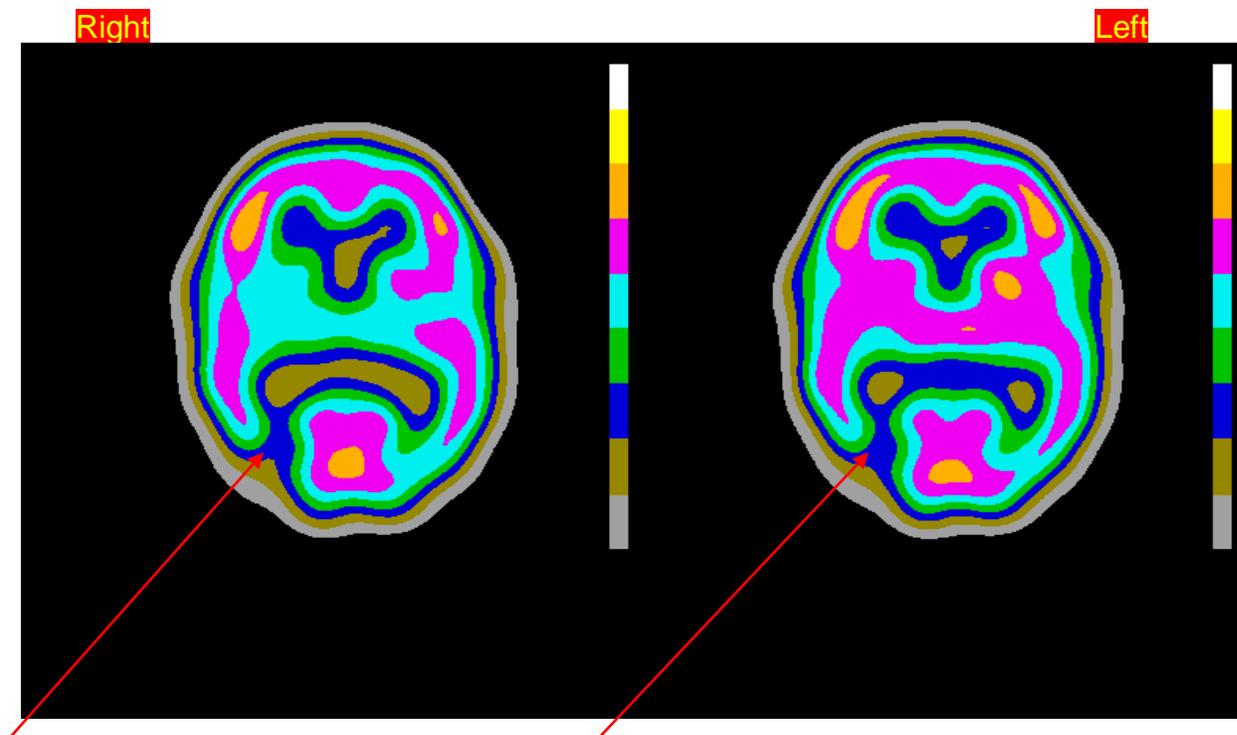
Figure 3.1: This figure demonstrates semi-quantitative scoring using a ten-band color scale. This scan shows reduced perfusion in the right parieto-occipital lobe with a difference of two color bands compared to the left site in two consecutive slices. Therefore, a score of two is given on the right parieto-occipital lobe.

Then we calculated the total asymmetry score (TAS) for each scan. A ROC curve was applied to determine the cut-off point with the highest accuracy and the area under the curve. Group differences between the NPSLE and the control group were analyzed with the Mann-Whitney U test.

Chapter 4 - Results

4.1. Study population:

A total of 200 patients seen in the Rheumatology Division with SLE between 1995 and 2009 were identified. Of these, 23 patients with neuropsychiatric manifestations underwent brain SPECT. Nineteen patients met the criteria to be included in the study. The other four patients were not included as we couldn't find the clinical data for two of them, and the other two had technically poor images. Demographic data of patients with NPSLE is depicted in Table 4.1. All patients were female, with a mean age of 30.5 years (range 16-45).

Table 4.1: Demographic data of NPSLE patients

Patient No	Date of birth	Scan date	Age	Gender
1	1965	2001	36	F
2	1965	1995	30	F
3	1988	2004	20	F
4	1973	2003	30	F
5	1968	2007	39	F
6	1973	2003	30	F
7	1976	2002	26	F
8	1950	1995	45	F
9	1963	1998	35	F
10	1974	2006	32	F
11	1973	2003	30	F
12	1983	2004	21	F
13	1975	2004	29	F
14	1993	2009	16	F
15	1967	2006	39	F
16	1967	2006	39	F
17	1968	2007	39	F
18	1967	2008	29	F
19	1976	2008	16	F

F = Female

The control group consisted of 14 males and five females, with a mean age of 36.9 years (range 23-48). (Table 4.2)

Table 4.2: Demographic data for the control group

No.	Date of birth	Scan date	Age	Gender
20	1954	2002	47	M
21	1954	2002	48	M
22	1954	2005	31	F
23	1974	2001	26	M
24	1956	2001	45	M
25	1962	2002	39	M
26	1968	2001	33	M
27	1981	2005	23	M
28	1957	2002	44	M
29	1967	2002	34	M
30	1972	2002	29	M
31	1970	2001	31	F
32	1965	2002	36	M
33	1964	2001	37	F
34	1970	2003	32	F
35	1969	2001	32	M
36	1965	2005	40	M
37	1944	2001	57	M
38	1963	2001	38	F

F = Female

M = Male

4.2. Clinical manifestations:

Table 4.3 shows the ARA criteria used for the diagnosis of SLE in the patients. The frequency of the selected clinical criteria of SLE included antinuclear antibodies (16/19), arthritis (13/19), renal disorder (12/19), serositis (7/19), immunological disorder (7/19), discoid rash (6/19), oral ulcer (5/19), malar rash (5/19), photosensitivity (3/19), anti-DNA (3/19), and hematological disorders (2/19).

Table 4.3: American College of Rheumatology criteria for SLE in the NPSLE group

Patient No.	SLE criteria
1	Nephropathy, discoid lupus, ANF+ve, anti-DNA+ve
2	Arthritis, oral ulcer, photosensitivity, ANF+ve
3	Oral ulcer, photosensitivity, proteinuria , ANF+ve
4	Discoid lupus, arthritis, serositis, thrombocytopenia, ANA +ve
5	Arthritis, photosensitivity, pericardial effusion, ANF+ve
6	Nephritis, malar rash, oral ulcer, pericarditis, ANF+ve
7	Arthritis, ANF+, anti-DNA+, pancytopenia
8	Discoid lupus, arthritis, ANF +ve, anti- DNA
9	Arthritis, oral ulcer, nephritis, discoid rash
10	Arthritis, protenuria, malar rash, ANF+ve
11	Nephritis, arthritis, ANF+ve, anti- DNA+, anti-SM+ve
12	Arthritis, discoid rash, pericardial effusion, proteinuria
13	Nephritis, ANF+ve, anti- DNA+ve
14	Nephritis, arthritis, proteinuria, serositis, ANF+ve,
15	ANF+, arthritis, proteinuria
16	Arthritis, ANF+, endocarditis
17	Discoid lupus, malar rash, oral ulcer, ANF+
18	Malar rash, arthritis, proteinuria, ANF+ve, anti-DNA+ve
19	Arthritis, serositis, malar rash ,protenuria, ANF+ve

ANF +ve = antinuclear factor positive

Table 4.4 shows the neuropsychiatric manifestations. All neuropsychiatric events occurred during, at, or after the first visit to the Rheumatology Division. With respect to neuropsychiatric events, a total of 10 out of the 19 syndromes occurred at least once. The most frequent syndromes were cognitive dysfunction (6/19), psychosis (4/19), mood disorders (3/19), cranial nerve palsy (3/19), seizures (3/19), movement disorders (2/19), cerebrovascular disease (2/19), meningitis (2/19) and others (6/19). According to the classification proposed by the American College of Rheumatology, 12 of the 19 patients were classified as having a diffuse syndrome, and the remaining seven had focal disease.

Table 4.4: Neuropsychiatric manifestations in the NPSLE group

Patient No.	Neuropsychiatric manifestations	Clinical classification
1	Depression	Diffuse
2	Meningitis, left blinded eye	Focal
3	Cognitive dysfunction	Diffuse
4	Weakness, aphasia	Focal
5	Memory loss (cognitive dysfunction)	Diffuse
6	nystagmus , retinopathy , ataxia	Focal
7	Psychosis	Diffuse
8	Chorea	Focal
9	Headache, visual hallucination (psychosis)	Diffuse
10	Psychosis, seizures, transient ischaemic attack	Diffuse
11	Loss of vision	Focal
12	Seizures	Focal
13	Meningitis	Focal
14	Depression, bilateral optic neuritis	Diffuse
15	Depression, memory loss, seizures	Diffuse
16	Psychosis	Diffuse
17	Memory loss	Diffuse
18	Cognitive dysfunction	Diffuse
19	Cognitive dysfunction	Diffuse

4.3. Visual assessment findings:

A list of findings for the visual assessment method was given in Tables 4.5

Table 4.5: Brain SPECT findings for the visual assessment for both groups

No	CD	R-fro	L-fro	R-par	L-par	R-tem	L-tem	R-bas	L-bas	R-thal	L-thal	R-cer	L-cer	Ove	TSS	mTSS
1	P	0	1	3	0	1	0	0	0	0	0	1	0	D	6	3
2	P	0	1	0	0	0	1	0	0	0	0	0	0	B	2	0
3	P	3	0	2	0	2	0	0	0	0	1	0	0	D	8	7
4	P	2	2	2	2	2	2	0	0	0	0	1	0	C	13	12
5	P	2	2	0	1	1	1	0	0	0	0	0	0	D	7	4
6	P	0	0	2	0	1	0	0	0	0	0	0	0	C	3	2
7	P	1	0	1	0	0	0	1	0	1	0	0	0	C	4	0
8	P	1	2	1	2	1	0	0	0	0	0	1	0	C	8	4
9	P	2	2	0	0	0	0	0	0	0	0	0	0	C	4	4
10	P	2	2	2	2	1	2	0	0	0	0	0	0	D	11	10
11	P	0	0	0	2	0	1	0	1	0	0	0	0	C	4	2
12	P	1	1	1	1	2	2	0	0	0	0	0	0	C	8	4
13	P	0	1	0	0	1	1	0	0	0	0	0	0	B	3	0
14	P	2	2	2	2	2	1	2	0	1	0	0	0	D	14	12
15	P	2	2	0	1	2	2	0	0	0	0	1	0	C	10	4
16	P	1	1	0	0	0	2	0	0	0	1	2	0	C	7	4
17	P	2	2	2	2	2	2	0	1	0	0	1	0	D	14	12
18	P	2	2	1	2	2	0	1	0	0	0	0	0	D	10	8
19	P	2	2	2	2	2	2	0	0	0	0	0	0	D	12	12
20	N	0	0	0	0	0	0	0	0	0	0	0	0	A	0	0
21	N	0	0	1	0	0	0	0	0	0	0	0	0	B	1	0
22	N	1	0	1	1	0	0	0	0	0	0	0	0	B	3	0
23	N	1	1	1	1	1	2	0	1	0	0	0	0	C	8	2
24	N	0	0	0	1	0	1	0	0	0	0	0	0	B	2	0
25	N	2	1	2	1	2	0	1	0	0	0	1	0	D	10	6
26	N	0	0	0	0	0	0	0	0	0	0	3	0	B	3	3
27	N	0	0	0	3	0	0	0	0	0	0	3	0	D	6	6
28	N	2	1	1	0	1	0	0	0	0	0	0	0	C	5	2
29	N	1	1	1	1	1	1	0	0	0	0	0	0	B	6	0
30	N	0	0	1	0	1	1	1	0	0	0	1	0	B	5	0
31	N	0	1	0	0	0	2	0	0	0	0	0	0	C	3	2
32	N	1	1	2	1	1	1	0	0	0	0	0	0	C	7	2
33	N	2	0	2	2	2	0	0	0	0	0	2	0	C	10	10
34	N	1	1	1	1	0	1	0	0	0	0	0	0	B	5	0
35	N	1	1	1	1	1	1	1	0	0	0	0	0	C	7	0
36	N	0	1	0	1	0	0	0	0	0	0	0	0	B	2	0
37	N	0	0	0	0	0	0	0	1	0	1	0	0	A	2	0
38	N	0	0	1	0	1	0	0	0	0	0	0	0	A	2	0

CD=clinical diagnosis, R=right, L= left, fro=frontal lobe, par=parieto-occipital lobe, tem=temporal lobe, bas=basal ganglia, thal=thalamus, cer=cerebellum, Ove=overall impression, TSS=total severity score, mTSS=modified total severity score. P= patient, N=normal. 0=normal perfusion, 1= mild hypoperfusion, 2=moderate hypoperfusion, 3=severe hypoperfusion. A=normal, B=probably normal, C=probably abnormal, and D=abnormal.

For the visual assessment method, 160 regions with reduced perfusion were observed in both groups. Eighty-seven (54.4 %) of these areas were found on the right hemisphere, while 73 (45.6 %) were seen on the left side. Areas of hypoperfusion were found most frequently in the frontal regions (29.4 %), parieto-occipital regions (28.8 %), and the temporal regions (26.3 %). Areas of hypoperfusion were seen less frequently in the cerebellum (6.8 %), basal ganglia (5.6%), and the thalamus (3.1 %).

Of these 93 regions with defects were noticed in the NPSLE group. Fifty -one (54.8 %) of them were seen on the right side, while 42 (45.6 %) were on the left side. The most frequently affected were the frontal regions (31.1 %), temporal regions (28.0 %), and the parieto-occipital regions (24.7 %). Areas of hypoperfusion were seen less frequently in the cerebellum (6.5 %), basal ganglia (5.4 %), and the thalamus (4.3 %). (Table 4.6)

Table 4.6: Regions of reduced perfusion seen on the visual assessment method

Region of abnormality	NPSLE group	Control group
Frontal	29	18
Parieto-occipital	23	23
Temporal	26	16
Basal ganglia	5	4
Thalamus	4	1
Cerebellum	6	5
Total	93	67

4.3.1. Overall impression:

Grading of the brain SPECT using the overall score resulted in 10 being graded as grade A (normal), three as grade B (probably normal), 15 as grade C (probably abnormal), and 10 as grade D (abnormal). From these figures we found that no NPSLE patients were graded as grade A. Two NPSLE patients were graded as grade B, 9 as grade C, and eight as grade D. For the control group 10 were graded as grade A, one as grade B, six as grade C and two as grade D.

A ROC analysis showed an acceptable diagnostic accuracy with an area under the curve of 0.76. A cut -off point at C showed 89 % sensitivity, 57 % specificity, 68% positive predictive value, 84 % negative predictive value, and 74 % accuracy. (Figure 4.1)

Figure 4.1: Overall impression using ROC curve
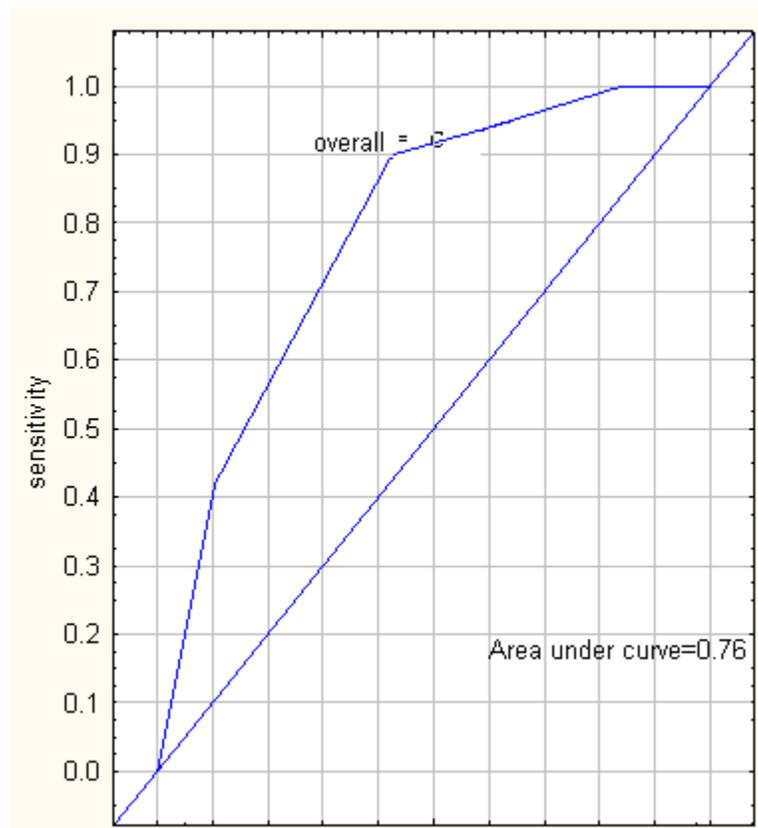
Group comparison showed that the NPSLE group had a significantly higher grade compared to the control group (*P =0.001*, Figure 4.2)

Figure 4.2: Overall impression using Mann-Whitney U test for group differences
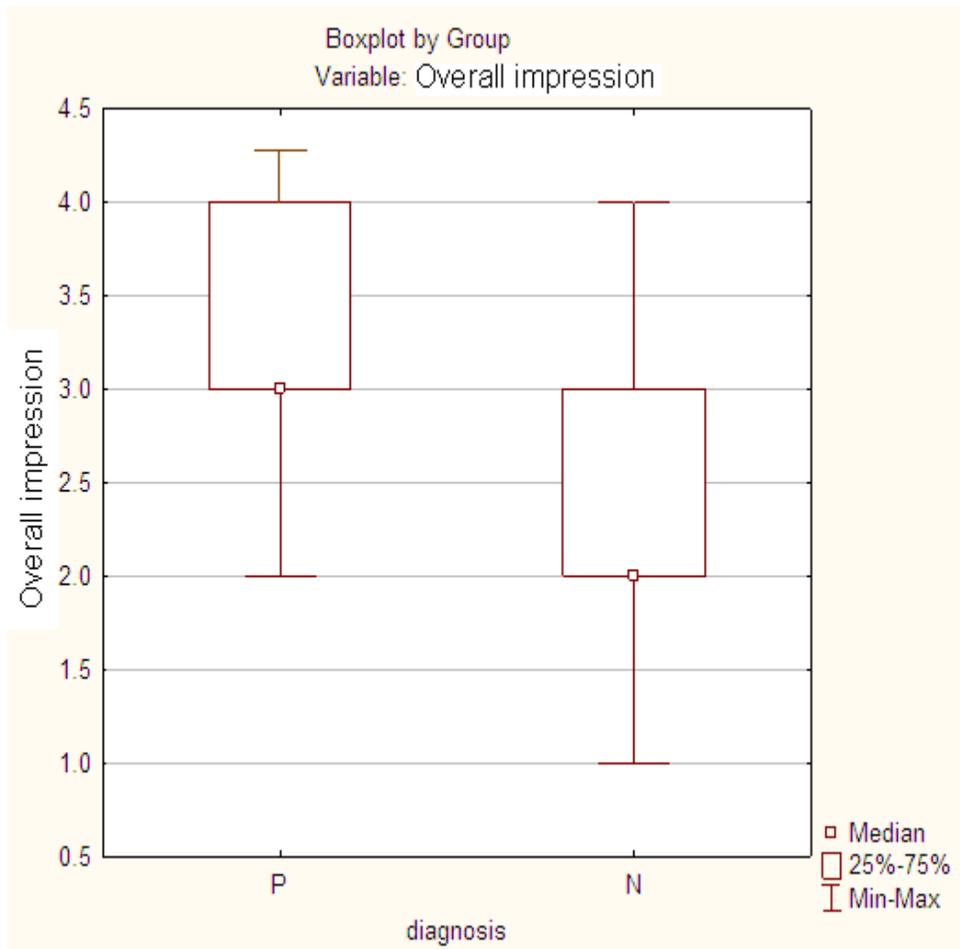
P = NPSLE group

N = control group

4.3.2. Severity score:

Regarding the severity score, we found 295 (64.7 %) regions were graded as normal, 94 (20.6 %) as having a mild defect, 63 (13.8 %) as having a moderate defect, and 4 (0.9 %) regions as having a severe defect. From these figures, we found moderate defects in 51 (22.4 %) of regions of the NPSLE patient group, while moderate defects were found only in 12 (5.2 %) of regions of the control group. (Figure 4.3)

Figure 4.3: SPECT perfusion severity scores for both groups
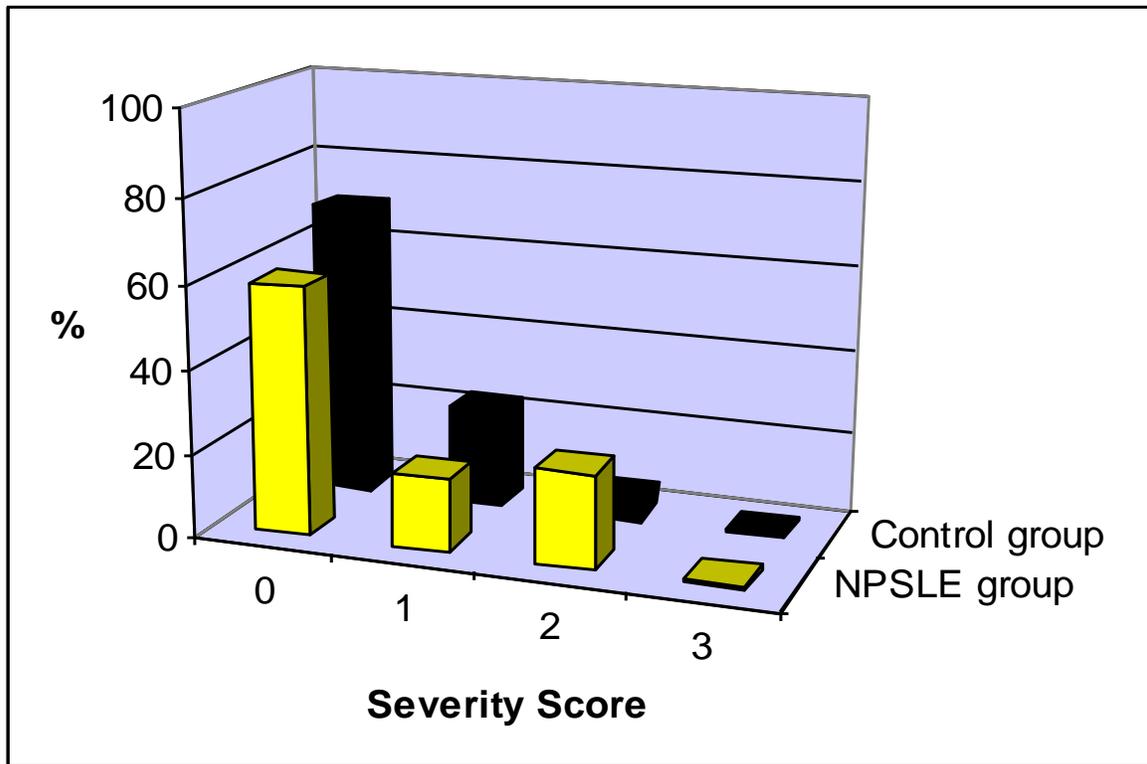
0 = normal, 1 = mild hypoperfusion, 2 = moderate hypoperfusion, 3 = severe

hypoperfusion

4.3.2.1. Total severity score (TSS):

The maximum severity sum score for the all regions we found was 14, while the minimum score was zero. A ROC analysis resulted in an area under the curve of 0.75. A cut-off point at seven showed 63 % sensitivity, 74 % specificity, 71 % positive predictive value, 67 % negative predictive value, and 68 % accuracy. (Figure 4.4)

A cut-off point at four showed an arguably more acceptable sensitivity of 84 %, with a corresponding 47 % specificity, 62 % positive predictive value, 86 % negative predictive value, and 65 % accuracy.

Figure 4.4: Total severity score (TSS) using ROC curve
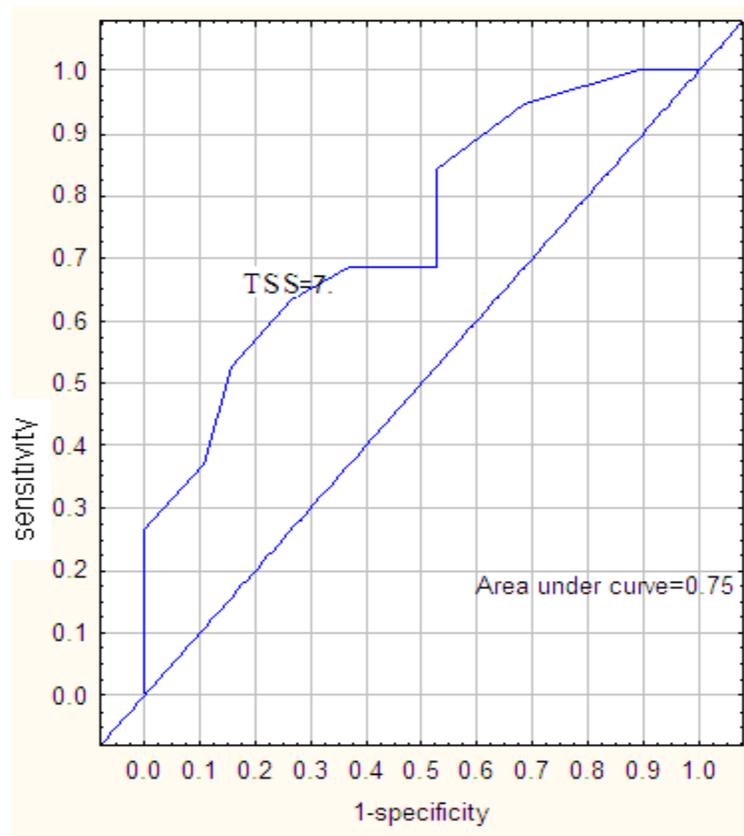
Group comparison showed that the NPSLE group had a significantly increased total severity score compared to the control group (*P= 0.008*, Figure 4.5).

Figure 4.5: Total severity score (TSS) using Mann-Whitney U test for group differences
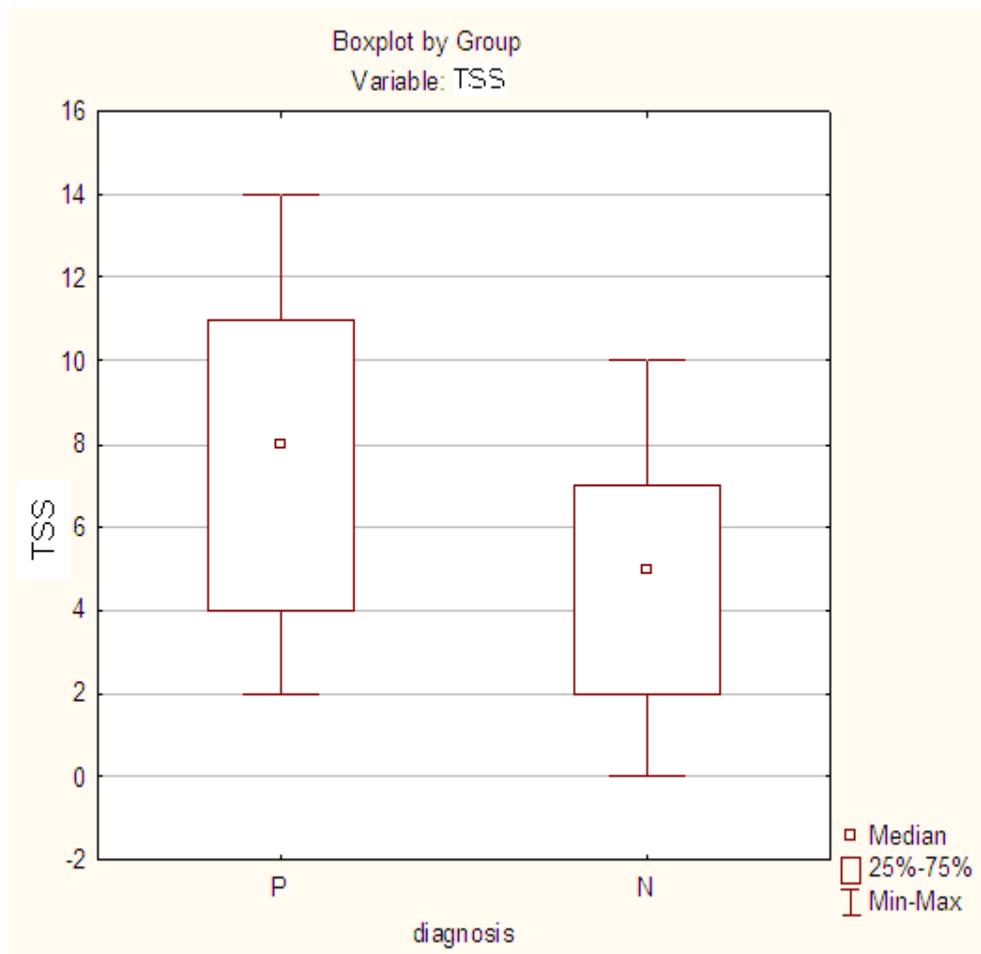
P = NPSLE group

N = control group

4.3.2.2. Modified total severity score (mTSS):

The maximum severity sum scores for the regions that had been scored as two or three was 12, while the minimum score was zero. A ROC analysis resulted in an area under the curve of 0.79. A cut-off point at three showed 74 % sensitivity, 79 % specificity, 78 % positive predictive value, 75 % negative predictive value, and 76 % accuracy. (Figure 4.6)

A cut-off point at two showed an arguably more acceptable sensitivity of 84 %, with a corresponding 58 % specificity, 67 % positive predictive value, 79 % negative predictive value, and 71 % accuracy.

Figure 4.6: Modified total severity score (mTSS) using ROC curve
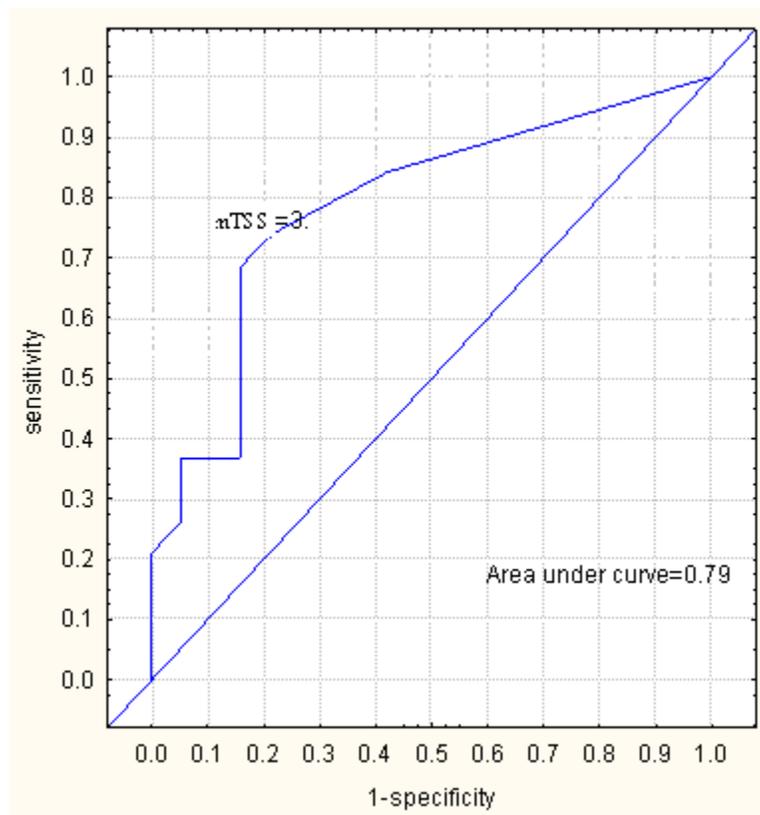
Group comparison showed that the NPSLE group had a significantly increased modified total severity score compared to the control group (*P = 0.005*, Figure 4.7)

Figure 4.7: Modified total severity score (mTSS): using Mann-Whitney U test for group differences
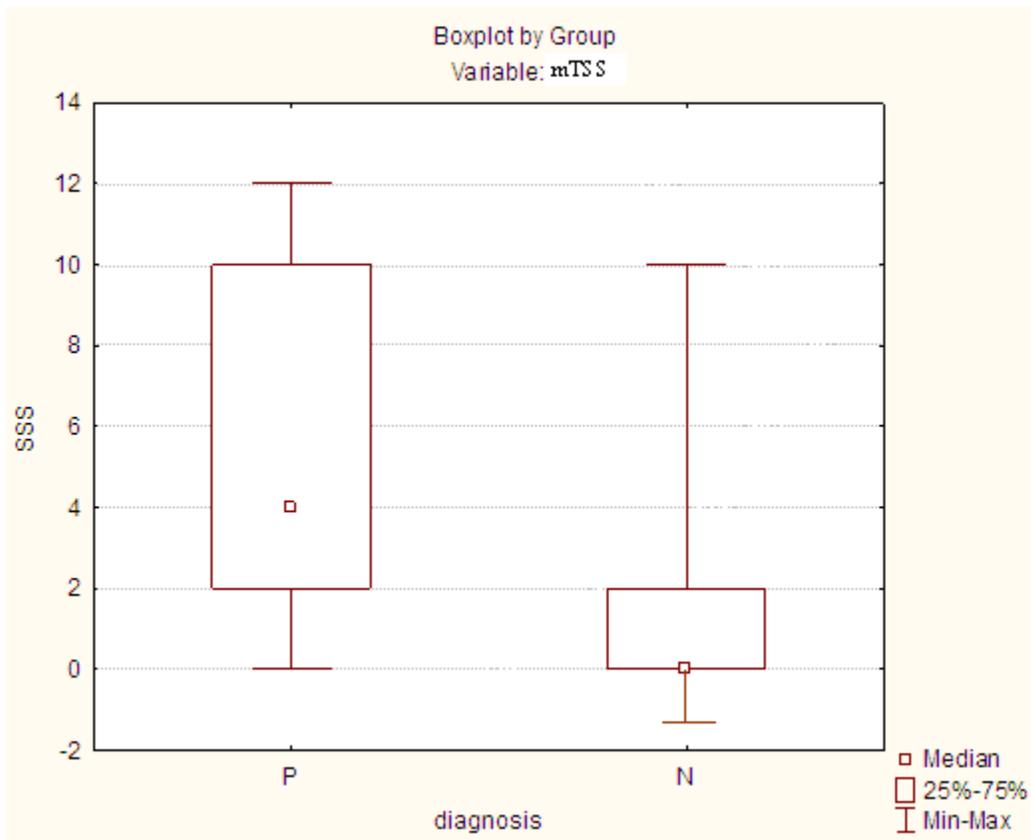

P = NPSLE group

N = control group

4.3.3. Correlation between SPECT pattern and the clinical classification:

Agreement was found between the SPECT pattern and the clinical classification in 14 of the NPSLE group (73.6 %, *kappa* = 0.379). Eleven (92 %) of 12 patients with clinically diffuse syndromes had abnormal SPECT findings that were classified diffuse defect, whereas one patient (8 %) showed a focal SPECT pattern. On the other hand, for the seven patients who were classified as having a clinically focal syndrome, SPECT findings showed focal defects in three patients (43 %), and diffuse defects in four patients (57 %).

4.4. Semi-quantitative assessment findings:

Table 4.7: Brain SPECT findings for the semi-quantitative assessment

No	CD	R-fro	L-fro	R-par	L-par	R-tem	L-tem	R-bas	L-bas	R-thal	L-thal	R-cer	L-cer	TAS
1	P	0	1	2	0	1	0	0	0	0	0	1	0	5
2	P	0	1	0	0	0	1	0	0	0	0	0	0	2
3	P	2	0	1	0	2	0	0	0	0	0	1	0	6
4	P	0	1	0	1	0	0	1	0	0	0	1	0	4
5	P	1	0	2	0	1	0	1	0	1	0	1	0	7
6	P	1	0	1	0	1	0	0	1	0	0	1	0	5
7	P	1	0	1	0	0	0	1	0	1	0	0	0	4
8	P	0	1	0	1	0	0	0	0	0	0	1	0	3
9	P	0	1	0	1	0	1	0	0	0	0	0	0	3
10	P	1	0	1	0	0	1	0	0	0	0	1	0	4
11	P	0	1	0	2	0	1	0	1	0	0	1	0	6
12	P	0	1	0	1	0	1	1	0	0	0	1	0	5
13	P	0	1	1	0	0	1	0	0	0	0	0	0	3
14	P	1	0	1	0	1	0	2	0	1	0	1	0	7
15	P	0	1	0	1	1	0	1	0	1	0	1	0	6
16	P	0	1	0	1	1	0	1	0	0	1	1	0	6
17	P	0	1	0	1	0	1	0	0	1	0	1	0	5
18	P	0	1	0	1	1	0	1	0	0	0	0	0	4
19	P	0	1	1	0	0	1	0	0	0	0	1	0	4
20	N	0	1	1	0	0	0	0	0	0	0	0	1	3
21	N	1	0	1	0	0	0	1	0	0	0	0	0	3
22	N	1	0	1	0	1	0	0	0	0	0	0	0	3
23	N	0	1	0	1	0	1	0	1	0	0	0	0	4
24	N	0	0	0	1	0	1	0	0	1	0	0	0	3
25	N	1	0	1	0	1	0	1	0	0	0	1	0	5
26	N	0	0	0	1	1	0	0	0	0	0	1	0	3
27	N	0	1	0	1	0	0	0	0	0	0	1	0	3
28	N	1	0	1	0	1	0	0	1	0	0	0	1	5
29	N	0	1	0	1	0	1	1	0	0	0	0	0	4
30	N	0	0	1	0	0	0	1	0	0	0	1	0	3
31	N	0	0	0	1	0	1	0	0	0	0	0	0	2
32	N	0	1	1	0	1	0	0	0	0	0	0	0	3
33	N	1	0	1	0	1	0	0	0	0	0	1	0	4
34	N	0	1	0	0	0	0	1	0	0	0	0	0	2
35	N	0	1	0	0	0	0	1	0	0	0	1	0	3
36	N	0	1	0	1	0	0	1	0	0	0	0	0	3
37	N	0	0	0	1	0	0	0	1	0	1	0	0	3
38	N	0	1	1	0	0	0	0	0	0	0	0	0	2

CD=clinical diagnosis R=right, L=left, fro=frontal lobe, par=parieto-occipital lobe, tem=temporal lobe, bas=basal ganglia, thal=thalamus, cer=cerebellum, TAS=total asymmetry score.0=no color difference, 1=one color difference to the contralateral side, and 2=two color differences to the contralateral side, etc.

The semi-quantitative asymmetry method resulted on a total of 145 regions with abnormalities in both groups. Eighty-five (58.6 %) of these areas were found on the right hemisphere, while 60 (41.4 %) were seen on the left side. Areas of hypoperfusion were found most frequently in the parieto-occipital regions (24.1 %), frontal regions (22.8 %), and temporal regions (19.3 %), and less frequently in the cerebellum (14.5 %), basal ganglia (13.8 %), and the thalamus (5.5 %).Of these 82 regions were noticed for the NPSLE group, most frequently in the frontal regions (23.1 %), parieto-occipital regions (21.9 %), and temporal regions (19.6 %), and less frequently in the cerebellum (15.9 %), the basal ganglia (12.1 %), and the thalamus (7.4 %). (Table 4.8)

Table 4.8: Regions of asymmetrical perfusion seen on the semi-quantitative method

| Region of abnormality	NPSLE group	Control group
Frontal	19	14
Parieto-occipital	18	17
Temporal	16	12
Basal ganglia	10	10
Thalamus	6	2
Cerebellum	13	8
Total	82	63

The maximum asymmetry sum score for all regions we found was seven, while the minimum score was two. A ROC analysis resulted in an area under the curve of 0.80. A cut-off point at 4 showed 79 % sensitivity, 74% specificity, 75 % positive predictive value, 78 % negative predictive value, and 76 % accuracy. (Figure 4.8)

Figure 4.8: Total asymmetry score (TAS) using ROC curve
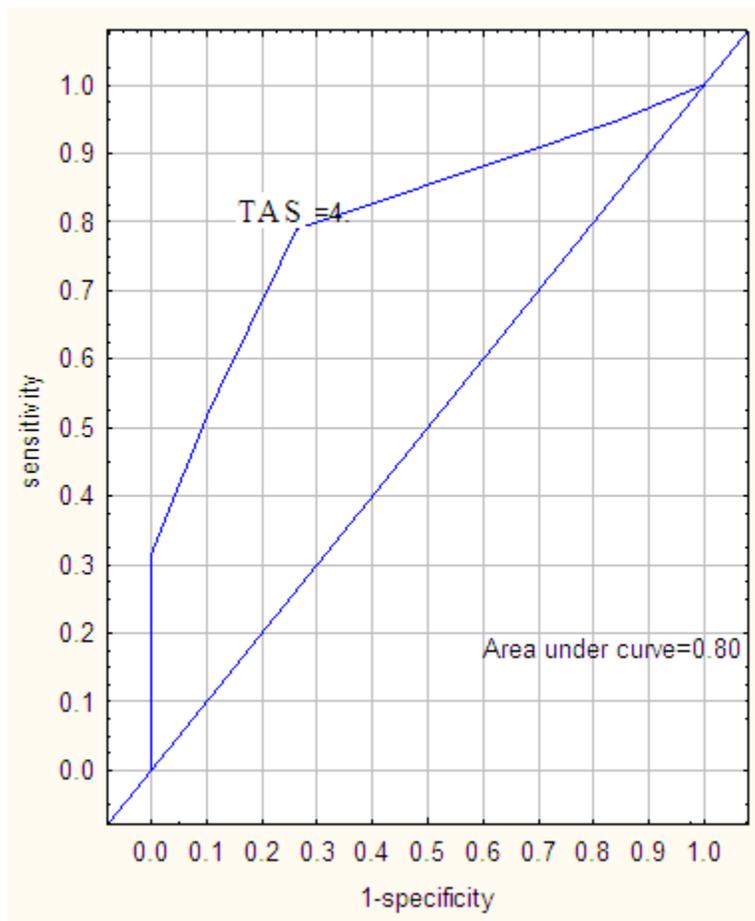
Group comparison showed that the NPSLE group had a significantly increased asymmetrical score compared to the control group. (Figure 4.9)

Figure 4.9: Total asymmetry score (TAS) using Mann-Whitney U test for group differences
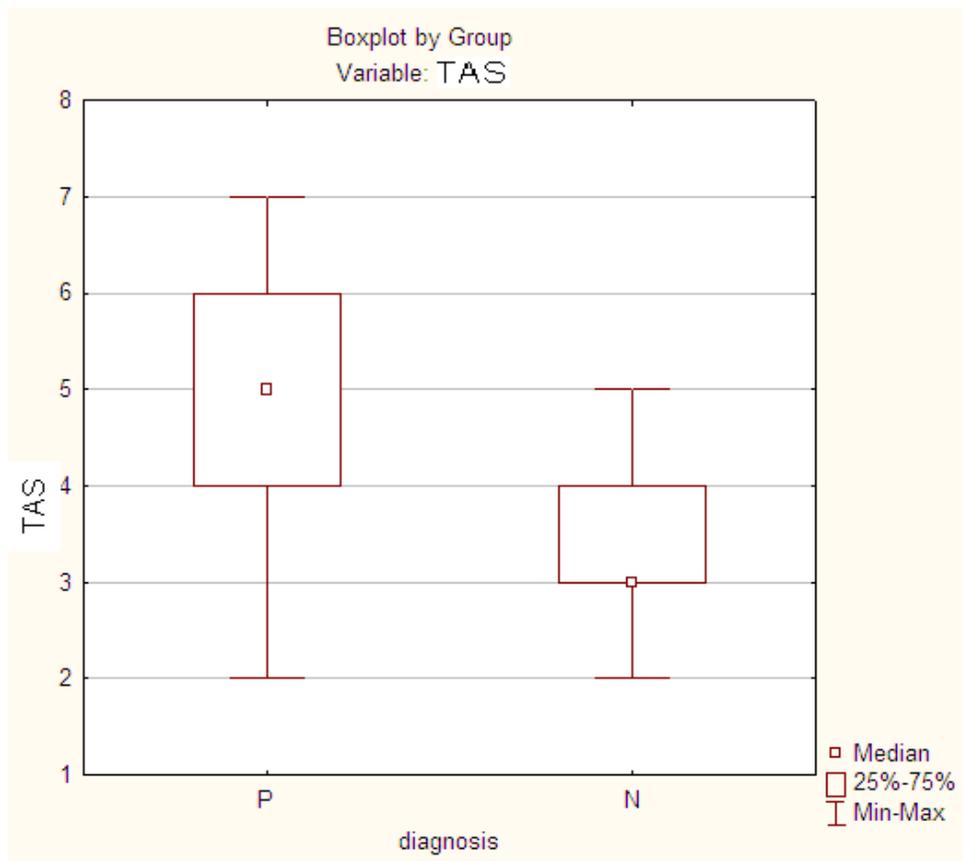
P = NPSLE group

N = control group

Table 4.9 summarized the optimal results that obtained from the ROC curve for the visual method (overall impression, total severity score and modified total severity score) and the semi-quantitative method (total asymmetry score).

Table 4.9: optimal cut-off point for the different techniques

Technique	Optimal cut-off point	Sensitivity	Specificity	PPV	NPV	Accuracy
Overall	C	0.89	0.57	0.68	0.84	0.73
TSS	7	0.63	0.73	0.70	0.66	0.68
mTSS	3	0.73	0.78	0.77	0.75	0.76
TAS	4	0.78	0.73	0.75	0.77	0.76

Overall = overall impression

TSS = total severity score

mTSS = modified total severity score

TAS = total asymmetry score

PPV = positive predictive value

NPV = negative predictive value

Chapter 5 - Discussion

One of the most important and disabling complications of SLE is the involvement of the central nervous system, which comprised a heterogonous group of clinical presentations, including focal neurological events or more diffuse patterns. However, no single mechanism can account for the broad spectrum of these manifestations and no test has proved consistently reliable in the diagnosis of NPSLE. The rationale for using SPECT to assess neuropsychiatric manifestations in SLE patients can be based on evidence that CNS disease in SLE may be secondary to abnormalities in the cerebral vessels, or that locally decreased neurological function will lead to decreased perfusion via autoregulation. However, the accuracy of SPECT has showed variable results, which could be attributed to different factors, such as the study design, as well as the different methods of image analysis (interpretation).[12 13 14 15 48 57]

In this study we found that:

1. SPECT was able to separate patients with active NPSLE from normal controls,

2. Compared to a visual impression, similar results were obtained using visual or semi-quantitative scores.

3. In patients with active NPSLE a significant correlation exists between the clinical disease pattern and perfusion patterns with SPECT.

The first finding of this study was that SPECT was able to separate patients with active NPSLE from normal controls. For the visual impression, we used a four-point scale which reflected the diagnosis as well as our level of certainty. Grade A (normal) and grade D (abnormal) indicate a high level of certainty, which were shown to have a high NPV (100 %) and PPV (60 %) respectively. Probability grades B and C are more equivocal. Although the diagnosis of NPSLE in all cases graded as C or D still resulted in a good sensitivity (89 %), specificity was moderate (57 %).

The results that we obtained from the ROC curve analysis showed that a cut-off point at C gave the best results. That means grade A and B were considered as normal and grade C and D as NPSLE. These results showed an area under the curve of 0.76 which is acceptable. The high sensitivity (89 %) obtained from this analysis, resulted in an ability to diagnose most of the NPSLE patients (17 out of 19), however we failed to identify a significant abnormality in two patients of the NPSLE group. Interestingly, those two patients were the only cases who presented with CNS symptoms of meningitis. That is in contrast to Kovacs *et al* and Zhang *et al*.[56] [57] where SPECT was found to be abnormal in patients with a septic meningitis. The reason for this discrepancy is unclear, but it could be due to the clinical condition of those patients. The high sensitivity in our study is comparable with the results of Longo *et al*.[48] where the sensitivity of SPECT was found to be 85 % using a similar four-point scale. Similar results were also seen in other studies; although they did not use a four-point scale for their intepretation.[12] [13]

Using the optimal cut-off point, this technique however showed a relatively low specificity (57 %). This indicates the high number of false positive scans that were reported (9 out of 19). These results demonstrate that the interpreters were unable to report many control scans as normal; even though it was known that half of the scans were from the control group. It therefore seems to be easer to detect abnormalities in the NPSLE group, than to exclude abnormalities in the control group. The moderate specificity in our study is similar to *Russo et al*. where specificity was 69 %.[12] However direct comparison with other studies is problematic, as we used a normal control group in our study, while most of control groups in previous studies were SLE patients with inactive NP manifestations or SLE patients without NPSLE. Only one study done by Sanna *et al* used healthy volunteers. That study showed homogonous and symmetrical perfusion for all the control cases.[15] This discrepancy with Sanna *et al*, could however be at least in part related to the fact that they did not anonymised both groups (control & NPSLE) and report them blindly as was done in this study.

In our study, we found that reduced perfusion was found more frequently in the frontal, parieto-occipital, and temporal regions, while the basal ganglia, thalamus and cerebellum were less frequently affected. This result is in agreement with Lin *et al.*[14] This could be due to fact that the major pathogenesis in SLE patients is probably related to a vasculopathy with thickening of the intima and fibrinoid degeneration, mainly of the small blood vessels. In addition to that, the abnormalities resembling embolic disease have been reported in approximately 40 % of SLE patients and since the territory of the middle cerebral artery which supplies mainly the cortical regions is at a higher risk for cerebral embolism than others, a relation between these two observations may exist.[80]

The second finding of this study, that similar results to the visual impression were obtained using the visual scoring and the semi-quantitative scoring. These all gave a result that statistically was no different from the overall impression. From the analysis, we found that the TAS allowed the most accurate classification with an area under the curve of 0.80, while TSS gave the least accuracy with an area under the curve of 0.75. However, the difference between all these analysis methods was not significant ($P > 0.05$). It could be argued that, these comparisons do not give a complete picture, as the ROC curves might cross at a particular false-positive fraction (FPF). Therefore, a method with a greater area under the curve (A_Z) might actually have a worse sensitivity for a given FPF.

For the visual scoring, we evaluated the relative cerebral blood flow for each region visually in a qualitative way using a severity score from 0 (normal) to 3 (severe hypoperfusion), in order to investigate whether this raised the accuracy of our interpretation. We found that 16/19 of the NPSLE patients had at least one area of moderate or severe hypoperfusion, while three patients did not have any areas of moderate or severe hypoperfusion. Of the second group, 8/19 of the controls had at least one area of moderate or severe hypoperfusion, while the rest had only areas of normal or mild hypoperfusion. If we simply consider scans with areas of moderate or severe hypoperfusion as positive, we will get a

sensitivity of 84 % and a specificity of 57 %, which is similar to our overall impression score. However, an important draw back of this method is that the definitions of mild, moderate, and severe is completely subjective.

After that, we calculated the total severity score for each scan, assuming that patients with NPSLE should have more total severity score than the control group. An ROC curve analysis was applied which demonstrated an area under the curve of 0.75. A total severity score of seven or more gave the best results with a sensitivity of 63 %, specificity of 73 %, and accuracy of 68 %. Similar accuracy (68 %) for the TSS was noticed at the cut-off point eight, where the sensitivity dropped from 63 % to 52 %, while the specificity increased from 73 % to 84 %.

The lower sensitivity using the visual scoring (TSS) is due to the fact that many of the NPSLE patients had a total severity score of four or less. That could be explained in two ways; firstly, those patients might have a mild form of the disease, and patients with severe disease should be expected to have more severe perfusion deficits.[81] This statement could tested if we had the opportunity to assess the clinical severity of the disease. However, this was not possible because the retrospective nature of the study making this information unavailable. A second explanation could be that the interpreters had difficulty differentiating mild hypoperfusion in NPSLE from normal perfusion, and scoring areas with mild hypoperfusion with a zero score, rather than one would underestimate the total severity score. Lonborg *et al.* stated that interpreting by eye alone would not be able to detect all rCBF abnormalities, especially if they are mild.[78] When we re-analyzed the data considering areas that had mild hypoperfusion as having a score of zero using the mTSS, the ROC curve analysis resulted in area under the curve of 0.79 which is higher than that of the TSS, although the difference was not significant. At a cut-off point of three, the mTSS improved over the TSS, achieving 76 % accuracy. The sensitivity was increased from 63 % to 73 %, and the specificity increased from 73 % to 78 %.

It is therefore likely that areas of mild hypoperfusion are often a normal variant rather than mild disease, and their exclusion from a combined score can enhance specificity, without a loss of sensitivity.

The improvement in accuracy using the mTSS is related to the fact that moderate and severe lesions were seen in most of the NPSLE group (16/19) compared to about half of the control group (8/19), while mild lesions were seen in all of the NPSLE group (19/19) and almost all of the control group (18/19). A similar accuracy (76 %) for the mTSS was noticed at the cut-off point four, where the sensitivity dropped from 73 % to 68 %, while the specificity increased from 78 % to 84 %. However, it can be argued that the cut-off point at seven for the TSS or at three for the mTSS will be clinically more useful, as it is more important to detect NPSLE than to exclude abnormalities in a normal person.

Finally, we can conclude that the presence of a severe defect or more than one moderate defect is unlikely in a normal person. In addition to that, differentiating severe or moderate defects from normal perfusion is much easier than differentiating mildly reduced perfusion from normal perfusion. Moreover, the TSS and mTSS could not do better than simply defining positivity based on moderate and severe lesions, so a combined score like this does not seem to be that useful.

Compared to visual interpretation, the accuracy did not improve by using semi-quantitative scoring with the TAS. The ROC curve analysis resulted in area under the curve (0.80) at a cut-off point of 4 with 76 % accuracy. This resulted in a sensitivity of 78 %, as we failed to identify four out of 19 NPSLE patients (22 %). That could be explained by the fact that this scoring system is based on asymmetry, while abnormalities could be present bilaterally. For example, you might have an abnormality in both frontal lobes, but with a color difference between the right and left of only one color, and therefore a score of only one.

As a second example, you might have an abnormality in the anterior part of the right frontal lobe and an abnormality in the posterior part of the left frontal lobe. Therefore, we would be able to give a score for either the anterior or the posterior lesions depending on the extent of abnormality. Therefore, dividing each hemisphere for more regions such as anterior frontal, posterior frontal, anterior parietal, posterior parietal ......etc, might be more useful. This would however make the method more time consuming.

When we analyzed the semi-quantitative results for the individual scores, we noticed that all scans had at least one area with a score of one or more, so we get 100 % sensitivity and 0% specificity. However, when we consider scans with at least one area with a score of 2 or more, we found none of the control group had a score of 2 or more (100 % specificity), but only 5/19 of the NPSLE patients (26 % sensitivity) had a score of 2 or more. Therefore, further research using a 20 band scale might be useful to determine the sensitivity and specificity of an equivalent of a score of 1.5.

The reported sensitivity of SPECT in active SLE using semi-quantitative methods based on ROI varied from 71 % to 88 %.[48 54 58] That supports our assumption about the capability of the method we used to give similar results. The reasonable specificity in this analysis indicates that asymmetrical involvement is less likely in the control group. Asymmetry was also seen more frequently in cortical areas compared to subcortical areas.

Although using the semi-quantitative score achieved the best result, however the difference is not statistically significant. However, it provides an objective method of interpretation that does not require a subjective decision as to what is mild, moderate or severe. In addition to that, it require less time, which can be useful in a busy department, and does not require special software or skills, so it would be ideally suited for routine practice and can be applied anywhere, even in centers with little brain SPECT experience and without special software.

The third finding of this study was that a significant correlation exists between the clinical disease pattern and perfusion patterns with SPECT. Correlations between the pattern of the perfusion defects and the clinical syndromes have been investigated in many studies. In this study, we found that the percentage agreement between the SPECT and the clinical pattern is 92 % in patients with diffuse disease. That is in agreement with most of the studies.[12][57][77] In patients with clinically focal disease, the SPECT pattern agreed in only in 43 %. That is in agreement with Russo *et al.*[12] In contrast to that Kovacs *et al.* found that SPECT agreed in all cases they reported.[56] This discrepancy could however be due to small number of only 4 patients that were included in their study. Although, the clinical importance of this finding is unclear, the differentiation of a diffuse from a focal syndrome may be important for the management and the clinical outcome of the patient, considering that it is not easy to distinguish these processes by clinical presentation.

Limitations of the study

Our study has several limitations, which are:

- Neuropsychiatric SLE is a difficult condition to define clinically even after the development of the nomenclature of the American College of Rheumatology (ACR) in 1999, as the condition needs in addition to proper clinical evaluation, a number of investigations which includes laboratory and imaging investigations. Therefore, an absolute 'gold standard' was not available to assess the interpretation of the SPECT.

- The retrospective nature of the study resulted in additional clinical data, such as the clinical assessment of the disease severity, being unavailable. This information, if available, could have been related to the severity of the perfusion abnormalities.

- This study did not compare active NPSLE to inactive NPSLE or to patients with SLE without known NPSLE. This may be a more realistic representation of the clinical situation. However a comparison like this may also be complicated by the presence of subclinical NPSLE giving apparent "false positive" results and falsely lowering the specificity. This is less of a concern using normal controls.

- The differences between the NPSLE group and the control group, in terms of age and sex is a potential confounding factor. Denays *et al.* found that there is slight tendency after 15 or 20 years for relative decline in the cerebral areas in healthy volunteer, particularly in the prefrontal and motor areas.[82] We tried to make both groups comparable in terms of age and sex. Although, there was a difference in the mean age between both groups, this wasn't statistically significant ($P = 0.67$). However, a statistical difference was found in sex ($P = 0.0001$), as males were predominant in the control group.

- The differences in the imaging instruments that we used is also a potential confound of the study, as five scans from the NPSLE were imaged using a GE Hawkeye gamma camera, while the rest of the NPSLE group and all controls were imaged using an Elscint Helix gamma camera.

Conclusion and recommendations:

Tools to assess brain function are clearly needed in numerous conditions which lack definitive diagnostic or specific patterns. In this study we evaluated our interpretation of brain SPECT in NPSLE using visual and semi-quantitative methods. The study showed that brain SPECT is able to diagnose active NPSLE with high sensitivity and moderate specificity. No significant differences were seen between the four techniques used.

The interpretation of SPECT images is difficult, and neuro-imaging studies are complementary and useful examinations in the evaluation of neurological involvement in patients with NPSLE. Furthermore, we recommend the use of a simple semi-quantitative score as an adjunct to a visual assessment. This requires little time, and does not require special software or skills, so it would be ideally suited for routine practice, especially in centers with little experience of brain SPECT in NPSLE, and lacking special software, normal databases and skills.

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Criteria	Definition
Malar rash	Fixed erythema, flat or raised over the malar eminence, tending to spare the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scaring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcer	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
Arthritis	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
Serositis	a) Pleuritis – convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion *OR* b) Pericarditis – documented by ECG or rub or evidence of pericardial effusion
Renal disorder	a) Persistent protenuria greater than 0.5 gram per day or greater than 3+ if quantification not performed *OR* b) Cellular cast – may be red cell, hemoglobin, granular , tubular, or mixed
Neurologic disorder	a) Seizures – in the absence of offending drugs or known metabolic derangement; e.g.,uremia,ketoacidisis,or electrolytes imbalance *OR* b) Psychosis – in the absence of offending drugs or known metabolic derangement; e.g.,uremia,ketoacidosis,or electrolytes imbalance

Hematologic disorder	a) Hemolytic anemia – with reticulocytosis
	   OR
	b) Leucopenia – less than 4,000/mm^3 total on 2 or more occasions
	   OR
	c) Lymphopenia – less than 1,500/mm^3 on 2 or more occasions
	   OR
	d) Thrombocytopenia – less than 100,000/mm^3 in the absence of offending drugs

Immunologic disorder	a) Positive LE cell preparation
	   OR
	b) Anti- DNA: antibody to native DNA in abnormal titer
	   OR
	c) Anti – Sm : presence of antibody to Sm nuclear antigen
	   OR
	d) False positive serologic test for syphilis

Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescense or an equivalent assay at any point in time and in the absence of drugs known to be associated with" drug-induced lupus" syndrome