Chapter 1
Epidemiology of Neuropsychiatric Systemic Lupus Erythematosus

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Abstract A variety of neuropsychiatric manifestations are observed in patients with SLE. The American College of Rheumatology (ACR) developed standardized nomenclature and case definitions for neuropsychiatric involvement in SLE (NPSLE) in 1999. One of the problems in the 1999 ACR classification is the inclusion of milder, less specific and more subjective manifestations such as headache, mild cognitive dysfunction and mood disorders, which resulted in an enormous variation in the prevalence between studies. Another critical point of the ACR classification is the lack of a number of other neurological manifestations, such as neuromyelitis optica spectrum disorders and reversible focal neurological deficits mimicking cerebrovascular disease. Steroid psychosis is sometimes a difficult differential diagnosis, but not necessarily an exclusion, of lupus psychosis. CSF IL-6 might be one of the surrogate markers to detect patients with headache, cognitive dysfunction and mood disorders, requiring immunosuppressive therapy.

Keywords Epidemiology · Prevalence · American College of Rheumatology Classification · Mortality

1.1 Introduction

Neuropsychiatric involvement in systemic lupus erythematosus (SLE) is one of the recalcitrant complications of the disease, leading to substantial impairment of quality of life as well as disability [1, 2]. A variety of neuropsychiatric manifestations are seen in patients with SLE. Thus, such complexity has made it difficult to make a correct diagnosis and introduce an appropriate treatment. The American College of Rheumatology (ACR) developed standardized nomenclature and case definitions

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for neuropsychiatric involvement in SLE (NPSLE) in 1999, which has enabled the epidemiological studies to be performed on an equal basis [3].

In this chapter, the overall epidemiological features in NPSLE will be described. Furthermore, the limitations in the ACR nomenclature will be discussed.

1.2 Classification

The first attempt for classification of NPSLE was the inclusion of seizures, psychosis and focal neuropsychiatric events in the preliminary SLE classification in 1971 [4]. In the 1982 ARA revised criteria for SLE only seizures and psychosis were included [5]. In 1985, Harris and Hughes summarized the classification of manifestations of NPSLE in the literature, providing the prevalence of various neuropsychiatric manifestations in several studies (Table 1.1) [2]. In this classification, psychiatric manifestations were classified into 2 categories, including organic brain syndrome and non-organic brain syndrome [2]. Organic brain syndrome, originally created for discrimination of psychiatric disturbances due to physical causes from functional psychiatric disorders, was characterized by impairment of orientation, perception, memory, or intellectual function [6]. Non-organic brain syndrome was characterized by neurosis, depression, psychosis or schizophrenia [7]. Most series of studies reported that psychiatric abnormalities and seizures were the most frequent neuropsychiatric disorders of SLE. In fact, both psychiatric abnormalities and seizures are included in the 1982 revised criteria for the classification of SLE [5].

Table 1.1 The frequency of neuropsychiatric manifestations in selected series of patients with SLE

Clinical manifestations	Authors (study design) [Reference]	
	Gibson and Mayers (retrospective) [1]	Grigor et al. (prospective) [6]
Number of patients studied	80	50
All neuropsychiatric features	51%	50%
Organic brain syndrome	19%	18%
Psychiatric illness	8%	22%
Seizures	20%	14%
Cranial nerve palsies	4%	16%
Stroke	10%	16%
Movement disorders[a]	4%	4%
Myelopathy	3%	–
Peripheral neuropathy	2%	6%
Visual defects	2%	–
Aseptic meningitis	1%	–

[a] Movement disorders include with cerebellar ataxia and chorea

Table 1.2 The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes (1999)

Central nervous system
Neurologic syndromes
Aseptic meningitis
Cerebrovascular disease
Demyelinating syndrome
Headache (including migraine and benign intracranial hypertension)
Movement disorder (chorea)
Myelopathy
Seizure disorders
Diffuse psychiatric/ neuropsychological syndromes
Acute confusional state
Anxiety disorder
Cognitive dysfunction
Mood disorder
Psychosis
Peripheral nervous system
Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome)
Autonomic disorder
Mononeuropathy, single/multiplex
Myasthenia gravis
Neuropathy, cranial
Plexopathy
Polyneuropathy

All types of seizures, including generalized seizures and focal seizures, may occur [2]. Organic brain syndrome, non-organic brain syndrome and seizures were the most frequent disorders [2]. It should be noted that seizures may arise alone or sometimes be associated with psychiatric abnormalities [8, 9].

The 1999 ACR nomenclature and case definitions for neuropsychiatric involvement in SLE consist of 12 central nervous system (CNS) manifestations and 7 peripheral nervous system (PNS) manifestations, which are considered to be related with SLE (Table 1.2) [3]. The 1999 ACR nomenclature and case definitions provide diagnostic criteria, exclusion criteria to rule out neuropsychiatric events unrelated to SLE, associations to consider concomitant or pre-existing comorbidities, a set of recommendations to confirm each neuropsychiatric events as appendix [3].

Since the term "organic brain syndrome" is sometimes misleading, it has been replaced by the term "diffuse psychiatric/neuropsychological syndromes" in the 1999 ACR nomenclature and case definitions [3]. Thus, organic brain syndrome and non-organic brain syndrome were reformed into 5 domains of diffuse psychiatric/ neuropsychological manifestations, including acute confusional state, anxiety

disorder, cognitive dysfunction, mood disorder and psychosis [3]. Among these, acute confusional state is the most severe manifestation, requiring extensive immunosuppressive therapy and sometimes resulting in poor prognosis [3, 10]. Acute organic brain syndrome and chronic organic brain syndrome in the previous classification are considered to correspond to acute confusional state and cognitive dysfunction, respectively, in the 1999 ACR criteria [2, 3]. Diffuse psychiatric/neuropsychological manifestation is sometimes called as lupus psychosis.

The frequency of each manifestation is variable depending mainly on the nature of the studies. Thus, headache is more frequent in the prospective studies, since milder forms of headache might be overlooked in the retrospective studies. Of note, in the study by Steup-Beekman et al., which included the patients referred for the purpose of evaluation on MRI scans, the frequencies of cerebrovascular disease, headache and cognitive dysfunction are much higher than those in other studies [11].

It should be pointed out that the ACR nomenclature and definitions contain such manifestations that might consist of different degrees of severity. For example, cognitive dysfunction comprises of manifestations from mild subclinical deficits to severe dementia, the former being more commonly observed even in the general population [12].

1.3 Demographic Features of NPSLE

1.3.1 Prevalence

A number of studies have explored the demographic features of NPSLE. The reported overall prevalence of NPSLE in the previous studies ranges widely between 14 to 95%, even after the introduction of 1999 ACR nomenclature and definitions [13–16]. A number of factors are involved in such variation between studies, including the design of the study, differences in selection criteria and ethnic differences in the studied population. In general, studies with a larger number of patients would result in less selection bias. However, even in studies with the largest cohorts of SLE patients, the prevalence of NPSLE was variable with a range from 19% to 57%, although the variation was smaller than studies with smaller number of patients [12, 17, 18]. It should be remembered that less specific manifestations such as headache, cognitive dysfunction, mood disorders tend to be more commonly observed even in the general population [12]. The inclusion or exclusion of minor neuropsychiatric manifestations, such as mild cognitive dysfunction detected only by a structured battery test, would result in a significant variability of the prevalence [14, 17].

The results of a meta-analysis of 5057 SLE patients have revealed the prevalence of NPSLE of 44.5% in prospective studies and 17.6% in retrospective studies (Table 1.3) [19]. In the subanalysis of the 10 prospective and elicited studies of higher quality (2049 patients) using the random effects model, the prevalence of NP

Table 1.3 Prevalence of neuropsychiatric manifestations according to study design

	Study design			
	All patients (n = 5057)	Prospective/ elicited studies (n = 2049)	Retrospective studies (n = 3008)	
Clinical manifestations	Number Prevalence	Prevalence	Prevalence	p value
Headache	617 12.2%	23.3%	4.7%	p < 0.001
Mood disorder	376 7.4%	14.9%	2.3%	p < 0.001
Seizure disorder	356 7.0%	8.0%	6.4%	p = 0.03
Cognitive dysfunction	334 6.6%	13.9%	1.6%	p < 0.001
CVD	255 5.0%	7.2%	3.6%	p < 0.001
Psychosis	165 3.3%	3.9%	2.8%	p = 0.03
Acute confusional state	155 3.1%	3.9%	2.5%	p = 0.004
Anxiety disorder	121 2.4%	5.3%	0.4%	p < 0.001
Polyneuropathy	76 1.5%	3.0%	0.5%	p < 0.001
Cranial neuropathy	49 1.0%	1.7%	0.5%	p < 0.001
Aseptic meningitis	46 0.9%	0.3%	1.3%	p < 0.001
Myelopathy	45 0.9%	1.0%	0.8%	p = 0.40
Mononeuropathy (single, multiplex)	45 0.9%	1.5%	0.5%	p < 0.001
Movement disorder	36 0.7%	0.9%	0.6%	p = 0.25
Demyelinating syndrome	17 0.3%	0.3%	0.3%	p = 0.96
Myastenia gravis	8 0.2%	0.4%	0%	p < 0.001
AIDP(GBS)	4 0.1%	0.1%	0.1%	p = 0.70
Autonomic disorder	4 0.1%	0.1%	0%	p = 0.16
Total	2709 28.5%	44.5%	17.6%	p < 0.001

[a] Plexopathy was omitted due to the presence of no patient [19]

SLE patients was estimated to be 56.3%, and the most frequent neuropsychiatric were headache 28.3%, mood disorders 20.7%, cognitive dysfunction 19.7%, seizures 9.9%, and cerebrovascular disease 8.0%, although there was a significant variation between studies [19]. In a recent study with lupus Canadian cohort including 1253 patients with mean disease duration of 12 years, the prevalence of NPSLE varied depending on the definition used: 6.4% in a group of NPSLE with seizures or psychosis by ACR classification criteria; 38.6% in a group with seizures, psychosis, organic brain syndrome, cerebrovascular accident, cognitive dysfunction, headache, cranial or peripheral neuropathy, and transverse myelitis with minor nonspecific manifestations such as mild depression, mild cognitive impairment, and electromyogram-negative neuropathies [20]. Thus, one should assume that it is difficult to obtain the exact figure of the prevalence for "NPSLE".

1.3.2 Age of Onset and Ethnicity

Although SLE is more frequent in females of child-bearing age, a similar gender-related tendency is not so evident in NPSLE [21]. As for ethnicity, Hispanics, African descendants and Asians were found to develop NPSLE more frequently than Caucasians [22–25]. Notably, Asian patients also have more severe disease activities of SLE, and possibly NPSLE, compared with Caucasians [22].

NPSLE may frequently occur early in the course of SLE. Thus, neuropsychiatric manifestations develop within the first or second year after diagnosis of SLE in about 50% of the patients [15]. Notably, some reports disclosed that 28–40% of NPSLE-related events occur before or around the time of the diagnosis of SLE [26, 27]. Thus, one needs to keep it in mind that NPSLE might be the initial manifestation of SLE.

1.3.3 Risk Factors

There have been at least 3 major risk factors for NPSLE acknowledged by 2010 EULAR recommendations [10] as well as by other studies. First, generalized SLE disease activity and cumulative damages have been shown to be associated with an increased risk of seizures and severe cognitive dysfunction [28–31]. Second, previous or concurrent occurrences of major NPSLE events, particularly stroke and seizures, have been found to predict similar recurrent events in the future [32, 33]. Third, anti-phospholipid antibodies were associated with cerebrovascular disesse (CVD) [29, 32], seizures [17, 28, 34], myelopathy [35], movement disorders [17] and moderate to severe cognitive dysfunction [17, 30, 36]. The results in the prospective study using the SLICC inception cohort disclosed that lupus anticoagulant (LAC) at baseline was associated with the development of cerebral thrombosis and that anti-ribosomal P antibodies were found to be a risk factor for

the occurrence of psychosis [37]. Therefore, it is suggested that the expression of certain autoantibodies due to the SLE disease activity might most likely predict the risk for NPSLE.

1.4 The Limitations of 1999 ACR Nomenclatures and Definitions

First of all, as mentioned above, it should be pointed out that in the 1999 ACR nomenclature and definitions milder forms of neuropsychiatric manifestations are included, such as headache, minor cognitive dysfunctions and subtle mood disorders [3]. In cases with these manifestations, there are a large number of patients who do not need immunosuppressive therapy and usually improve only with a conservative, symptomatic or supportive therapy. However, there are a fraction of patients with cognitive dysfunction or mood disorder who require immunosuppressive therapy [10, 38, 39]. Needless to say, the ACR criteria do not refer to the discrimination of such a fraction of patients. In addition, for lupus headache, included in SLEDAI-2 K [40] and in British Isles Lupus Assessment Group 2004 index [41], corticosteroids (1 mg/kg/day prednisone) proved to be more effective than conventional antimigraine therapy [42]. Thus, it is mandatory to discriminate patients with these manifestations who need immunosuppressive therapy from those who require only supportive therapy. In fact, there are some studies that claimed to exclude milder, less specific and more subjective NP syndromes such as headache, mild cognitive dysfunction and mood disorders along with peripheral neuropathy in order to increase the specificity for SLE [13].

On the next topic, CVD is defined as neurologic deficits usually due to arterial insufficiency or occlusion, venous occlusion disease, or hemorrhage [3] . Most of the patients with CVD have evidence of thrombosis due to antiphospholipid antibodies and suffer from irreversible neurological damages, which do not respond to immunosuppressive therapy [43]. Meanwhile, recent studied have disclosed the presence of patients showing neurological focal deficits along with MRI abnormalities which respond to immunosuppressive therapy to improve almost completely [44]. Such reversible focal neurological deficits have not been included in the 1999 ACR nomenclature [3]. Thus, one cannot help classifying such disorders as CVD.

Finally, in the 1999 ACR nomenclature, myelopathy does not discriminate neuromyelitis optica spectrum disorders (NMOSD) caused by anti-AQP-4 antibodies from transverse myelitis due to vasculitis [45]. These 2 conditions result in different prognosis, and therefore need to be differentiated. Even the ACR criteria encourage the classification of Devic's syndrome (currently NMOSD) as both myelopathy and demyelinating syndrome. It is quite doubtful that NMOSD most suitably classified as demyelinating syndrome in the 1999 ACR nomenclature and definitions [3].

Definitely, reclassification of demyelinating syndrome and myelopathy would be mandatory in the future.

1.5 NPSLE in Childhood

In general, patients with pediatric SLE has been associated with greater severity and poorer prognosis than those with adult SLE [46, 47]. There have been few studies comparing clinical features and prevalence of NPSLE in children and adults. Overall, neurological manifestations are more severe in children, leading to permanent damages at higher rates than adults [48–50]. Previous studies in children over a 6-year study period revealed that neurological manifestations were more common than lupus nephritis (95% versus 55%) [46]. The common NPSLE manifestations in this longitudinal study included headaches in 72% of children, mood disorder in 57%, cognitive dysfunction in 55%, seizure disorder in 51%, acute confusional disorder in 35%, peripheral nervous system impairment in 15%, psychosis in 12%, and stroke in 12%.

Somewhat strangely, although pediatric SLE patients were found to present more frequent renal disease and encephalopathy than adults [51], long-term survival for pediatric patients with NPSLE was as high as 97% [52].

Of note, the presence of antiphospholipid antibodies was seen in 70% of children as compared with 25–30% in adult SLE patients in the study by Harel et al. [53]. However, their association with NPSLE was unremarkable except for CVD [53]. Although neurocognitive deficits have been found in 55–59% of pediatric SLE patients [46, 54], the true prevalence rates and impacts on academic performance as well as on quality of life status remain to be elucidated [55].

1.6 Steroid Induced Psychosis

It is often difficult to determine whether psychiatric manifestations are caused by SLE itself (NPSLE) or induced by steroids (steroid psychosis), especially when the patients present the manifestations during the course of SLE. Steroid psychosis is defined as psychiatric syndrome that newly appears after the introduction or increase of steroids in patients with SLE. The incidence of steroid psychosis appears to be much lower than expected. Thus, it has been reported that approximately 5.4% (28/520) presented steroid psychosis [56]. Similar incidence rate (5%) of steroid psychosis has been reported in the other study [57].

It should be noted that about 50% of patients with diffuse NPSLE presented apparent manifestations after the induction or increase of steroid. Therefore, surrogate markers for diffuse NPSLE, such as CSF IL-6 [58], would be important and useful for the correct diagnosis. It is also notable that ACS is much more frequently observed in diffuse NPSLE than in steroid psychosis, whereas mood

Table 1.4 Comparison of neuropsychiatric manifestations between lupus psychosis and steroid psychosis

Neuropsychiatric manifestations	Lupus psychosis (NPSLE)[a] (n = 37)	Steroid-induced psychosis (n = 25)
Acute confusional state	22	0
Psychosis	4	3
Anxiety disorder	2	2
Mood disorder	7	19
Cognitive dysfunction	2	1

[a]One patient showed anxiety disorder and mood disorder, one patient presented acute confusional state and psychosis and one patient had acute confusional state with anxiety disorder and mood disorder

disorder is much more common in steroid psychosis in our series of patients (Table 1.4).

1.7 Mortality

It has been reported that patients with SLE have a 3 fold increased risk of mortality with standardized mortality ratio (SMR) [59, 60], the ratio between the observed number of deaths of patients and the expected number of deaths in the general population adjusted for age, sex and time of diagnosis. SMR increases to 6 in lupus nephritis, and to 9.5 (95% CI 6.7–13.5) in NPSLE [60]. Thus, in NPSLE the five-year survival estimate and the 10-year survival estimate were 0.85 and 0.76, respectively [60]. As can be expected, hazard ratios (HRs) were highest in patients with acute confusional state (HR 3.4). We have recently demonstrated that the presence of abnormalities on MRI scans significantly increased the mortality of patients with ACS (5-year survival 0.55 compared with 1.9 in patients without MRI abnormalities) [61]. In patients with NPSLE, most common causes of death were infection and NPSLE itself [60].

Of interest, a decreased mortality risk was seen in patients with antiplatelet therapy (HR 0.22) [60]. It is suggested that such effect of anti-platelet therapy might be due to its action on CVD or atherosclerosis. However, prospective studies need to be done to draw any definite conclusion.

1.8 Emerging Problems from the Epidemiological Studies

As mentioned above, the most critical issue on the 1999 ACR nomenclature and definition [3] is that a minor and milder manifestations are mixed up with a serious manifestation within each category, especially headache, cognitive dysfunction and mood disorders [3]. For example, the prevalence of all headache types, particularly

that of tension-type headache and migraine, does not differ between SLE patients and the general population [62]. Thus, it remains unclear which type of headache is caused by immunological processes related with SLE and requires immunosuppressive therapy. In this regard, it has been found that headache due to intracranial hypertension and intractable non-specific headache, but not migraine, are characterized by the inflammatory profile in CSF, such as the elevation of IL-6, IL-8, and IP-10 [63], providing rationale for immunosuppressive therapy.

The ACR committee also proposed a standard battery of neuropsychologic tests to detect cognitive dysfunction [3]. However, such a test would be sometimes confusing, resulting in inclusion of patients with subclinical cognitive dysfunction who do not require immunosuppressive therapy. It is therefore likely that the prevalence of cognitive dysfunction in retrospective studies might reflect the real prevalence of patients who require immunosuppressive therapy. Similarly, as to mood disorders, the retrospective studies might provide the more likely prevalence of patients requiring immunosuppressive therapy. Some testing is necessary to determine whether the patients require the immunosuppressive therapy instead of detecting very subtle changes in cognitive function. In this regard, CSF IL-6 has been shown to be useful to make a differential diagnosis of patients with diffuse NPSLE, including cognitive dysfunction and mood disorders, from those with psychiatric manifestations not requiring immunosuppressive therapy [64].

In conclusion, although the prevalence of headache, cognitive dysfunction and mood disorders is relatively high in the prospective studies, the percentage of patients who required immunosuppressive therapy is very limited, possibly accounting for the lower prevalence of these manifestations in the retrospective studies. It should be emphasized that the establishment of surrogate markers to detect patients requiring immunosuppressive therapy.

1.9 Summary

A variety of neuropsychiatric manifestations occur in patients with SLE. The ACR developed standardized nomenclature and case definitions for NPSLE in 1999, which has enabled the epidemiological studies to be performed on an equal basis. One of the problems in the 1999 ACR classification is the inclusion of minor and milder and less specific manifestations, including headache, mild cognitive dysfunction and mood disorders, resulting in some confusion in the decision of immunosuppressive therapy. Another critical point of the ACR classification is the lack of attention to a number of other neurological manifestation, especially NMOSD, posterior reversible encephalopathy syndrome and reversible focal neurological deficits mimicking CVD. The overall prevalence of NP SLE was estimated to be 56.3%, predominantly affecting CNS (93.1%) rather than PNS (6.9%). Hispanics, African descendants and Asians were found to develop NPSLE more frequently as well as severely than Caucasians. NPSLE usually occur early in the course of SLE. It should be kept in mind that steroid psychosis is sometimes a

differential diagnosis, but not necessarily an exclusion, of lupus psychosis. NPSLE increased the mortality rate with SMR 9.5. It should be emphasized that the establishment of surrogate markers to detect patients with headache, cognitive dysfunction and mood disorders requiring immunosuppressive therapy is important for a better management of patients with NPSLE.

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