On cerebral lupus: from pathogenesis to clinical outcomes

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OUTCOMES OF NEUROPSYCHIATRIC EVENTS IN SYSTEMIC LUPUS ERYTHEMATOSUS BASED ON CLINICAL PHENOTYPES – PROSPECTIVE DATA FROM THE LEIDEN NP-SLE COHORT

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ABSTRACT

Objective: To assess whether clinical and patient's reported outcomes are associated with a different pathophysiologic origin of neuropsychiatric (NP) events presenting in systemic lupus erythematosus (SLE).

Methods: A total of 232 NP-events presenting in 131 SLE-patients were included. NP-SLE diagnosis was established per event by multidisciplinary evaluation. All NP-events were divided according to a suspected underlying pathophysiological process into one of the next: non-NP-SLE related, inflammatory and ischemic NP-SLE. The clinical outcome of all NP-events was determined by a physician-completed four-point-Likert scale. Health-related quality of life was measured with the subscales of the patient-generated Short Form 36 (SF-36) health survey questionnaire. The change between scores at paired visits of all domain scores, mental component summary (SF-36 MCS) and physical component summary (SF-36 PCS) scores were retrospectively calculated and used as patient reported outcome. The association among these outcomes and the different origin of NP-events was obtained using multiple logistic regression analysis.

Results: The clinical status of 26.8% non-NP-SLE events, 15.8% ischemic NP-SLE and 51.6% inflammatory NP-SLE improved after re-assessment. Almost all SF-36 domains had a positive change at re-assessment in all groups independently of the origin of NP-events. NP-SLE ($B = 0.502$; $p < 0.001$) and especially inflammatory NP-SLE ($B = 0.827$; $p < 0.001$) had better clinical outcome being change in disease activity the only important predictor. The change in SF-36 MCS was also independently associated with NP-SLE ($B = 5.783$; $p < 0.05$) and inflammatory-NP-SLE ($B = 11.133$; $p < 0.001$). Disease duration and change in disease activity were the only predictors in both cases. The change in SF-36 PCS was only negatively associated with age.

Conclusion: Inflammatory NP-SLE events have better clinical outcome and a meaningful improvement in SF-36 MCS than ischemic NP-SLE or non-NP-SLE.

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease that has protean manifestations.(1) Nervous system involvement in SLE leads to a heterogeneous group of neurological and psychiatric symptoms (Neuropsychiatric systemic lupus erythematosus). Any of these neuropsychiatric (NP)-events can be directly attributed to SLE (NP-SLE) or to an alternative aetiology (non-NP-SLE). Although NP-SLE pathogenesis is incompletely understood, two underlying mechanisms are recognized: a) Inflammatory NP-SLE: associated with dysfunction due to pathogenic antibodies with a disrupted blood-brain barrier, and b) ischemic NP-SLE: associated with focal neurological deficits due to the interruption of the blood-flow in a specific region of the brain.(2,3) In order to guide therapeutic decisions in clinical practice, we have previously proposed a pathophysiological clustering of NP-SLE patients based in these two mechanisms; therapy is thus directed to inflammation with immunosuppressive therapy or to ischemia/thrombosis with anticoagulants and antiaggregants.(2)

The clinical outcome of NP-events presenting in SLE has been scarcely studied. A 2-year follow-up study of 32 hospitalized NP-SLE patients showed an improvement and stabilization of symptoms in 69% and 19%, respectively.(4) Some authors have not found a difference in outcome when the aetiology of NP-events (NP-SLE vs non-NP-SLE) was analysed.(5) Two previous investigations explored the short and long-term outcome of NP-events, regardless its aetiology, presenting in the large inception Systemic Lupus International Collaborating Clinics (SLICC)-cohort. Both analysis found that the outcome of NP-SLE-events were more favourable than in non-NP-SLE-events.(6,7)

The occurrence of NP-events in SLE patients, independently of its aetiology, has been associated with a considerable comorbidity resulting in a marked adverse repercussion on health related quality of life (HRQoL).(6) Among all the available tools for measuring HRQoL, the 36-item Short-Form Health Survey (SF-36) is a valid and reliable tool to identify the effect of SLE in the physical, mental and social domains of these patients.(8-10) Previous research has shown how SF-36 is associated with the clinical outcome of NP-events in SLE patients, especially the domains concerning self-report mental health where the improvement of disease activity may play an important role.(11)

So far, the clinical outcome and HRQoL of NP-events in SLE have never been investigated in a large multidisciplinary assessed NP-SLE-cohort. Moreover, it is unknown how a certain underlying pathophysiological mechanism of NP-events presenting in SLE may impact clinical outcome and SF-36 domains change over time. Inflammatory NP-SLE may be thought to have a better outcome after immunosuppressive therapy is given and subsequently the origin of the NP-event eradicated while a smaller improvement may be expected in ischemic NP-SLE after receiving secondary prevention.

Our current work aims to (a) assess clinical outcome and change in HRQoL measured by SF-36 on a multidisciplinary assessed and prospectively followed cohort of SLE patients with NP-events either related and non-related to SLE, (b) investigate whether the different pathophysiological NP-SLE mechanisms have an impact in these outcomes and in which magnitude this results would be dependent on other disease characteristics.

METHODS

Patients

Patients from the Leiden NP-SLE-clinic were used. Our study group comprised 131 SLE patients presenting at least one NP-event either related or non-related to SLE. Our hospital, the Leiden University Medical Centre, serves as a national referral centre for NP-SLE in the Netherlands. All patients fulfilled the ACR 1982 revised criteria for SLE.(12,13) For the present study, only patients with completed SF-36 questionnaires at the appropriate assessments were included. The study was approved by the local medical ethics committee. All patients have provided written informed consent.

Multidisciplinary assessment of NP-events

All patients included in our study were evaluated twice. In both visits all patients were admitted for a 1-day period. They underwent the same standardized assessment including a combination of multidisciplinary medical assessment and extensive complementary testing. During the admission all patients were assessed by a multidisciplinary team including specialists in rheumatology, neurology, clinical neuropsychology, psychiatry and vascular medicine. An experienced rheumatologist calculated SLE disease activity with the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K).(14) Irreversible damage due to SLE was assessed with the SLICC/ACR damage index (SDI) at the first visit.(15) In both cases, SLEDAI-2K and SDI were calculated without the NP variables included in these indexes. Furthermore, extensive laboratory tests, neuropsychological evaluation and a brain magnetic resonance imaging (MRI) were routinely performed. When needed additional tests, such as cerebrospinal fluid analysis or MRI of the spine were also performed. Evaluations included in the multidisciplinary assessment and MRI-scanning protocol are described elsewhere.(2,16) The multidisciplinary team met every 2 weeks to discuss the patients and evaluate the complementary assessments. The next aspects were taken into account: a) objective confirmation of symptoms assessed to standard of care of the appropriate medical specialty, b) attribution to SLE or other aetiology. Both NP-SLE and non-NP-SLE-events could coexist in the same patient, c) assessment of the suspected pathogenic mechanism when NP-SLE was diagnosed, differentiating between inflammatory and ischemic NP-SLE as previously reported.(2,16) Both phenotypes could also coexist, and d) Classification of

NP-events according to the 1999 ACR-nomenclature for NP-SLE.(17) More than one NP-SLE diagnosis per patient was possible. Thereafter, an individualized therapeutic decision per NP-event was made depending on presentation and severity.(18) In general, when inflammatory NP-SLE was suspected, immunosuppression therapy was initiated; in case of ischemic NP-SLE, secondary prevention with antiaggregants or anticoagulation when indicated was given; and when a NP-event was not related to SLE, optimization of symptomatic therapy or/and psychotherapy were indicated. Furthermore, all patients were closely followed by the referral doctor in between visits. After re-assessment, a final diagnosis was established taking into account the evolution over time of NP status and response to therapy of every NP-event.

Patient's and physician's reported outcomes of NP-events

Likert scale

A 4-point Likert scale was used to assess the clinical outcome of every NP-event between the first visit and re-assessment (1=worsening of symptoms including death; 2=no change; 3=improvement of symptoms; 4=resolution of symptoms). Likert scales have been previously used by other groups as physician reported outcome in NP-SLE studies.(11,19) For ischemic NP-events and transverse myelitis we used the modified Rankin scale, a validated tool for evaluating disability and dependence in daily activities.(20) A positive change in the Rankin score between first visit and re-assessment of > 2 points was assessed as improvement; a negative change of ≥ 1 was assessed as worsening.

SF-36 score

The SF-36 was used as measure of HRQoL at first visit and re-assessment. All SF-36 domains and both subscales the SF-36 Physical Component Summary Score (SF-36 PCS) and the SF-36 Mental Component Summary Score (SF-36 MCS) were calculated.(21) All these scores were retrospectively calculated and not available to the multidisciplinary team and subsequently not taken into account to decide the diagnosis at re-assessment. The difference between the SF-36 MCS and PCS at the paired visits was used as dependent variable. SF-36 questionnaires were assessed per patient; however, since multiple concurrent NP-events may occur in our patients and since clinical outcome was assessed per NP-event, we decided to use also this approach to assess HRQoL. The same values of change in SF-36 MCS and PCS were used for all NP-events occurring in the same patient. Although this approach may have an impact in our results we preferred this situation over leaving out of the study patients presenting multiple NP-events of different origin.

Statistics

All data are expressed as mean (± standard deviation), medians with interquartile range (IQR) or proportion if applicable. All variables were normally distributed.

Firstly, independent associations between a large number of clinical-demographic variables (age, gender, disease duration, duration NP-event, lag time between SLE diagnosis and NP-event presentation, time interval between visits, change in SLEDAI-2K [cSLEDAI-2K], SDI at first visit, antiphospholipid syndrome diagnosis, NP-SLE diagnosis and NP-SLE phenotypes) were investigated by univariate linear regression analysis, using the change in Likert scale, SF-36 MCS and PCS as the dependent variables. There was not a statistical interaction between age or gender and the dependent variables. Variables with univariate associations with a $p<0.20$ were retested in a multivariate model.

Secondly, a multiple variable analysis was performed in order to test for the contributory or confounding effect of several independent variables. The variables were included one by one in the model. Separate multivariate models were run using either NP-SLE diagnosis or NP-SLE phenotype per event as independent variables. For NP-SLE phenotype we used dummy variables for inflammatory (yes = 1, else = 0) and ischemic (yes = 1, else = 0) with non-NP-SLE-events as reference.

Furthermore, ANOVA test with Bonferroni correction was performed to compare the change in all SF-36 domains among groups. All tests were two-sided and p values <0.05 were considered statistically significant. Statistical analysis was performed with commercially available software (IBM SPSS statistics, version 20.0 for Windows; SPSS, Chicago, IL, USA).

RESULTS

Patient´s characteristics

In total 131 SLE patients had two completed SF-36 questionnaires at first visit and re-assessment. **Table 1** shows the clinical characteristics, autoantibody profile and therapies given after first visit in the study population. There were 115 women (87.8%), mostly Caucasian (70.2%) with a mean age at diagnosis of 35.61±13.66 years and mean disease duration at first visit of 7.16±7.72 years. SLE activity and cumulative organ damage at the first visit were moderate as showed by the mean SLEDAI-2K (8.11±6.34) and SDI (1.45±1.2) scores after exclusion of NP variables. The median interval between visits was 0.5 years (IQR 0.4–1.1).

Characteristics of the NP-events

A total of 232 NP-events were diagnosed at first visit. Patients presented a median number of 2 NP-events (range 1–5). A total of 120 NP-events were attributed to SLE and 112 NP-

Table 1. Characteristics at enrolment of 131 SLE patients presenting NP-events

		%
Female, n (%)	115	87.8
Age at diagnosis (years)	35,61 ± 13,66	
Age at study (years)	42,77 ± 13,02	
Ethnicity, n (%)		
Caucasian	92	70.2
Black	9	6.9
Asian	26	19.8
Mixed	3	2.3
SLE duration (years)	7,16 ± 7.72	
NP-event duration (years)	1,11 ± 2,71	
Number of SLE criteria, median (IQR)	5 (4-6)	
ACR SLE criteria, n (%)		
Malar rash	56	42.7
Discoid rash	23	17.6
Photosensitivity	42	32.1
Oral ulcers	46	35.1
Arthritis	86	65.6
Serositis	37	28.2
Renal disorder	33	25.2
Neuropsychiatric disorder	16	12.2
Hematologic disorder	64	48.9
Immunologic disorder	103	78.6
Positive antinuclear antibody	129	98.5
Antibodies, n (%)		
aCL IgG	30	22.9
aCL IgM	14	10.7
LAC	54	41.2
B2GP-1 IgG †	16	
B2GP-1 IgM †	5	
Antinuclear antibody	124	94.7
ENA	65	49.6
Anti-dsDNA	70	53.4
Anti-SSA	39	29.8
Anti-SSB	9	6.9
Anti-RNP	27	20.6
Anti-Sm	12	9.2
SLEDAI-2K *	8.11 ± 6.34	
SDI *	1.45 ± 1.2	
Therapies after first visit, n (%)		
Corticoids	76	58
Immunosuppressants	64	48.9
Cyclophosphamide	24	18.3
Rituximab	4	3.1
IVIG	1	0.8
Azathioprine	27	20.6
Mycophenolate	11	8.5
ASA	39	29.8
Dipyridamole	10	7.6
Antidepressants	28	21.4
Anticonvulsants	19	14.5
Vitamin K antagonists	30	22.9
Clopidogrel	6	4.6
Benzodiazepines	12	9.2
Antipsychotics	10	7.6
Triptans	7	5.3
Statines	22	16.8
Psychotherapy	26	19.8

aCL: anticardiolipin antibodies; ACR: American College of Rheumatology; ANA: antinuclear antibody; ASA: acetyl salicylic acid; B2GP-1: anti–β2-glycoprotein 1; IVIG: intravenous immunoglobulin; LAC: Lupus anticoagulant; NP: neuropsychiatric; NP-SLE: neuropsychiatric systemic lupus erythematosus; SLE: systemic lupus erythematosus; SDI: systemic lupus international collaborating clinics (SLICC)/American College of Rheumatology damage index; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000.
† Only 91 patients were assessed for B2GP IgG and IgM.
* Calculated without neuropsychiatric variables.

events to other aetiologies. Among the 120 NP-SLE-events a total of 74 were addressed as inflammatory NP-SLE and 46 NP-events as ischemic NP-SLE. Among the 112 non-NP-SLE-events, a total of 38 NP-events (33.9%) were concomitant in patients presenting at least one NP-SLE-event. **Supplementary Table 1** shows a description of all NP-events by attribution and according to the ACR nomenclature. Attribution to SLE varied significantly depending on the different NP-event included in this nomenclature (i.e. 85% cerebrovascular disease and 8% headaches).

Outcomes of NP-events

After re-assessment 19% of all NP-events resolved, 32.7% improved, 34.5% were unchanged and 13.8% worsened in NP status. A total of 46/120 (38.3%) NP-SLE-events improved and 35/120 (29.2%) resolved. A total of 30/112 (26.8%) non-NP-SLE-events improved and only 9/112 (8%) resolved after re-assessment. A total of 15.8% ischemic NP-SLE and 51.6% inflammatory NP-SLE improved. NP-SLE-events and especially inflammatory NP-SLE had markedly better HRQoL outcomes than ischemic NP-SLE and non-NP-SLE. **Figure 1** shows the change in the eight domains of SF-36 among 232 NP-events presenting in SLE patients depending on the final diagnosis and phenotype.

Relationship between NP-SLE diagnosis and clinical outcome, change in SF-36 MCS and SF-36 PCS

In general, NP-events attributed to SLE had better clinical outcome and a positive change in SF-36 MCS and PCS. **Table 2** shows the results of univariate and multivariate logistic **(Model 1)** regression analysis exploring the association between clinical outcome measured by Likert scale, change in SF-36 MCS and PCS, the NP-SLE diagnosis and the clinical-demographic variables of interest:

- Clinical outcome: univariate regression analysis showed that NP-SLE (regression coefficient [B] = 0.582; $p<0.001$), age (B=–0.011; $p<0.05$), Asian and mixed ethnicity (both $p<0.05$) and cSLEDAI-2K (B=0.031; $p<0.001$) were associated with clinical outcome.
- Using multivariate analysis NP-SLE was still independently associated with clinical outcome (B=0.502; $p<0.001$) and the only important predictor was cSLEDAI-2K (B=0.021; $p<0.05$).
- SF-36 MCS: NP-SLE (B=8.966; $p<0.001$), age (B=–0.402; $p<0.001$), disease duration (B=–0.588; $p<0.001$) and cSLEDAI-2K (B=0.864; $p<0.001$) were associated with change in SF-36 MCS. Multivariate analysis showed that NP-SLE remained significant (B=5.783; $p<0.05$) although it was significantly influenced by adding disease duration (B=–0.552; $p<0.001$) and cSLEDAI-2K (B=0.705; $p<0.001$) to the model.

- SF-36 PCS: NP-SLE diagnosis (B=6.086; p<0.05), age (B=–0.297; p<0.05) and cSLEDAI-2K (B=0.493; p<0.05) were associated with change in SF-36 PCS. However, after multivariate analysis only age showed still a negative association (B=–0.216; p<0.05).

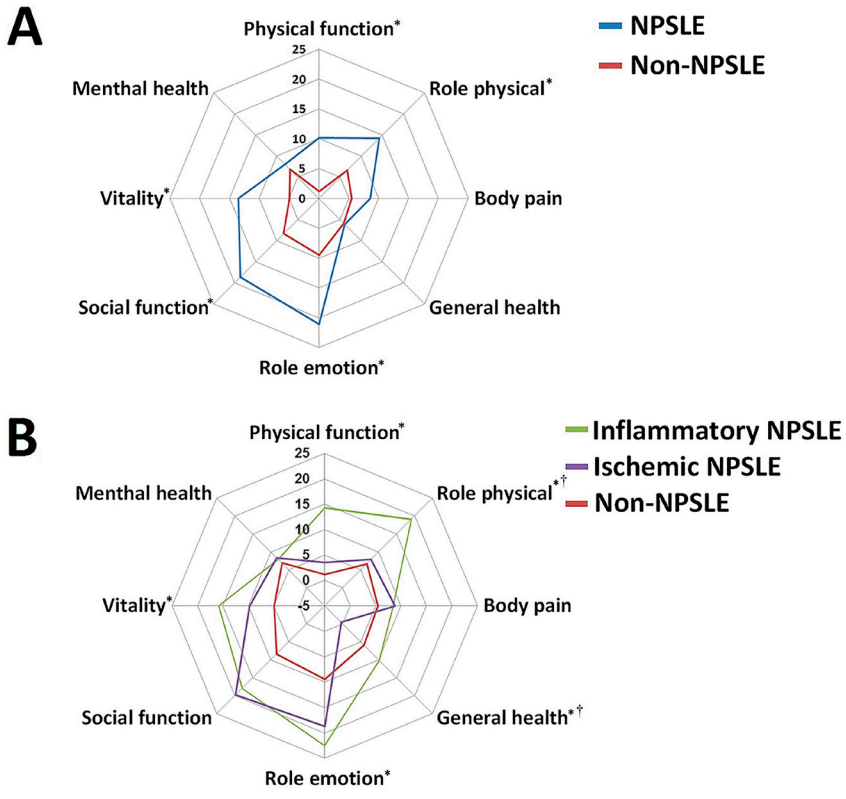

Figure 1. Spidergram representing the change in HRQOL of the 8 domains of SF-36 among 232 NP-events presenting in SLE patients depending on its pathogenesis. **A**. Comparison between NP-events attributed to SLE (NP-SLE) and to other aetiologies (Non-NP-SLE). * p < 0.05; **B**. comparison between NP-SLE events attributed to inflammation (inflammatory NP-SLE), to ischemia (ischemic NP-SLE) or to other aetiologies (Non-NP-SLE). * p< 0.05 for comparison between inflammatory-NP-SLE and non-NP-SLE; † p < 0.05 for comparison between inflammatory NP-SLE and ischemic NP-SLE.

Table 2. Univariable and multivariable logistic regression analysis exploring the association between clinical outcome, change in SF-36 MCS, SF-36 PCS (dependent variables), attribution of NP-events according to diagnosis and phenotype and clinical-demographic variables

	Clinical Outcome (Likert)			**Change in SF-36 MCS**			**Change in SF-36 PCS**		
	Univariable	**Multivariable**		**Univariable**	**Multivariable**		**Univariable**	**Multivariable**	
		Model 1 – NP-SLE diagnosis	Model 2 – NP-SLE phenotype		Model 1 – NP-SLE diagnosis	Model 2 – NP-SLE phenotype		Model 1 – NP-SLE diagnosis	Model 2 – NP-SLE phenotype
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
Diagnosis NP-SLE	**0.582 (0.374 to 0.817)****	**0.502 (0.257 to 0.747)****		**8.966 (4.115 to 13.817)****	**5.783 (1.017 to 10.548)***		**6.086 (0.997 to 11.174)***	3.739 (-1.533 to 9.012)	
Phenotype NP-SLE									
Non-NP-SLE (Ref.)									
Inflammatory NP-SLE	**0.894 (0.640 to 1.149)****		**0.827 (0.560 to 1.093)****	**14.715 (9.395 to 20.035)****		**11.133 (5.866 to 16.400)****	**6.133 (0.319 to 11.948)***		3.337 (-2.712 to 9.385)
Ischemic NP-SLE	0.080 (-0.218 to 0.378)		0.028 (-0.272 to 0.328)	-0.283 (-6.502 to 5.936)		-2.075 (-8.016 to 3.866)	6.009 (-0.788 to 12.806)		4.327 (-2.483 to 11.137)
Age at enrolment (years)	**-0.011 (-0.020 to -0.001)***	-0.003 (-0.013 to 0.007)	0.001 (-0.010 to 0.009)	**-0.402 (-0.594 to -0.210)****	-0.176 (-0.373 to 0.021)	-0.138 (-0.329 to 0.054)	**-0.297 (-0.498 to -0.095)***	**-0.216 (-0.428 to -0.004)***	**-0.219 (-0.433 to -0.006)***
SLE duration (years)	-0.001 (-0.018 to 0.015)			**-0.588 (-0.913 to -0.262)****	**-0.552 (-0.865 to -0.238)****	**-0.525 (-0.828 to -0.222)****	-0.237 (-0.581 to 0.106)		
NP-event duration (years)	-0.022 (-0.078 to 0.033)			-1.098 (-2.218 to 0.022)			0.168 (-0.997 to 1.333)		

Gender (Female vs Male)	-0.271 (-0.636 to 0.095)			-0.268 (-7.698 to 7.162)			-3.608 (-11.262 to 4.047)		
Ethnicity									
Caucasians (Ref.)									
Black	0.360 (-0.436 to 1.156)			-4.908 (-21.162 to 11.347)			7.289 (-9.528 to 24.105)		
Asian	**0.780 (0.077 to 1.482)***			-2.645 (-16.991 to 11.700)			7.530 (-7.311 to 22.371)		
Mixed	**0.147 (0.013 to 0.282)***			-1.395 (-4.145 to 1.356)			1.792 (-1.054 to 4.637)		
cSLEDAI-2K †	**0.031 (0.012 to 0.049)****	**0.021 (0.002 to 0.039)***	**0.020 (0.002 to 0.038)***	**0.864 (0.502 to 1.226)****	**0.705 (0.342 to 1.069)****	**0.690 (0.339 to 1.041)****	**0.493 (0.106 to 0.879)***	0.323 (-0.078 to 0.724)	0.324 (-0.078 to 0.726)
SDI at enrolment †	-0.032 (-0.134 to 0.069)			-1.853 (-3.886 to 0.180)			1.739 (-0.362 to 3.840)		
APS (Yes vs No)	-0.127 (-0.409 to 0.156)			-2.495 (-8.210 to 3.221)			-2.743 (-8.641 to 3.155)		
Time between visits (years)	-0.062 (-0.163 to 0.038)			-0.588 (-2.604 to 1.488)			-1.106 (-3.214 to 1.002)		

APS: antiphospholipid syndrome; MCS: mental component summary score; PCS: physical component summary score; NP: neuropsychiatric; NP-SLE: neuropsychiatric systemic lupus erythematosus; cSLEDAI-2K: change of SLEDAI-2K (Systemic Lupus Erythematosus Disease Activity Index 2000) between first visit and re-assessment; SF-36: 36-item Short-Form Health Survey. *P < 0.05, **P<0.001; † Calculated without neuropsychiatric variables

Relationship between NP-SLE phenotypes and clinical outcome, change in SF-36 MCS and SF-36 PCS

We further investigated the association between the outcome variables and the underlying pathophysiological mechanism of NP-events and whether the association was independent of differences in clinical-demographic variables **(Table 2, Model 2)**:

- Clinical outcome: only inflammatory NP-SLE was significantly associated with a favourable outcome (B=0.894, $p<0.001$), remaining significant in a multivariate analysis (B=0.827; $p<0.001$). Multivariate analysis showed that cSLEDAI-2K was a significant predictor (B=0.020, $p<0.05$) of this association.

- SF-36 MCS: an association between inflammatory NP-SLE (B=14.715; $p<0.001$) and improvement in SF-36 MCS was observed, remaining significant after multivariate analysis (B=11.133; $p<0.001$). Disease duration (B=−0.525, $p<0.001$) and cSLEDAI-2K (B=0.690; $p<0.001$) accounted as strong additional potential predictors.

- SF-36 PCS: inflammatory NP-SLE was significantly associated with an improvement in SF-36 PCS (B=6.133, $p<0.05$); after multivariate analysis only age was associated with change in SF-36 (B=−0.216, $p<0.05$).

DISCUSSION

Our results show that inflammatory NP-SLE-events have a better clinical outcome and a meaningful improvement in SF-36 MCS than non-NP-SLE-events and ischemic NP-SLE-events. Moreover we show that SLE disease activity is key as predictor of these results.

We propose that these findings may be related to reversibility of brain inflammation/dysfunction after starting immunosuppressive therapy as well as to spontaneous decrease of disease activity. Inflammatory NP-SLE reflects neuronal dysfunction or brain inflammation thought to be mediated by autoantibodies, other inflammatory factors and increased SLE disease activity. Histopathological studies in NP-SLE have shown findings compatible with inflammation (e.g. parenchymal oedema, glial hyperplasia).(22) Furthermore, studies using quantitative MRI have reported a parallel improvement of clinical status and cerebral changes in white matter of NP-SLE patients after receiving immunosuppressive therapy.(16) Reversibility of symptoms after immunosuppressive therapy has been also described in other immune mediated diseases of the central nervous system presenting with a heterogeneous group of NP symptoms such as anti-NMDA-receptor encephalitis.(23)

The results of our study show that only inflammatory NP-SLE may explain the better clinical outcome in NP-SLE found by other authors.(6,7) Ischemic NP-SLE-events, mainly represented by patients with cerebrovascular symptoms, improve slightly over time after starting secondary prevention, which may indicate the irreversibility of cumulative chronic damage on the brain.(16)

Previous research has shown that the focal events have better clinical outcome and higher resolution when compared with diffuse NP-events.(7) Our results do not support these data; probably due to the different inclusion of NP-SLE-events in these subgroups (focal and diffuse vs ischemic and inflammatory), suggesting that both approaches are not comparable. For example, the SLICC-cohort includes seizure in the focal group while in most seizures included in our study an inflammatory mechanism was suspected. We suggest that a differentiation per NP-event based in the underlying pathophysiological mechanism may be preferable since it can be used to guide therapeutic decisions. The presence of NP-events in SLE patients, independently of the aetiology, is associated with a significant HRQoL burden.(5-7) Our study confirms these results and shows how almost all SF-36 variables have a positive change at re-assessment in all groups independently of the origin of NP-events. Previous research has found that the mean SF-36 MCS is markedly lower in SLE patients presenting with NP-events, especially in diffuse NP-events.(6) We show similar results, principally for inflammatory NP-SLE; the subsequently meaningful positive change in the mean SF-36 MCS in this group may respond to the fact that these patients have more room for improvement.

We may speculate that certain NP-events included in this group, such as acute confusional state, may have an important impact in our results, since they lead to a more impaired clinical status. The change in HRQoL is slightly higher than in previously reported(7), suggesting that multidisciplinary assessment and therapeutically orientated interventions per NP-event may be a good approach in SLE. Further studies are warranted to evaluate and identify which specific therapeutic interventions may be required to improve the outcome of different subgroups in NP-SLE. In general, our results support the hypothesis of reversibility in inflammatory NP-SLE and therefore the use of SF-36 as outcome in future clinical trials.

Our data suggest that the change in disease activity measured without neuropsychiatric variables plays an important role determining both clinical outcome and change in SF-36 MCS. Previous studies in SLE without NP-events have shown greater reductions in disease activity accompanied by a meaningful improvement in HRQoL measures after starting immunosuppression.(24,25) In SLE patients presenting with NP-events, an association between lower mean SF-36 MCS and higher disease activity has been observed.(7) In the current study, disease activity does not interfere with the association between NP-SLE-events and both clinical outcome and change in SF-36 MCS, especially inflammatory NP-SLE-events, which may reflect a direct effect of immunosuppression. Moreover, our results show that SF-36 MCS is also influenced by disease duration. Patients who are in the early stages of the disease and are diagnosed with NP-SLE will have more positive change in SF-36 MCS than later in the disease, which may imply that longer disease leads to a burden in brains of SLE patients.

Our study has limitations. First of all, since response to medication influences the attribution of NP-events to SLE, especially in inflammatory NP-SLE, we may not avoid a certain circular reasoning in these studies until we have more specific tools to diagnose NP-SLE. Other limitation and also a generally recognized problem in NP-SLE studies is the high heterogeneity of the NP syndromes which leads to a low prevalence of individual NP-SLE syndromes, which does not allow us to know in which magnitude our results conducted by a certain NP-SLE syndrome. Our results represent a single-centre experience. However, an advantage comparing with other studies is that patients underwent the same multidisciplinary assessment, so far the best and most trustable method to reach NP-SLE diagnosis. Other limitation is that due to the impaired clinical status of some NP-SLE patients we had to postpone the fulfilling of the SF-36. Moreover, due to referral matters, some of the inflammatory NP-SLE patients were evaluated soon after they had been started with immunosuppression. Therefore, we believe that probably the change may have been even higher than those reported here. Furthermore, it is unknown what would have happen if all patients would have strictly been seen every 6 months or after longer periods of follow-up. To avoid bias at this point, time between visits was used as an independent variable in the multivariate analysis.

In conclusion, our results show for the first time that inflammatory NP-SLE-events have a better clinical and patient's reported outcome than non-NP-SLE and ischemic NP-SLE-events, reflecting reversibility of brain inflammation and improvement of disease activity after starting immunosuppression. We believe that these outcomes are helpful as measurements of SLE burden on the brain and follow-up of these patients; subsequently they can be used for monitoring of future therapy NP-SLE trials.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Description of all NP-events presenting in 131 SLE patients by attribution and according to the ACR nomenclature *

ACR definition	Diagnose		Total
	Non-NP-SLE	NP-SLE	
Cerebrovascular disease	7	40	47
Psychosis	5	7	12
Headache	23	2	25
Mood disorder	36	7	43
Myelopathy	1	10	11
Cognitive dysfunction	25	21	46
Seizure	7	12	19
Anxiety	4	2	6
Acute confusional state	0	7	7
Movement disorder	1	4	5
Aseptic meningitis	0	1	1
Polyneuropathy	2	3	5
Cranial neuropathy	0	2	2
Mononeuropathy	1	0	1
Autonomic disorder	0	1	1
Plexopathy	0	1	1
	112	120	232

ACR: American College of Rheumatology
*Possible >1 NP-SLE event per patient