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Central nervous system involvement in systemic lupus erythematosus: Overview on classification criteria.

Savino Sciascia¹, Maria Laura Bertolaccini, Simone Baldovino, Dario Roccatello, Munther A. Khamashta, Giovanni Sanna

¹Lupus Research Unit, The Rayne Institute, Division of Women's Health, King's College London, UK.
savino.sciascia@unito.it

Abstract

Central nervous system (CNS) involvement is one of the major causes of morbidity and mortality in systemic lupus erythematosus (SLE) patients. Clinical manifestations can involve both the central and peripheral nervous systems, and they must be differentiated from infections, metabolic complications, and drug-induced toxicity. Recognition and treatment of CNS involvement continues to represent a major diagnostic challenge. In this Review, we sought to summarise the current insights on the various aspects of neuropsychiatric SLE with special emphasis on the terminology and classification criteria needed to correctly attribute the particular event to SLE.

1. Introduction

Nervous system involvement has been recognised in systemic lupus erythematosus (SLE) patients for over 100 years and several classification criteria have been proposed in an attempt to capture the diverse clinical expressions. Since the first description in the 19th century by Kaposi and Osler of an SLE patient with pleurisy, pneumonia, *disturbed neurologic function*, and rapid progression to death [1] and [2], it soon became obvious that neuropsychiatric manifestations in SLE are frequent and broad and that management is not an easy task. Neuropsychiatric SLE includes a variety of focal, diffuse, central, peripheral, psychiatric, isolated, complex, simultaneous and sequential symptoms and signs, representing both active and inactive disease states. Central nervous system disease predominates and may take the form of either diffuse disease (e.g. psychosis or depression) or focal disease (e.g. stroke or transverse myelitis) [3], [4], [5], [6] and [7].

In this Review, we sought to summarise the current insights on the various aspects of neuropsychiatric SLE with special emphasis on the terminology and classification criteria needed to correctly attribute the particular event to SLE.

2. Search strategy and selection criteria

References were selected by a PubMed search of English language publications and covered the period from 1946 to April 2012. Search terms included “systemic lupus erythematosus”, “lupus”, “neuropsychiatric”, “neuropsychiatric lupus classification”, “neuropsychiatric lupus criteria”, “neuro-lupus”, and “cerebrovascular lupus”. Further articles were identified through the references cited in those articles. Abstracts were reviewed, and when relevant findings were reported, the full article was retrieved

and reviewed. We also identified articles from our personal knowledge on the subject and from our own files.

3. American College of Rheumatology (ACR) classification criteria for SLE and neuropsychiatric involvement

The first preliminary classification criteria for SLE dates back to 1971 when seizures, psychosis and focal neurologic disorders were the only neuropsychiatric manifestations encompassed [8]. The succeeding 1982 revised criteria considered dementia and coma among the NP clinical settings to be evaluated. Nevertheless, only seizures and psychosis were formally included in this revised classification criteria [9], which is far from enough to cover the whole spectrum of neuropsychiatric involvement in SLE.

Kassan and Lockshin were probably among the first researchers to draw attention to the complexity of nervous system manifestations in SLE, and they highlighted the need for a more 'organised and easily translatable' classification [10]. It was clear that because of the diversity of neurologic manifestations in this disorder and their complex pathogenesis, no single test was sufficient to confirm the diagnosis rapidly and accurately in all cases.

In 1985, How et al. developed the first classification model of neuropsychiatric SLE which also took into account the presence of autoantibodies (i.e. antineuronal antibodies) [11]. Major and minor neurologic and psychiatric manifestations were established to support the diagnosis of neuropsychiatric SLE. The presence of one major criterion alone or one minor criterion plus an abnormality on electroencephalography, nuclear brain scanning, cerebrospinal fluid (CSF) examination or cerebral angiography was necessary for the diagnosis. This approach was also an attempt to rule out other potential aetiologies, such as infection, drugs, uremia or hypertension, prior to attributing the neuropsychiatric event to SLE. However, this classification scheme did not prove to be engaging and, despite the number of years that have gone by, it has not yet been properly validated.

In their 1990 paper [12], Singer and Denburg reported the conclusions of a consensus conference held in 1987 which aimed to ascertain the level of agreement on neuropsychiatric SLE manifestations amongst a group of international experts in autoimmune diseases. Although the majority of participants (70%) felt that the ACR criteria for neuropsychiatric SLE were 'insufficient for clinical usage', the level of agreement on grading the different elements to potentially evaluate for the diagnosis of neuropsychiatric SLE was poor. Starting from a list of more than 50 possible clinical, laboratory and imaging manifestations of neuropsychiatric SLE, only four items were selected, namely atypical psychosis, several categories of seizures, transverse myelitis and global cognitive dysfunction. This approach would have represented the basis for further studies and could have possibly expanded the ACR classification criteria for SLE.

Although this was a valuable exercise subsequent validation studies were never performed.

4. ACR case definitions for neuropsychiatric SLE

An ad hoc multidisciplinary committee of 35 members representing the areas of rheumatology, neurology, psychiatry, neuro-psychiatry and haematology was convened by the American College of Rheumatology Research Committee in April of 1997 for the purpose of developing standard nomenclature for neuropsychiatric SLE [13]. The committee developed neuropsychiatric SLE case definitions with

diagnostic criteria, exclusions, associations and ascertainment. Standards and recommendations were also included for essential laboratory evaluations and imaging techniques. This inclusion was probably one of the main advances that were made and it addressed many of the previous flaws that had hampered attempts to classify neuropsychiatric SLE [14].

The committee aimed to use the existing nomenclature and definitions whenever possible rather than to create an *ex novo* classification.

Case definitions for 19 neuropsychiatric syndromes were developed and their diagnostic agreement by the committee members was empirically evaluated by comparing diagnoses of randomly generated vignettes from a pool of 108 neuropsychiatric SLE patients before and after the nomenclature evolved.

Aetiologies other than SLE were identified by exclusion, or when they were recognised as an ‘association’ for each NP syndrome.

The ACR case definitions were firstly validated in a cross-sectional population-based study by Ainiala et al. [15] involving a geographical area with 440,000 subjects. A total of 46 patients, aged 16 to 65 years, fulfilled the criteria for a definite diagnosis of SLE. One control for each patient, matched by age, sex, education and place of residence was randomly chosen from the population register. Although all the syndromes included in the proposed ACR criteria for neuropsychiatric SLE were more frequent among SLE patients, most of them were also found among controls. These findings resulted in low specificity for the proposed ACR case definition criteria. In addition, at least one neuropsychiatric manifestation was identified in 91% of the SLE patients and in 54% of the controls, with a 9.5 fold increase in risk, a specificity of 0.46 and a detection rate of 91% among SLE patients.

Headache, anxiety, mild depression, mild cognitive impairment and polyneuropathy are common in otherwise healthy subjects and even more so among patients with a chronic disease [16] and [17], making the attribution of such symptoms to SLE itself a challenge in those settings. Taking into account the high prevalence of some NP manifestations in both SLE and control groups, they set up a different model excluding headache, anxiety, mild depression, mild cognitive impairment and polyneuropathy without electrophysiological confirmation. With this approach, the prevalence of neuropsychiatric disease fell to 46% in their SLE patients and to 7% in controls. This provided an odds ratio of 7.0 (95% CI 2.09–23.47) and specificity of 93% [15].

Several other groups have used the ACR nomenclature to classify neuropsychiatric SLE [18], [19], [20] and [21]. The overall prevalence of neuropsychiatric disease in these study populations varies widely, ranging from 37% up to as much as 95%. Surprisingly, this range in prevalence is as wide as what had been reported prior to the introduction of the ACR nomenclature [14].

Thus, although the ACR classification represented a big step forward in the field in its efforts to standardise the classification for neuropsychiatric SLE, it was in no way fully inclusive of all the possible neuropsychiatric manifestations that may occur in SLE.

5. Current ACR classification criteria: grey areas and potential solutions

Several studies have criticised the ACR nomenclature [22] and some of them have proposed revised versions for the classification, claiming that the proposed 19 ACR criteria did not differentiate SLE patients

from controls, nor neuropsychiatric SLE patients from other SLE patients [15], [22], [23], [24], [25] and [26]. Some authors have reported an inadequate performance of the proposed ACR criteria, criticising the lack of criteria based on neuro-pathogenic features [15].

As a matter of fact, some milder and more subjective signs and/or symptoms, such as migraine, cognitive dysfunction and minor psychiatric disorders are still the most challenging to identify [15] as there are no gold standards, they have a high prevalence in otherwise healthy subjects and, most importantly, because the possible pathogenic attribution to SLE is still under debate.

Migraine has been reported as being the most prevalent manifestation in SLE patients, associated with depression as it occurs in the general population, but with no disease activity or abnormalities detected on cerebral MRI or CSF, with the exception of photosensitivity [27]. More recently, a study [28] analysing seventy-two SLE/control pairs and 48 multiple sclerosis patients for a 12-month follow-up period showed that migraine should no longer be considered a neurologic manifestation of systemic or organ-specific autoimmunity, since the higher prevalence of migraine in SLE patients could be due to methodological weaknesses [28]. At the moment, the inclusion of migraine among the SLE disease activity features remains questionable.

Cognitive defects are relatively common in patients with SLE, with an incidence ranging from 21% to 80% when applying tests such as the Stanford–Binet Intelligence Test, the Wechsler Adult Intelligence Scale, the Complex Attention Task and the Pattern Comparison Task [29], [30] and [31]. There is great disagreement on the association of cognitive dysfunction, and antibodies, cytokines, matrix metalloproteinases, vascular abnormalities, and neuropeptides possibly implicated in this setting [32]. Although the underlying pathogenic mechanism is still unclear, some evidence [33] shows that antiphospholipid antibodies, disease activity, and chronic damage are associated with cognitive dysfunction in SLE. These results also suggest that neuropsychological testing should be used for the assessment of SLE patients when cognitive defects are suspected. Nevertheless, although desirable for research purposes, their routine use in a clinical setting is complex.

Psychiatric disorders, especially when they appear as mild manifestations, represent another controversial topic and grey area of the ACR case definition [34]. Estimated prevalence of psychiatric syndromes alone is even more heterogeneous among centres when compared to other neuropsychiatric SLE manifestations [35]. Mood disorders have been reported in 6–44% of SLE patients, mainly including depressive disorders. Manic or mixed disorders have been reported in 0–4.4% [18] and [36] and anxiety in 13–27% [18] and [37].

Distinguishing between depressive–anxious psychopathologic syndromes resulting from the underlying organic disease and those that are the consequence of the negative influence of the debilitating and chronic illness is very difficult and sometimes, not possible [38]. Most authors have failed to find a relationship between psychiatric symptoms and SLE activity [39]. In addition, Shortall et al. [40], did not observe any relationship between anxiety and mood disorders and psychosocial factors, but highlighted the importance of the meaning and perceived consequences of the illness for the patient. Patients' interpretations of their illness and its impact on daily life were found to have a greater influence on mood and mood disorders than any clinical or biological factors. Interestingly, Ishikura et al. [41] proved that the prevalence and intensity of anxious and depressive symptoms in the course of SLE positively correlated with insufficient knowledge

on the disease and its therapy as perceived by the patient at the beginning of disease, and did not correlate with SLE activity. These findings were in agreement with those by Hawro et al. [35], who reported shorter SLE duration in patients with anxiety disorder, speculating that anxiety was the consequence of inadequate knowledge about the course of the disease and treatment methods.

In summary, in these complex settings, accurate differential diagnosis and the attribution of the neuropsychiatric event as being primary to SLE or secondary to another concomitant condition which may concur in SLE are mandatory before any therapeutic approach can be decided [42].

Although the ACR case definition represents a step forward in the diagnosis and management of SLE patients [29], some manifestations such as headache, some forms of anxiety and mood disorders, as well as cognitive dysfunction are still being misdiagnosed and consequently mistreated. Thus, from a clinical point of view, distinguishing between severe and mild manifestations and between thrombotic and non-thrombotic neuropsychiatric SLE disease may be helpful [43]. Since making a clear-cut differentiation can sometimes be challenging, this practical approach could represent a valid tool in the daily clinical-decision making practice. Focusing on the severity of the disease and on the thrombotic or non-thrombotic nature of the neuropsychiatric manifestation could represent the first practical approach, reserving the attempt of a further definition according to the ACR criteria to a second step in the diagnostic process (Table 1).

Take-home messages

- Central nervous system involvement is one of the major causes of morbidity and mortality in systemic lupus erythematosus (SLE) patients.
- Neuropsychiatric SLE includes a variety of focal, diffuse, central, peripheral, psychiatric, isolated, complex, simultaneous and sequential symptoms and signs, representing both active and inactive disease states.
- The American College of Rheumatology case definition represents a step forward in the diagnosis and management of SLE patients; in spite of this, some manifestations such as headache, some forms of anxiety and mood disorders, as well as cognitive dysfunction are still being misdiagnosed and consequently mistreated.
- From a clinical point of view, distinguishing between severe and mild manifestations and between thrombotic and non-thrombotic neuropsychiatric SLE disease may be helpful and could represent a valid tool in the daily clinical-decision making practice.

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Table 1. Neuropsychiatric manifestations in SLE as defined by the different classifications.

1971 [8]	1982 [9]	1999 [13]	2001 [15]	2008 [43]
Seizures	Seizures	Aseptic meningitis	Aseptic meningitis	Severe/mild manifestations
Psychosis	Psychosis	Cerebrovascular disease	Cerebrovascular disease	Thrombotic/non-thrombotic disease
Focal neurologic disorders		Demyelinating syndrome	Demyelinating syndrome	
		Headache	Movement disorder (chorea)	
		Movement disorder	Myelopathy	
		Myelopathy	Seizure disorders	
		Seizure disorders	Acute confusional state	
		Acute confusional state	Cognitive dysfunction	
		Anxiety disorder	(moderate or severe)	
		Cognitive dysfunction		
		Mood disorder	Severe depression	
		Psychosis	Psychosis	
		Guillain Barre syndrome	Acute inflammatory demyelinating polyradiculo- neuropathy	
		Autonomic neuropathy		
		Mononeuropathy		
		Myasthenia gravis	Autonomic disorder	
		Cranial neuropathy	Mononeuropathy, single/multiplex	
		Plexopathy		
		Polyneuropathy	Myasthenia gravis	
			Neuropathy, cranial	
			Plexopathy	
			Polyneuropathy (with ENMG confirmation)	