

Neuropsychiatric Lupus: Classification Criteria in Neuroimaging Studies

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ABSTRACT: This systematic review described the criteria and main evaluations methods procedures used to classify neuropsychiatric systemic lupus erythematosus (NPSLE) patients. Also, within the evaluations methods, this review aimed to identify the main contributions of neuropsychological measurements in neuroimaging studies. A search was conducted in PubMed, EMBASE and SCOPUS databases with the terms related to neuropsychiatric syndromes, systemic lupus erythematosus, and neuroimaging techniques. Sixty-six abstracts were found; only 20 were completely analyzed and included. Results indicated that the 1999 American College of Rheumatology (ACR) criteria is the most used to classify NPSLE samples together with laboratorial, cognitive, neurological and psychiatric assessment procedures. However, the recommended ACR assessment procedures to classify NPSLE patients are being used incompletely, especially the neuropsychological batteries. Neuropsychological instruments and neuroimaging techniques have been used mostly to characterize NPSLE samples, instead of contributing to their classifications. The most described syndromes in neuroimaging studies have been seizure/cerebrovascular disease followed by cognitive dysfunctions as well as headache disorder.

RÉSUMÉ: Lupus neuropsychiatrique : critères de classification utilisés dans les études de neuroimagerie. Cette revue systématique décrit les critères et les principales méthodes d'évaluation utilisés pour classer les patients atteints de lupus érythémateux aigu disséminé avec atteinte neuropsychiatrique (LÉADNP). Parmi les méthodes d'évaluation, cette revue a également pour objectif d'identifier les principales contributions des mesures neuropsychologiques dans les études de neuroimagerie. Nous avons effectué une recherche dans les bases de données PubMed, EMBASE et SCOPUS au moyen de mots clés en lien à des syndromes neuropsychiatriques, au lupus érythémateux aigu disséminé et aux techniques de neuroimagerie. Nous avons identifié 66 résumés dont seulement 20 ont été analysés complètement et inclus dans notre étude. Les résultats de cette analyse indiquent que les critères établis en 1999 par l'American College of Rheumatology (ACR) sont les plus utilisés pour classer les échantillons de patients atteints de LÉADNP ainsi que les tests de laboratoire et les méthodes d'évaluation cognitive, neurologique et psychiatrique. Cependant, les critères recommandés par l'ACR pour classer ces patient sont utilisés de façon incomplète, particulièrement les batteries neuropsychologiques. Les instruments neuropsychologiques et les techniques de neuroimagerie ont été utilisés surtout pour caractériser les échantillons de patients atteints de LÉADNP au lieu de servir à leur classification. Les syndromes les plus fréquemment décrits dans les études de neuroimagerie sont les crises convulsives/la maladie cérébrovasculaire suivies des dysfonctions cognitives et de la céphalée.

Can J Neurol Sci. 2013; 40: 284-291

Neuropsychiatric manifestations occur with frequency in systemic lupus erythematosus (NPSLE)¹. However, attribution of these manifestations to SLE are considered one of the greatest challenges among behavioural and neuroimaging studies². There still seems to be a long way towards a comprehension of the neuropsychiatric (NP) syndromes in SLE, even though the American College of Rheumatology (ACR) has started to facilitate and to enhance clinical research by developing standards for terminology, definitions and some assessment methods to describe 19 NP syndromes in SLE³. Nevertheless, it is still quite a challenge to differentiate the NPSLE from the non-NPSLE, mainly due to the heterogeneity of assessments even after ACR recommendations, not sufficiently reported or unreported methods to classify each syndrome. American College of Rheumatology proposed nomenclature for NPSLE is mainly intended for didactic purposes, clinical research and reporting rather than clinical setting³. The general SLE is a recurrent, chronic, systemic, autoimmune disease which causes morbidity in between 161,000 to 322,000 adults⁴. The NPSLE is a set of neurologic syndromes of the central and peripheral nervous system and/or of psychiatric syndromes observed in

patients with SLE in which other causes are excluded^{3,5,6}, by clinical, laboratory, neuroimaging and neuropsychological tests³. These syndromes include twelve manifestations from the central nervous system, as follows, “aseptic meningitis, cerebrovascular disease, demyelinating syndrome, headache (including migraine and benign intracranial hypertension), movement disorder (chorea), myelopathy, seizure disorders, acute confusional state, anxiety disorder, cognitive dysfunction, mood disorder, psychosis” and seven manifestations related to the peripheral nervous system, “acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré

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RECEIVED AUGUST 27, 2012. FINAL REVISIONS SUBMITTED NOVEMBER 26, 2012.
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syndrome), autonomic disorder, mononeuropathy, single/multiplex, myasthenia gravis, neuropathy, cranial, plexopathy, polyneuropathy³. The neuropsychiatric manifestations can occur as single or multiple events at any time during the course of SLE⁷. These manifestations have been considered very frequent among SLE patients, with occurrences varying from 57% to 91%, being up to two-thirds of patients with this disease⁶⁻⁸. Among the 19 neuropsychiatric syndromes in SLE, the four most reported ones have been cognitive impairment (ranging from 70 to 80%), mood disorders (from 60 to 70%), headache (from 50 to 60%) and cerebrovascular disease (from 20 to 40%)^{7,9,10}. This variability is due, in part, to methodological differences among studies such as inclusion criteria of samples, type of design (retrospective), heterogeneous procedures of assessments and lack of reporting procedures⁶.

Neuroimaging techniques have been continually improving and ACR considers them to be important complementary tools for some case definitions in NPSLE and to rule out evidence of other disorders^{5,11}, being useful for differential diagnosis. Some reviews have shown that advanced magnetic resonance imaging (MRI) techniques are able to detect white matter changes, which is frequently present in NPSLE¹. However, advanced MRI techniques are still not clearly established as essential tools contributing to the diagnosis of NP syndromes in SLE^{12,13}.

The ACR had also considered a neuropsychological battery based on formal instruments important to identify one of the most frequent syndromes, cognitive impairment, which also can contribute to the classification of NP in SLE. In spite of these recommendations by ACR, 1999, several studies have not presented homogeneity on this method of cognitive measurement^{10,12,14,15}. Among the main advantages of using neuroimaging and neuropsychological tools for complementary diagnosis of NPSLE are that they can be non-invasive as well as sensitive in detecting central nervous system manifestations¹³.

The correct attribution of NP events to SLE or to other causes is still very challenging, and methodological approaches for assessment are a problem that still remain unresolved, lacking explicit case and terms definitions, comprehension of their pathogenesis, and pathognomonic tests findings, amongst other consequences that have been hampering the possibilities to compare results, reproduce methods, test hypotheses or conduct intervention studies³. Considering these difficulties, it seems very relevant to systematically review data generated in studies of neuropsychiatric syndromes classification in SLE². Although the ACR system of classification for the 19 neuropsychiatric syndromes has been traditionally used, there still seems to be a lack of methodological homogeneity in the classification of NP in SLE.

In addition to the ACR consensus in 1999, as far as we know, only six general reviews or critical analyses have been published related to NPSLE^{7,12,16-19}. However, none of them had systematically reviewed the factors contributing to inclusion criteria, sample's characteristics, assessment methods and heterogeneous outcomes, for NPSLE descriptions which consider neuroimaging studies.

The present systematic review aims to verify and to describe the criteria and main methods of assessment procedures employed to classify NP syndromes in SLE patients in neuroimaging studies. Also, within the assessment procedures, this review aims to identify the main contributions of

neuropsychological tests in these neuroimaging studies. According to Popescu and Kao's²⁰ review, the development of treatments for NPSLE is still a great challenge, due to the broad spectrum of manifestations of these syndromes and limitations in diagnostic tests. Since ACR considered neuroimaging evaluations important enough to change the direction and to enhance clinical investigations in NPSLE classification³, this systematic review may point out some important issues to better understand how neuroimaging study methods characterize and differentiate NPSLE from non-NPSLE samples. Regarding neuropsychological evaluations in neuroimaging studies, Borchers et al's¹³ review brings out two important issues that may limit improvements in NPSLE treatment: one is the limited knowledge of the pathophysiology of this disease and the other is the fact that patients have simultaneously more than one NP syndrome. These authors concluded that advances in neuroimaging technology and neuropsychological testing have been contributing to NPSLE diagnostic improvements and have allowed more effective interventions.

METHOD

This systematic review was based on a search in the PubMed, EMBASE and SCOPUS databases with the following search terms: ("neuropsychiatric syndromes") and ("systemic lupus erythematosus") and ("magnetic resonance imaging" or "MRI" or "magnetization transfer imaging" or "MTI" or "diffusion-weighted imaging" or "DWI" or "diffusion tensor imaging" or "DTI" or "magnetic resonance spectroscopy" or "MRS" or "susceptibility weighted imaging" or "SWI" or "voxel-based morphometry" or "VBM" or "magnetoencephalography" or "MEG" or "electroencephalography" or "EEG" or "optical imaging" or "fNIRS" or "positron emission tomography" or "PET" or "single-photon emission computed tomography" or "SPECT" or "functional neuroimaging" or "fMRI" or "neuroimaging cortical thickness" or "default network" or "resting state" or "default mode network" or "volumetry"). Some filters were applied, only articles with adults, humans and

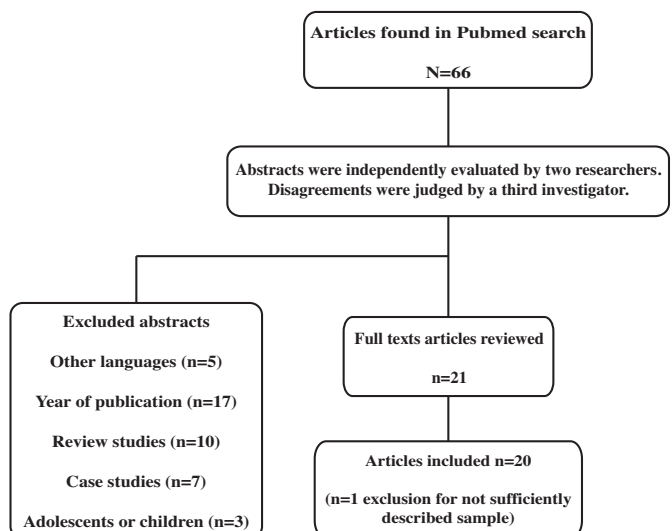


Figure: Fluxogram of reviewed NPSLE studies.

Table 1: Characterization of criteria used and procedures for assessment of the samples

Reference	Criteria of characterization	Procedures for criteria assessment				
		Clinical	Laboratorial	Cognitive	Neurological or neuroimaging	Psychiatric / Functional
Luyendijk et al. (2011)+	ACR (1999) case definitions for NPSLE syndromes assessed and classified by 2 rheumatologists NP symptoms were considered for NP-SLE if one or more criteria was accomplished	Retrospectively assessed by two rheumatologists	Described.	Not described.	Lesions were categorized as hyperintensities, parenchymal defects, or areas of focal atrophy through an MRI	Not described.
Kozora et al. (2011)-	Judgment by the patient's rheumatologist to ensure no current or prior important neuropsychiatric disorder other than cognitive impairment	10–15 minute interview to ensure inclusion/exclusion criteria and a structured psychiatric interview to rule out current depression	Not described.	The Cognitive Failures Questionnaire	10–15 minute interview to ensure inclusion/exclusion criteria and a structured psychiatric interview to rule out current depression Neurological Rating Scale	Structured psychiatric interview 10–15 minute interview to ensure inclusion/exclusion criteria and a structured psychiatric interview to rule out current depression
Emmer et al. (2010)-	ACR (1999) case definitions for NPSLE syndromes assessed and classified by one expert rheumatologist	Assessment by specialist for exclusion of secondary causes of NP	Described.	Not described.	MRI	Not described.
Azarpazhooh et al. (2010)-	ACR (1999) case definitions for NPSLE syndromes	Review of medical records	Described.	Neuropsychological Testing (Mini-mental State Examination (<24=moderate cognitive impairment) Bender-Gestalt test Block Design (WAIS-R) Not described.	Neurologic examination MRI to verify the existence of micro embolic signals	Not described.
Cotton et al. (2004)+	ACR (1999) case definitions for NPSLE syndromes	Clinical exam and eventual complementary exams	Described.	Not described.	MRI and clinical neuropsychiatric	Clinical neuropsychiatric
Wilmer et al. (2003)+	ACR (1999) case definitions for NPSLE syndromes	Not described.	Not described.	Mini-Mental State Examination	Neuro-SLEDAI	Not described.
Whitelaw & Spangenberg (2009)-	Exclusion of all criteria for NPSLE except for headache.	Not described.	Not described.	Wechsler Adult Intelligence Scale; Wechsler Memory Scale – Logical Memory; visual memory; Associated Learning – Easy; Associated learning – difficult; Rey Complex figure recall; Stroop color word interference test and Auditory Verbal Learning Test	Assessment of headache according to International Headache Society criteria	Assessment of psychiatric symptom criteria from American Psychiatric Association
Harboe et al. (2008)+	ACR (1999) case definitions for NPSLE syndromes Systemic Lupus assessed in a consensus meetings	Review of the medical history Clinical examination by a specialist in internal medicine Clinical interview	Described.	Assessment by a specialist in neuropsychology: Trail Making Test, Category Test, Seashore Rhythm Test, Lafayette Hand Dynamometer Test, Finger Tapping Test, Tactual Performance Test, Lafayette Grooved Pegboard Test, Wechsler Adult Intelligence Scale (WAIS), Wechsler Memory Scale Revised, Wisconsin Card Sorting Test, FAS Verbal Fluency test, and Stroop Colour-Word Interference Test.	Neurological assessment Nerve conduction studies (NCS)	Short Form-36 Fatigue Severity Scale Fatigue Visual Analogue Scale Beck Depression Inventory
Emmer et al. (2008)+	ACR (1999) case definitions for NPSLE syndromes Diagnosed by an experienced rheumatologist	Not described.	Described.	Not described.	Not described.	Not described.
Cho et al. (2007)+	ACR (1999) case definitions for NPSLE syndromes	Retrospective clinical assessment of medical records	Described.	Not described.	Not described.	Not described.
Roldan et al. (2006)-	Detailed prospectively collected NPSLE and SLE histories were available	Clinical evaluation for general health	Described.	Not described.	Brain MRI to detect focal and non-focal injuries Color Doppler TEE to detect left-sided VHD other cardiac or aortic substrates for embolism	Neuropsychiatric evaluation
Tatsukawa et al. (2005)-	The CNS involvement was previously assessed by clinical symptoms such as organic brain syndrome seizures, cerebral infarction and psychiatric disorder.	Clinical assessment of CNS involvement	Described.	Not described.	Not described.	Not described.
Lampropoulos et al. (2005)+	Not utilized	Clinical interview	Described.	Not described.	EEG	Reported neuropsychiatric symptom
Davey et al. (2010)+	ACR (1999) case definitions for NPSLE syndromes	Clinical interview	Described.	Repeatable Battery for the Assessment of Neuropsychological Status considering cognitive dysfunction with at least one impaired function	Evaluated by experienced neurologist	Not described.
Sanna et al. (2003)+	ACR (1999) case definitions for NPSLE syndromes	Clinical NP questionnaire	Described.	One hour neuropsychological battery: Trail Making Test, Letter-Number Sequencing, Logical Memory, Rey-Osterrieth Complex Figure Test (copy, immediate recall, and delayed recall), Controlled Oral Word Association Test (COWAT/FAS), Animal Naming Test, Digit Symbol Substitution Test, and Stroop Color and Word Test in order to document deficits in any or all of the following cognitive domains: Simple attention, Complex attention/Executive functions, Memory, Visual-spatial processing, Language, Psychomotor speed, and Motor function. Premorbid IQ was estimated by means of the National Adult Reading Test	Questionnaire prepared with particular attention to history and objectively documented NP manifestations.	Questionnaire prepared with particular attention to history and objectively documented NP manifestations.
Ainiala et al. (2004)+	ACR (1999) case definitions for NPSLE syndromes According to the clinical impression of one evaluator	Clinical assessment and examination records of medical history, clinical examination, review of medical records	Described.	Neuropsychological assessment not described in this paper	Not described.	SLICC.
Walecki et al. (2002)- Kumral et al. (2002)-	American Rheumatological Association ACR (1999) case definitions for NPSLE syndromes	Not described. Physical examination	Described. Described.	Not described. Neuropsychological tests with established cut-off points for deficits based on normative data. Attention – Digit Span Test; Global Cognitive Function - Mini-Mental state Exam; Rey Auditory Verbal Learning Test; Visual Memory – Rey Visual Design Learning Test; Stroop test Raven's Colored progressive Matrices	Not described. Neurological examination	Not described. Depression and Psychosis were assessed with DSM-IV.
Karassa, et al. (2000)+	Neuropsychiatric syndromes by rheumatologist and neurologist staff Adapted ACR (1999) case definitions for NPSLE syndromes	Follow-up, observation and clinical evaluations	Described.	Not described.	EEG	Not described.
Podrazilová et al. (2008)	ACR (1999) criteria	Review of medical records	Described.	Not described.	MRI	Not described.

Note. +studies that characterize the participants according to the 19 ACR neuropsychiatric syndromes; - studies that do not characterize the sample according to the neuropsychiatric syndromes; NP= Neuropsychiatric; WAIS-R= Wechsler Adult Intelligence Scale-Revised; SLEDAI =Disease Activity Index; SLICC= The Systemic Lupus International Collaborating Clinics; DSM= Diagnostic and Statistical Manual of Mental Disorders; EEG=electroencephalogram; MRI=magnetic resonance imaging; TEE=Transesophageal echocardiography; VHD=Valvular heart disease.

Table 2: Characterization of neuroimaging studies: aim and methods

Reference	Aim	Study design	Sample	Neuroimaging
Luyendijk et al. (2011)	To provide an inventory of brain abnormalities on conventional MRI in NPSLE and to interpret pathogenetic mechanisms.	Observational retrospective	Active NPSLE patients (n=74)	MRI (T1- and T2-weighted images and either proton density-weighted or FLAIR in the axial plane)
Kozora et al. (2011)	To examine hippocampal volumes and neurometabolic alterations in relation to memory in non-NPSLE.	Comparative prospective	Non-NPSLE patients (n=81) Healthy controls (n=34)	Volumetric MRI and MRS of the right and left hippocampal areas (right and left)
Emmer et al. (2010)	To quantify any perfusion abnormalities and to determine their contribution to NPSLE.	Comparative	Active NPSLE patients (n=15) Inactive NPSLE patients (n=26) Control subjects (n=11)	Cerebral blood flow Cerebral blood volume Mean transit time MRI Bolus-tracking perfusion MRI
Azarapzoooh et al. (2010)	To clarify the pathophysiology of the CNS involvement in SLE.	Prospective	Patients with SLE (n=68), NPSLE (n=24) and non-NPSLE (n=44)	Transcranial Doppler (middle cerebral arteries)
Davey et al. (2010)	To investigate the role of CED in SLE and in NPSLE.	Comparative	Patients with SLE (N=61) Control subjects (N=70)	Transcranial Doppler Ultrasonography (middle central artery)
Whitelaw and Spangenberg (2009)	To investigate the possible association between impaired cognitive function and chronic headache in SLE.	Comparative	Patients with SLE but without the antiphospholipid (n=61), no headaches group (n=21), migrainous headaches (n=19), aura (n=11), other headaches (n=11), tension type headaches (n=7)	MRI using gadolinium (Ventriculo-brain ratios was calculated)
Harboe et al. (2008)	To compare the prevalence and pattern of NPSLE to Primary Sjögren syndrome using the ACR criteria.	Comparative	Patients with SLE (n=68) Patients with Primary Sjögren syndrome (n=72)	MRI
Emmer et al. (2008)	To investigate if, in NPSLE patients, MTR histogram parameters are related to neurochemical findings from proton MRS and to determine whether MTR changes are specific to NPSLE.	Comparative	SLE patients (n=18) NPSLE patients (n=34) Healthy controls (n=15)	MRI (Axial T1-weighted spin-echo, axial slices) MTI (3-dimensional gradient-echo pulse, axial slices) 1 H-MRS (Single-voxel) with double spin-echo point-resolved spectroscopy sequence
Podrazilová et al. (2008)	To determine the volume of pathological foci in the brain tissue of NPSLE and non-NPSLE patients and to find out if that volume depends on clinical records.	Comparative	Patients with NPSLE (n=29) Participants without (n=24) Healthy controls (n=16)	Volumetric MRI in FLAIR
Cho et al. (2007)	To compare clinical manifestations, brain MRI findings and prognosis of NPSLE and NBD.	Comparative	Patients with NPSLE (n=25) Patients with NBD (n=18)	MRI (T1-weighted images, T2-weighted images and FLAIR).
Roldan et al. (2006)	To determine whether VHD and brain injury are associated with nonfocal NPSLE.	Comparative	Patients with nonfocal NPSLE (n=18) Patients with non-NPSLE (n=10) Healthy controls (n=28)	MRI (T1-weighted volume, T2-weighted axial series, DWI series and a FLAIR)
Tatsukawa et al. (2005)	To evaluate the usefulness of the average amount of CBF for NPSLE.	Correlational	Patients NPSLE (n=16) Patients non-NPSLE (n=57)	SPECT (rCBF and BPI values were evaluated)
Lampropoulos et al. (2005)	To describe the prevalence and clinical associations of abnormalities on EEG in patients with APS and/or NPSLE.	Comparative, descriptive and correlational	APS with NPSLE (n=14) NPSLE without aPL (n=19)	EEG (electrodes were positioned according to the international 10-20 system, and standard recordings were performed for 15–20 minutes during relaxed wakefulness, with sessions of overbreathing and photic stimulation)
Cotton et al. (2004)	To evaluate with high-field MRI the CNS involvement in a series of SLE patients with or without NPSLE and to detect a possible relationship between MRI and clinical parameters.	Comparative retrospective	Patients with a SLE (n=58) Patients with NPSLE (n=30) Patients with non-NPSLE (n=28) Healthy controls (n=18)	MRI (including diffusion weighted-images, high-resolution 3D T1 weighted-images)
Ainiála et al. (2004)	To evaluate whether serum matrix metalloproteinase 9 levels are associated with NPSLE, particularly cognitive dysfunction, evaluated by neuropsychological tests and MRI.	Comparative prospective	Healthy controls (N=43) Patients with SLE (N=44)	MRI (sagittal T1-weighted, axial T1-weighted, axial T2-weighted, and coronal FLAIR sequences; axial 3-dimensional T2 fast spin-echo and gadoliniumdiethylenetriaminepentaacetic acid-enhanced 3-D T1 spoiled gradient-echo images).
Sibbit et al. (2003)	To compare FLAIR imaging with proton density/T2 weighted (PD/T2) imaging in NPSLE.	Comparative	Patients with NPSLE (n=28) Healthy controls (n=25)	MRI (T1, PD/T2, and FLAIR)
Sanna et al. (2003)	To apply the new ACR nomenclature for NPSLE, to determine the prevalence of the different NPSLE and to evaluate which of these manifestations correlate with aPL.	Descriptive, correlational	323 patients with SLE	MRI (standard spin-echo technique).
Walecki et al. (2002)	To determine the value of modern imaging techniques (MR sequences - FLAIR, DWI) in the diagnosis of cerebral changes in NPSLE.	Observational	Patients with neurological symptoms of SLE (N=50)	MRI (SE, FSE, FAST, FLAIR sequences and in 12 cases also in EPI DWI sequences; T1 and T2-weighted images in sagittal and transverse planes were analysed)
Kumral et al. (2002)	To investigate the association of microembolic signals with NPSLE manifestations and to compare the results with those from patients non-NPSLE and normal controls.	Comparative	Patients patients with SLE (N=53) Normal controls (N=50)	MRI and/or MRA Extracranial Doppler Transcranial Doppler Sonography Duplex sonography Electrocardiography Transthoracic/transesophageal Echocardiography
Karassa et al. (2000)	To identify variables that are associated with the evolution of cerebral changes on sequential MRI scans as well as with clinical outcomes in NPSLE.	Observational prospective, follow-up	Patients with SLE (including 14 with the APS) who had been hospitalized with primary NP disease (n=32)	MRI (T1-weighted 600/20 ms and double echo proton density T2-weighted 2,500/30/90 ms, axial and coronal scans).

Note. Neuro Behçet's disease (NBD); Cerebral Blood Flow (CBF); antiphospholipid syndrome (APS); cerebrovascular endothelial dysfunction (CED); antiphospholipid antibodies (aPL); Magnetic resonance imaging (MRI); Non-neuropsychiatric systemic lupus erythematosus (non-NPSLE); neuropsychiatric systemic lupus erythematosus (NPSLE); Fluid Attenuated Inversion Recovery (FLAIR); systemic lupus erythematosus (SLE); fast spin echo (FSE); diffusion weighted imaging (DWI); magnetization transfer ratio (MTR); fast spin echo (FAST); valvular heart disease (VHD); antiphospholipid syndrome (APS).

those published in English, French, Spanish, or Portuguese were reviewed. Repeated articles and papers published before 2000 were excluded because they occurred prior to the ACR classification criteria. Sixty six articles were reviewed manually, resulting in 21 full text reviewed papers, after exclusion criteria analysis. Abstracts were excluded for not having included at least one group with NPSLE, not using at least one neuroimaging technique as a tool for assessment, not being

empirical, and with single or multiple case studies. The systematic review fluxogram can be viewed in the Figure.

RESULTS

Table 1 presents the characterization of adopted criteria and procedures for each article. The majority of studies (70%) classified NPSLE according to ACR recommendations. However, a great number of them did not use all ACR

recommendations. Most of them used laboratorial (85%), clinical (75%) and neurological/neuroimaging (60%) assessments and less than half used cognitive (45%) and psychiatric/functional evaluations (40%).

Table 2 characterizes each study included in this systematic review according to their aim, design, sample distribution, main features and administered neuroimaging techniques for brain structure or function measurement as dependent variables. Regarding their aims, 70% of the studies used neuroimaging findings to characterize NPSLE^{2,17,21-32}, 25% aimed to investigate the relationship between clinical and neuroimaging findings of this population^{26,29,31,33,34}, 20% investigated technological issues of neuroimaging tools to identify NPSLE^{25,35-37}, and 15% searched for both neuroimaging and cognitive findings to describe SLE in general^{17,23,30}. The majority of samples analyzed included two groups, general SLE patients

compared to healthy controls (20%)^{17,22,30,32} or NPSLE compared to a non-NPSLE (15%)^{21,28,35}. Moreover, two groups continue to be compared, but in these studies NPSLE were compared with other diseases (10%)^{27,33}, NPSLE with healthy controls (10%)^{18,36}, general SLE with other disorders (5%)²⁴. Finally, a few studies had only one group of NPSLE patients (15%)^{2,34,37}. In this way, 70% of these studies had a comparative design^{15,17,22-28,30-33,36}. The most common neuroimaging techniques to measure brain structure or function as dependent variables were MRI (75%)^{2,17,18,23-32,34,37}, then transcranial Doppler (15%)^{21,22,32}, MRS (10%)^{17,25}, and the following techniques, MTI, SPECT, EEG and extracranial Doppler, with 5% each.

In Table 3 it can be observed that only 14 of 20 articles, included in this analysis, had cited specifically the 19 neuropsychiatric syndromes. It also shows the ten most prevalent

Table 3: The four neuropsychiatric (NP) manifestations most prevalent in patients with SLE according to ACR case definitions for NPSLE

References	NPSLE (n=)	Four most prevalent ACR criteria for NPSLE – Peripheral Nervous System (PNS)	n(%)	Four most prevalent ACR criteria for NPSLE - Central Nervous System (CNS)	n(%)
1-Luyendijk et al. (2011)	74	Not included as the four most prevalent ACR criteria for NPSLE		Headache disorders Seizure disorder Cognitive dysfunction Psychosis	27 (36.4) 19 (25.6) 16 (21.6) 13 (17.5)
2-Azarpazhooh et al. (2010)- 3-Davey et al. (2010)+	24 61	Not described Not included as the four most prevalent ACR criteria for NPSLE		Not described Headache disorder Cognitive dysfunction Mood disorder Cerebrovascular disease	55 (90) 27 (45) 24 (39) 13 (21)
4-Emmer et al. (2010)-	15	Not included as the four most prevalent ACR criteria for NPSLE		Cerebrovascular Disease Cognitive Dysfunction Headache disorders Seizure disorder	12 (80) 11 (73.3) 10 (66.6) 10 (66.6)
5-Emmer et al. (2008)+	34	Not included as the four most prevalent ACR criteria for NPSLE		Cerebrovascular Disease Seizure disorder Cognitive Dysfunction Headache disorders	14 (41) 11 (32.3) 7 (20.5) 6 (17.6)
6-Harboe et al. (2008)	68			Cognitive dysfunction Mood disorder Headache disorder	38 (55.8)* 26 (38.2)* 18 (26.4)*
7-Podrazilová et al. (2008)	29	polyneuropathy Not included as the four most prevalent ACR criteria for NPSLE	18(26.4)*	Headache disorder Psychosis Cerebrovascular Disease Cranial Neuropathies	11 (38) 9 (31) 8 (27.58) 6 (20.68)
7-Cho et al. (2007)	25	Not included as the four most prevalent ACR criteria for NPSLE		Mood Disorder (Major Depression, Depressive features, Manic features, Mixed features) Seizure Cerebrovascular disease Cognitive dysfunction Headache disorders (Migrain, Tension, Cluster, Pseuditumor cerebri, Nonspecific)	8 (32) 8 (32) 5 (20) 3 (12)
8-Ainiiala et al. (2004)+	44	Not included as the four most prevalent ACR criteria for NPSLE		Cognitive dysfunction Cerebrovascular disease Seizure disorder Acute Confusional state	11 (24) 7 (15) 4 (9) 3 (7)
9-Cotton et al. (2004)	30	Not included as the four most prevalent ACR criteria for NPSLE		Acute Confusional State Headache disorder Cerebrovascular disease Cognitive Dysfunction/ Mood disorder	7 (23.3) 6 (20) 3 (10) 2 (6.6)
10-Sanna et al. (2003)+	323	Not included as the four most prevalent ACR criteria for NPSLE		Headache Cerebrovascular disorder Mood disorder Cognitive dysfunction	78 (24) 57 (17.6) 54 (16.7) 35 (10.8)
11-Wilmer et al. (2003)	28	Not included as the four most prevalent ACR criteria for NPSLE		Cognitive disorder Mood disorder Seizure disorder Headache	22 (78)* 16 (59)* 11 (41)* 9 (33)*
12-Kumral et al. (2002)-	25	Not included as the four most prevalent ACR criteria for NPSLE		Depression Stroke Seizures Psychosis	14 (56) 1 (4) 1 (4) 1 (4)
13- Karassa, et al. (2000)+	32	Not included as the four most prevalent ACR criteria for NPSLE		Cerebrovascular disease Seizures Acute confusional state/ Psychosis/Headache/cranial Neuropathies/Demyelinating syndrome/Cognitive Dysfunction	9 (28.1) 8 (25) 6 (18.7) 3 (9.3)
14- Podrazilová et al. (2008) +	29	Not included as the four most prevalent ACR criteria for NPSLE		Headache Psychosis Cerebrovascular disease Seizure disorder	11 (38) 9 (31) 8 (27.58) 8 (27.58)

Note. + studies that characterize the participants according to the 19 ACR neuropsychiatric syndromes; - studies that did not characterize the sample according to the 19 ACR neuropsychiatric syndromes.

ACR criteria identified by the 14 neuroimaging studies were, seizure/cerebrovascular disease (85.71%)^{2,18,22,25-27,29-32,34}, the most prevalent; followed by cognitive dysfunction (78.57%)^{2,18,22,24,25,27,29-31,34} and headache (78.57%)^{2,18,22,24-27,29,31,34} then by mood disorder (57.14%)^{22,24,27,29,31,32,36,37}; psychosis (28.57%)^{2,26,32,34}; acute confusional state (21.42%)^{29,30,34}, cranial neuropathies (14.28%)^{26,34}; stroke³² and demyelinating syndromes (7.14%)³⁴.

Neuropsychological functions most frequently assessed by the studies were concentrated attention (33.33%)^{21-24,31,32,36}, cognitive flexibility (28.57%)^{23,24,31,32}, visual episodic memory (28.57%)^{23,24,31,32}, processing speed (28.57%)^{23,24,31,32} and verbal episodic memory (23.81%)^{22,24,32}, as can be seen in Table 4. The frequency was calculated considering that each article and instrument could have assessed one or more cognitive function. The most used neuropsychological tests, aiming to assess different cognitive components, were: Rey Complex figure, Stroop Color and Word Test, Mini-Mental State Auditory Verbal Learning Test.

DISCUSSION

This systematic review showed some important issues to better understand the main classification criteria and assessment methods used to differentiate NPSLE from non-NPSLE samples in neuroimaging studies. In regard to the criteria and evaluation procedures used to characterize the samples, more than half of the articles from this present review had classified their neuropsychiatric samples according to the recommendations of 1999 ACR NPSLE criteria¹. However, only three of these articles^{24,31,37} fully described the ACR recommendations including laboratorial, clinical, neurological/neuroimaging, as well as cognitive and psychiatric/functional evaluations³. Among the ones that employed cognitive assessment, less than half used the same or similar instruments to the neuropsychological battery recommended by ACR. Several of these studies did not describe whether they used cognitive measurements. Furthermore, a couple of these studies used only two instruments in which one of them was the Mini Mental State Examination.

Although the ACR criteria developed a system in which researchers could have one name for each of 19 neuropsychiatric syndromes to advance knowledge and investigation of this pathology³, there are still a large number of studies, as shown in this review, which do not totally benefit from the ACR nomenclature. Neuroimaging studies have used different definitions of NP syndromes and presented lack of evaluation descriptions, methodological heterogeneity of design, with some of them being based on retrospective chart reviews, and all of these factors have contributed to important limitations in this field⁶. There is still a large discrepancy amongst neuroimaging studies that can be strongly related to not following all of the recommendations for NPSLE of ACR.

Among the 19 neuropsychiatric syndromes from ACR, it was observed that even though the studies included in this review were not necessarily trying to investigate the prevalence of these syndromes, most of them had reported the most frequent NP manifestations. The most prevalent syndrome in this review was seizure/cerebrovascular disease; this result may be related to the neuroimaging exam sensitivity to capture alterations in the white matter. Accordingly with clinical diagnosis, cognitive

Table 4: Frequency of cognitive functions assessed

Cognitive function	Number of articles
Attention - Concentrated	7
Cognitive flexibility	6
Episodic memory - Visual	6
Processing speed	6
Episodic memory - Verbal	5
Inhibition	4
Praxis	4
Attention - Alternated	3
General cognitive status	3
IQ	3
Visuo-spatial and motor functioning	3
Working memory	2
Attention - Not specified	1
Language	1
Lexical-semantic access	1
Naming	1
Reading	1
Semantic memory	1
Verbal planning	1

Note. Most articles investigated more than one cognitive function.

dysfunctions as well as headache disorder were reported in more than half of these investigations. Unlike the results of this review, several studies have highlighted cognitive dysfunction as one of the most common NP manifestations followed by headaches^{7,18,21}. Even though these two syndromes were not reported as the most frequent ones in this review, they were still highly classified. The high frequency of cognitive dysfunctions can be related to the fact that most of the neuropsychiatric syndromes classified by the ACR may affect the central nervous system, causing cognitive alterations⁷. In regard to the other syndromes, mood disorders were present in approximately half of the studies and the least prevalent ones were stroke and demyelinating syndromes. Although the ACR criteria for the 19 NPSLE syndromes also include disorders of the peripheral nervous system, they were not added in this review due to the selection of studies that have been in neuroimaging.

Formal neuropsychological assessments have not been used routinely in these neuroimaging studies, possibly for logistical reasons, as there is currently no validated universally accepted screening tool for cognitive dysfunction regarding each probable impaired component in SLE. The Mini-Mental Status Examination that has been used quite often, is not sufficiently sensitive to measure specific cognitive deficits in this population⁶. Moreover, cognitive dysfunction may vary over time in patients with NPSLE, and standardized cognitive instruments may contribute to identification of cognitive status of these patients over time. However, it is crucial that cognitive test results be interpreted based on normative data appropriate for age, education, sex, and ethnic group³. Standardized neuropsychological tests are noninvasive tools that can evaluate the effect of SLE on the brain. They can be used as a follow-up

or to monitor alterations or progress of the disease. In addition, it can be very useful to measure treatment outcomes¹. Usually most studies do not use these guidelines as Kozora et al¹⁵ did. Their study found that the ACR-SLE neuropsychological battery is valid and reliable¹⁵, even though constant development of new batteries or investigation about accuracy for diagnosis in SLE patients of existing batteries is the focus of several studies¹⁰.

Regarding the frequency of test utilization and assessed cognitive processes, sustained attention, cognitive flexibility, verbal and visual episodic memory and processing speed have been more focused. Amongst the main assessment methods, sustained attention was investigated mainly by means of bi and tripartite paradigms (such as Digit Span, Trail Making Test and Stroop Color and Word test), which were developed to measure components of executive function; episodic memory was assessed through classical paradigms of Rey Complex Figure and Auditory Verbal Learning, which are highly sensitive but at the same time do not use verbal complex stimuli, such as discourse; and processing speed was indirectly evaluated through tasks that required mostly focused attention, praxis and executive functions, which requires careful interpretation of results mainly when motor output is required. In general, it is noteworthy to point out assessment methods in these studies are mainly standardized and inherently artificial tools, lacking of ecological approaches.

Characterization of cognitive impairment is still a challenge, when the complexity of the disease in its physical and emotional aspects is considered. However, many studies suggest these cognitive functions are also the most frequent or significantly impaired³⁸⁻⁴⁰, and that some deficits are present even when psychological and emotional aspects are controlled³⁶. In Olazarán et al³⁹ language function showed a high rate of impairment, especially in language comprehension, notwithstanding the findings of the present research pointed out that language and communication do not seem to be a priority for most neuroimaging studies investigating SLE. This review has shown that neuroimaging and neuropsychological measurements are mostly used to characterize NPSLE samples, instead of contributing to the diagnosis of this disease.

In regard to brain imaging techniques, our frequency analysis demonstrated that MRI is the most used neuroimaging procedure in the neurological assessment of NP in SLE patients. This technique is able to visualise common lesions found in SLE patients, such as atrophy, hemorrhage, focal and diffuse hyperintensities³⁴. A challenge in the use of this method is that it is not always correlated with clinical symptoms, and might indicate gaps in the diagnostic understanding of the mechanisms of SLE¹¹. Although this technique may indeed be sensitive, this sensitivity and recent developments by no means makes them a standard of care for NPSLE at the present time.

It has been observed, however, that few studies have utilized more advanced neuroimaging techniques to investigate other aspects than lesion location that might be of interest for the comprehension of functional or structural-related organization of cognitive functioning⁴¹. Few studies administered DTI, for example, illustrating that, in spite of recent evidence of the sensitivity of these techniques and the relationship between white matter damage and other clinical variables of the disease, such as medications⁴², studies still favor traditional techniques

instead of advanced ones. This present systematic review will not discuss the peripheral nervous syndromes from the 19 NPSLE ACR classifications, due to our selection of only neuroimaging studies, which was one of our limitations.

Considering the remaining limitations in the field investigating NPSLE, some of these seem to need more specific solutions. The 19 NP syndromes or even others still not officially recognized can be assessed by means of standardized and specifically validated, cognitive assessments and imaging techniques based on discriminating findings that could accurately differentiate NPSLE from non-NPSLE. Among these assessment procedures, in order to solve the confounding variables, one of the possible solutions could be to assess the performance and functional impact of the neuropsychiatric syndromes in SLE, exploring together the neural correlates by means of advanced neuroimaging techniques. However, while some of these techniques may indeed be sensitive, their sensitivity and recent development by no means makes them a standard of care for NPSLE at the present time. In summary, the ACR system seems to be the best way to classify neuropsychiatric syndromes associated with SLE, although the application of neuropsychological and neuroimaging procedures seems to still not be frequently present in neuroimaging studies as recommended by ACR, 1999. In this review, we have focused on methodological issues - future studies could explore neuroimaging correlates of NPSLE and include other studies besides neuroimaging to describe how NP syndromes in SLE samples are classified.

ACKNOWLEDGEMENTS

The authors thank the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) of the Brazilian Government for providing financial support for the authors who participated in this research project.

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