Lifting the fog of neuropsychiatric lupus

Monahan, R.C.

Clinical outcome in patients with suspected inflammatory neuropsychiatric lupus treated with immunosuppression: an observational cohort study

RC Monahan, LJJ Beaart- van de Voorde, R Fronczek, J de Bresser, J Eikenboom, M Kloppenburg, HAM Middelkoop, GM Terwindt, NJA van der Wee, TWJ Huizinga, GM Steup-Beekman

Lupus Sci Med. 2023;10:e000850

ABSTRACT

Background: The short- and long-term outcome of inflammatory neuropsychiatric lupus (NPSLE) with immunosuppressive treatment is largely unknown. We used clinical data from our tertiary referral centre for NPSLE to investigate type of inflammatory NPSLE manifestations, type of immunosuppressive treatment prescribed for these manifestations and clinical outcomes.

Methods: All SLE patients visiting the Leiden University Medical Centre NPSLE clinic between 2007-2021 receiving immunosuppressive therapy for neuropsychiatric symptoms were included. Clinical, immunological and radiological information was collected in a standardized way during a one-day multidisciplinary assessment. In a multidisciplinary consensus meeting, the presence of NPSLE, as well as the type of NPSLE manifestations and treatment were determined. For this study, short-term (0-6 months) and long-term outcomes (7-24 months) of the NP symptoms were assessed by two independent readers and scored on a 7-point Likert scale, ranging from death to resolved.

Results: In total, 95/398 (24%) patients visiting the NPSLE clinic between 2007-2021 received any form of immunosuppressive treatment for 101 separate NPSLE events. The most common NP manifestation was cognitive dysfunction (50%) as identified by formal cognitive assessment, often present in combination with other NPSLE manifestations. Treatment modalities were induction (24%), induction and maintenance (73%) and other therapy (3%). The treatments mostly consisted of (combinations of) prednisone (97%), methylprednisolone (53%), azathioprine (generally 2mg/kg/day) (49%) and cyclophosphamide (generally induction 750 mg/m^2 every 4 weeks for 24 weeks or 500mg biweekly for 12 weeks) (42%). Short-term outcome showed improvement on the Likert scale in 73% (improved: 22%, much improved: 29%, resolved: 22%), no change in 21% and worsening in 6% of patients. Long-term outcome was available for 78/101 events and showed improvement in 70% (improved: 14%, much improved: 28%, resolved: 28%), no change in 17%, worsening in 10% and death in 3% of patients (none directly NPSLE-related).

Conclusion: The outcome of inflammatory NPSLE after immunosuppressive treatment is generally good, with improvement of neuropsychiatric symptoms occuring in approximately 70% of events.

INTRODUCTION

Neuropsychiatric systemic lupus erythematosus (NPSLE) is a complex and heterogenous manifestation of SLE. Neuropsychiatric (NP) symptoms may arise through different mechanisms, such as side-effects of medication, metabolic disturbances and psychological impact of a chronic disease.[1-4] Only a minority of NP manifestations are thought to be caused by active inflammation due to SLE.[5-7] Autoantibodies, blood-brain barrier disruption and inflammatory mediators are hypothesized key players in a diverse range of inflammatory NPSLE manifestations, such as an acute confusional state and psychosis.[8]

In case inflammatory NPSLE is suspected, recommended treatment includes glucocorticoids alone or in combination with other immunosuppressants (e.g. azathioprine or cyclophosphamide).[3] However, studies evaluating therapy and clinical outcomes in patients with inflammatory NPSLE are extremely scarce. Only one pilot study and one clinical trial with immunosuppressive treatment have been performed in small numbers of patients with different (severe) NPSLE manifestations.[9,10] Furthermore, several reviews have been published regarding recommended treatment in patients with inflammatory NPSLE based on the limited evidence available.[11-13]

In the absence of high-level evidence for the treatment of inflammatory NPSLE, observational cohort data on NPSLE are useful to develop pragmatic therapeutic strategies.[14] The Leiden NPSLE clinic has a unique cohort of patients, that all undergo a standardized multidisciplinary evaluation to use all clinical expertise to achieve the best possible attribution of NP manifestations.[15] This creates the opportunity to study inflammatory NPSLE in detail and to shed light on the prognosis of inflammatory NPSLE, which is currently unknown.

The present study aimed to describe all patients that received immunosuppressive treatment for NP manifestations attributed to SLE in a specialist tertiary referral centre for NPSLE and to assess the type of manifestations, therapy and clinical outcomes of inflammatory NPSLE.

PATIENTS AND METHODS

Study design and population

All patients with the clinical diagnosis of SLE that visited the Leiden University Medical Centre (LUMC) NPSLE clinic between September 2007 - May 2021 that received immunosuppressive therapy for NP symptoms and that signed informed consent were included in this study. The LUMC NPSLE clinic is a tertiary referral clinic for patients with (suspected) SLE and NP symptoms, which has been described in detail previously.[15,16] Patients are evaluated in a multidisciplinary team during one day, in which consultations by an advanced nurse practitioner, neurologist, psychiatrist, clinical neuropsychologist, rheumatologist and internist of vascular medicine take place. In addition, laboratory assessment, neuropsychological testing and a brain magnetic resonance imaging (MRI) scan are performed. Furthermore, evaluation of cerebral spinal fluid (CSF) takes place on indication as part of the neurological assessment. As no formal protocol for the diagnosis and treatment for NPSLE exists, the obtained information is discussed

and weighed in a multidisciplinary meeting with experienced physicians and a consensus is reached regarding the attribution and treatment of the NP symptoms.[11] The presence of an inflammatory NPSLE manifestation was generally based on a combination of laboratory markers (such as increased erythrocyte sedimentation rate (ESR), low C3/C4, leucopenia, presence of anti-dsDNA antibodies), radiological markers (such as the presence of vasculitis or oedema) and clinical presentation (such as non-focal NP manifestations and concurrent lupus organ manifestations). Referring physicians (80% external referrals) are responsible for prescribing and monitoring treatment. Ethical approval for this study was obtained from the Leiden-The Hague-Delft medical ethical committee (P07.177).

Follow-up

In general, follow-up visits take place six months after the initial clinic visit. Patients may be evaluated earlier for reasons such as worsening of symptoms or diagnostic uncertainty. Diagnosis at follow-up visit is considered the golden standard.[6] A second follow-up visit takes place after two years in patients receiving immunosuppressive therapy for a longer period of time or with severe NP manifestations. If official follow-up visits were missing, information regarding NP status was retrieved from referral letters or regular clinic visits.

Patient characteristics

The following patient information was routinely collected during patient interview and later retrieved from electronical medical files: sex, age, 1997 American College of Rheumatology (ACR) classification criteria for SLE[17], SLE duration, SLE disease activity index-2000 (SLEDAI-2K)[18], Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index (SDI)[19], smoking status, education level, medication use, NP presentation (including 1999 ACR syndromes for NPSLE[20]), NPSLE phenotype (inflammatory/ischemic/combined), whether NPSLE diagnosis was retracted at follow-up visit and if relevant presence and duration of immunosuppressive therapy initiated for NP symptoms prior to the NPSLE clinic visit. Patients with NP events at different timepoints were included separately for new events.

Laboratory assessment

IgG anti-dsDNA antibodies were detected using the indirect immune fluorescence technique (Immuno Concepts, Sacramento, CA, USA). Anti-Sm (IgG) as well as anticardiolipin (aCL) and anti-β2 glycoprotein 1 antibodies (Anti-β2-GP1, both IgG and IgM) were determined using Phadia® 250 EliA fluorescence enzyme immunoassay (Thermo Scientific, Freiburg, Germany). Anti-β2-GP1 (IgM + IgG) and anti-Sm antibodies were considered positive if levels were >10 U/ml based on the standard laboratory reporting. aCL (IgM and IgG) was considered positive if levels were >30 GPL U/ml. Lupus anticoagulant (LAC) was determined using STA-Rack and STA Evolution coagulation analyzers (Stago, Parsippany, NJ, USA). ANA analysis was performed with an immunofluorescence assay test on Hep-2 cells using a dilution of 1:40. C1q, C3 and C4 were measured in serum using laser nephelometry and were defined low or normal/high based on the normal limits for our laboratory.

Radiological assessment

A standardized brain MRI scan was performed in all patients using a Philips Achieva 3 T MRI scanner (*Philips Healthcare, Best, the Netherlands*). The standardized protocol consisted of: a T1-weighted, T2-weighted, fluid attenuated inversion recovery (FLAIR), diffusion weighted imaging (DWI) and susceptibility weighted imaging (SWI) sequence. The presence of abnormalities on brain MRI were assessed by an experienced neuroradiologist and for this study, the following information was collected from the radiological reports: the presence of an abnormal number of white matter hyperintensities (more than expected for age), global atrophy, infarction, oedema, and haemorrhage.

Neuropsychological testing

All patients underwent extensive neuropsychological assessment, including an interview and cognitive assessment as suggested by the 1999 ACR NPSLE nomenclature and case definition system.[20]

Treatment outcome

Physician global assessment (PGA) as measured by a 7-point Likert scale by two independent readers (RCM + GMS-B) was performed in 2021 retrospectively based on the medical records including cognitive assessment, laboratory and imaging test results. The change in clinical NP status for which immunosuppressive therapy was initiated between the onset of the event and at follow-up was assessed and scored as follows: 1, patient death; 2, much worse; 3, worse; 4, no change; 5, improved; 6, much improved; 7, resolved. The level of certainty of the rated outcome was assessed on a 10-point scale (absolutely uncertain - absolutely certain). Outcome after induction therapy and outcome during or after maintenance therapy were reported. Induction therapy was defined as a high dosage of immunosuppressive therapy for 0-6 months for the NP manifestation and maintenance therapy as a low-dosage immunosuppressive therapy (usually up to 24 months) for the NP manifestation. In case no clear distinction was present between induction and maintenance therapy, the treatment effect at 0-6 months and 7-24 months was reported. Disagreements between the two independent readers were discussed and resolved. Cohen's kappa was calculated prior to reaching consensus, excluding missing outcomes.[21] Cohen's kappa was 0.72 for short-term and 0.75 for long-term outcomes. In nearly all cases of differences in observation (86%), the difference between the observers was solely one point (19/22 of differences in short-term and 13/15 in long-term outcomes). Median certainty of the two readers of short-term outcomes was 8.5 (interquartile range (IQR): 8 – 9) and 7.75 (IQR: 6.5 – 8.5) for long-term outcomes.

The primary outcome was the average PGA at short- and long-term follow-up. For this study, short-term outcome was defined as the (Likert scale) outcome at evaluation at 0-6 months after initial presentation, long-term outcomes at 7-24 months. Secondary outcomes included frequency and reasons of treatment alteration and frequency of relapse within two years.

Statistical analysis

All statistical analyses were performed using StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC.

RESULTS

Study population

Of the 398 patients with SLE referred to the NPSLE clinic between 2007-2021, 95 patients received immunosuppressive treatment for NP manifestations. In the other patients (n = 303) the attribution of the symptoms was minor flare, thrombotic events or other diseases and they received respectively symptomatic treatment, anticoagulant treatment or other (treatment) recommendations. 5/95 patients received immunosuppressive therapy more than once for NP symptoms (four patients: two presentations with >2 years apart, 1 patient: 3 presentations, all >2 years apart). This led to a total of 101 separate NP presentations (hereafter referred to as 'events'). These separate NP events consisted of one or more NP symptoms, which are referred to as NP manifestations. In these 101 events, 195 NP manifestations were present for which immunosuppressive treatment was initiated. For the five patients with multiple events, patient characteristics are presented at time of the first presentation (*Table 1*). The majority of patients was female (84%) and mean age (SD) was 42 ± 14 years. In 42/101 events (42%), immunosuppressive therapy was received for a median duration of one month (IQR: 0.5 – 3.0) prior to the NPSLE clinic visit.

In the 101 events, mean erythrocyte sedimentation rate (ESR) was 34 (IQR: 14-51) at time of clinic visit and low complement levels (C3/C4) were present in 48 (48%) (*Table 2*). Antinuclear antibodies were present in 86 events (85%) at time of clinic visit (ever present: 98%) and anti-double stranded DNA (anti-dsDNA) in 42%. In 17 events (17%), a completely normal brain MRI was present. Most common abnormalities on brain MRI were infarction(s) (37%), abnormal burden of white matter hyperintensities (29%) and global atrophy (14%).

Table 1 Characteristics of patients with SLE presenting with neuropsychiatric symptoms for which immunosuppressives were initiated (n = 95)

	Patients with (suspected) inflammatory NPSLE (n = 95)
Female	80 (84)
Age (years)	42 ± 14
1997 ACRcriteria	
Malar rash	32 (34)
Discoid rash	14 (15)
Photosensitivity	38 (40)
Oral ulcers	34 (35)
Nonerosive arthritis	64 (67)
Pleuritis or pericarditis	28 (29)
Renal disorder	27 (28)
Neurologic disorder	13 (14)

Hematologic disorder	49 (52)
Immunologic disorder	80 (84)
Positive ANA	93 (98)
Duration of SLE, years	1 [0 – 9]
SLEDAI-2K	6 [2 – 12]
SDI	1 [0 – 2]
Current Smoking	20 (21)
Education	
Low (0-6 years)	5 (5)
Middle (7-12 years)	63 (66)
High (<12 years)	24 (25)
Unknown	3 (3)

Results are presented as n (%), mean ± SD or median [IQR]
SDI = SLICC/ACR damage index, SLE = systemic lupus erythematosus, SLEDAI-2K = SLE Disease Activity Index 2000

Table 2 Laboratory and radiological characteristics during NPSLE events (n=101) for which immunosuppressive treatment was initiated

	Neuropsychiatric presentations for which immunosuppressive therapy was initiated (n = 101)
Laboratory results	
ESR (mm/hr)	34 [14 – 51]
Low C3 and/or C4	48 (48)
Antinuclear antibodies	86 (85)
Anti-dsDNA	42 (42)
Anti-Smith	12 (12)
Lupus anticoagulant	31 (31)
Anti-β2-GP1 IgM/IgG[a]	12 (12)
Anti-cardiolipin IgM/IgG	14 (14)
MRI	
Brain	
Normal[b]	17 (17)
WMH	29 (29)
Infarct(s)	37 (37)
Global atrophy	13 (13)
Edema	5 (5)
Hemorrhage	5 (5)
Myelum	
Myelopathy	6 (6)

Results are presented as n (%), median [IQR]
[a] Unavailable for 26 events [b] Of which events with diagnosis retraction at follow-up: 2/17
dsDNA = double stranded DNA, β2-GP1 = beta-2-glycoprotein-1, ESR = erythrocyte sedimentation rate, WMH = white matter hyperintensities

NPSLE manifestations

Attribution to an inflammatory NPSLE flare was present in 70% of events and attribution to a combined flare (inflammation and ischemia) in 30% (*Table 3*). The most common NPSLE syndromes according to the 1999 ACR case definitions for NPSLE were cognitive dysfunction (50%) and cerebrovascular disease (30%). Cerebrovascular disease (CVD) was present in combination with at least one other NP manifestation. Hence, not necessarily the cerebrovascular disease itself, but the combination with the other manifestation (such as cognitive dysfunction, cranial neuropathy, polyneuropathy) led to the consideration of the presence of inflammation. In other cases (n= 10), cerebral vasculitis was present, which was diagnosed based on radiological, serological and clinical observations. Imaging showed signs of inflammation with secondary ischemia, leading to the (additional) diagnosis of cerebrovascular disease. These 30 individuals with CVD reflect the same individuals as the combined NPSLE phenotype. In 13 events with 26 NP manifestations (13%), the diagnosis of NPSLE was retracted at follow-up. Of these events, ten were cognitive dysfunction, sometimes in combination with other symptoms (mood disorder: n=2, sensibility disorder: n=1, extreme headache: n=1) and the other three patients presented with chorea (n=1), cerebral vasculitis (n=1) and polyneuropathy (n=1). The diagnosis changed to solely ischemic NPSLE (n=2), vascular damage unrelated to SLE (n=1), primary psychiatric disorder (n=1), meningioma in the patient with suspected cerebral vasculitis (n=1), polyneuropathy of other origin (n=1) and functional neurological disorder (n=1). In the remaining patients (n=6), no clear alternative diagnosis was present, but often psychiatric comorbidity, such as depressive symptoms and coping problems were present.

Table 3 NPSLE manifestations (n=195) in 95 patients with 101 events for which immunosuppressive treatment was initiated

	Neuropsychiatric events for which immunosuppressive therapy was initiated (n = 101)
NPSLE phenotype	
Inflammatory	70 (70)
Combined (inflammatory + ischemic)	31 (30)
1999 ACR NPSLE syndromes	
Aseptic meningitis	1 (1)
Cerebrovascular disease	31 (30)
Demyelinating syndrome	0 (0)
Headache	11 (11)
Movement disorder (chorea)	4 (4)
Myelopathy	11 (11)
Seizure disorders	8 (8)
Acute confusional state	10 (10)
Anxiety disorder	2 (2)

Cognitive dysfunction	50 (50)
Mood disorder	15 (15)
Psychosis	8 (8)
Acute inflammatory demyelinating polyneuropathy	0 (0)
Autonomic disorder	1 (1)
Mononeuropathy	2 (2)
Myasthenia gravis	0 (0)
Neuropathy, cranial	9 (9)
Plexopathy	0 (0)
Polyneuropathy	8 (8)
Other than ACR1999 syndromes	**24 (24)**
Cerebral vasculitis	10 (10)
Organic brain syndrome/lethargy	4 (4)
(Pyramidal) walking disorder	4 (5)
Ocular problems, other	2 (2)
Increased cranial pressure	1 (1)
Paresis left arm and dysarthria	1 (1)
Motor disorder left arm	1 (1)
Apraxia	1 (1)

Results are presented as n (%)

Immunosuppressive treatment

In most inflammatory NPSLE events, induction and maintenance treatment was initiated (73%, *Table 4*). In the other events, only induction treatment (24%) or treatment without specific induction or maintenance phase (3%) was given. Most common treatment regimens were prednisone (97%) most often 1mg/kg/day with tapering scheme of 10mg/month, methylprednisolone (53%) 1000mg for 3 days, azathioprine (49%) with a target dose of 2mg/kg/day for one year and IV cyclophosphamide (42%) according to the National Institute of Health (NIH) protocol (750mg/m2 monthly for six months followed by quarterly up to 24 months)) or Euro-Lupus protocol (500mg biweekly for 12 weeks).[22,23] In general, prednisone and methylprednisolone were used as induction therapy, frequently in combination with cyclophosphamide. Continuation with cyclophosphamide or azathioprine were generally used as maintenance therapy, and in a smaller number of patients mycophenolate mofetil (MMF) (12%). An overview of what type of treatment and which medications were (originally) initiated per NPSLE manifestation are provided in *Supplementary Table S1*.

Table 4 NPSLE manifestations (n=195) in 95 patients with 101 events for which immunosuppressive treatment was initiated

	Neuropsychiatric events for which immunosuppressive therapy was initiated (n = 101)
Treatment regimen	
Induction	24 (24)
Induction and maintenance	74 (73)
General	3 (3)
Type of medication	
Methylprednisolone	54 (53)
Prednisone	98 (97)
Cyclophosphamide	43 (42)
NIH, 6x	*29 (67)*
NIH, complete (12x)	*10 (23)*
Euro-Lupus	*4 (10)*
Azathioprine	49 (49)
Mycophenolate mofetil	12 (12)
Biological	3 (3)
Rituximab	*2 (2)*
Belimumab	*1 (1)*
Other	4 (4)
IVIG	*2 (2)*
Methotrexate	*1 (1)*
Cyclosporin	*1 (1)*
Concomitant treatment*	
Hydroxychloroquine	66 (65)
Antiplatelet	54 (53)
Anticoagulant	18 (18)

Results are presented as n (%)

IVIG = intravenous immune globulin; NIH = National Institute of Health

*Treatment already present at time of presentation with NP symptoms or started for ischemic manifestations

Primary outcome

Clinical outcome of patients treated with immunosuppressive therapy for NP manifestations

Short-term follow-up (induction therapy/0-6 months) was available for 100/101 events and demonstrated improvement in most events (resolved: 22%, much improved: 29%, improved: 22%), no change in 21% and worsening in 6 events (worse: 5%, much worse: 1%) (see *Figure 1A*).

Long-term follow-up (maintenance therapy/7-24 months) was available for 78/101 events and demonstrated improvement in most events (resolved: 28%, much improved: 28%, improved: 14%), no change in 17%, worsening in 10% (worse: 9%, much worse: 1%) and death in two patients (3%). In one case, the cause of death was unknown (patient age: 54 years), while in the other patient the cause of death was sepsis during cyclophosphamide treatment (patient age: 37 years).

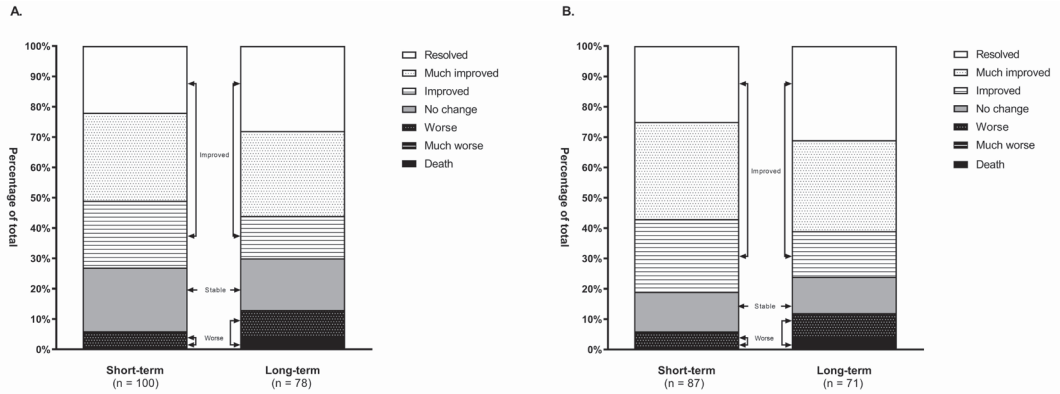
No large differences in clinical outcome were observed between individuals with an inflammatory NPSLE phenotype compared to a combined NPSLE phenotype.

Secondary outcomes related to clinical outcomes

Patients with retracted diagnosis

In patients in which the diagnosis of inflammatory NPSLE was retracted (n = 13), both short- and long-term clinical outcome were generally worse. On the short term, worsening was present in 1/13 events, no change in 10/13 events and improvement in 2/13 events. On the long term, worsening was present in 1/13, no change in 5/13, improvement in 1/13 and unknown outcomes in 6/13 events. Outcomes excluding patients with a retracted diagnosis are presented in *Figure 1B*.

Figure 1 Clinical outcomes of inflammatory NPSLE with immunosuppression: all patients (A) and patients without a retracted diagnosis (B)



Short-term outcome was defined as outcome of the induction therapy or six months (available for n = 100 (A) and 87 (B) respectively), long-term outcome was defined as outcome of the maintenance therapy until two years or between seven months - two years (available for n = 78 (A) and 71 (B) respectively)

Patients with vs without clinical improvement

Characteristics of patients with and without improvement of NP symptoms (Likert scale >4 and ≤4 respectively) on short-term were compared. A clinical improvement was present in 73 patients (73%) and absent in 27 patients (27%) at short-term follow-up. In patients lacking improvement, the diagnosis NPSLE was retracted in 11/27 (41%). The remaining patients showing no improvement of NP symptoms on short-term (n = 16) had a similar age (mean (SD): 43 ± 11 vs 41 ± 15 years), but were more often male (19% vs 13%) and a longer disease duration

(median (IQR): 4 (2 –11) vs 1 (0 – 7) than those that did improve. Treatment was altered in some of the patients that did not improve over time (see paragraph "*Insufficient improvement or worsening*"). In others, damage was considered irreversible based on amongst others imaging modalities and treatment was not altered.

At long-term follow-up, improvement of NP symptoms was present in 55 patients (71%) and absent in 23 patients (29%). In 6/23 of these patients (26%), the diagnosis NPSLE was retracted. Remaining patients without clinical improvement (n = 17) at long-term follow-up had a similar sex distribution (12 vs 13% male), were slightly older (age (mean (SD)): 44 ± 12 vs 39 ± 14 years) and had a longer disease duration (median (IQR): 6 (2 –13) vs 2 (0 – 9) years.

In *Supplementary Table S2*, improvement at short- and long-term follow-up is depicted separately for all NP manifestations. Polyneuropathy, mood disorder, anxiety disorder and seizure disorder showed worse outcomes on short- and long-term.

Change in outcome between short- and long-term follow-up

In 77 patients, both short- and long-term outcome were available. In 54/77 patients the outcome did not change between short- and long-term follow-up (41/54: improvement, 11/54 no change and 2/54 worsening). In 13/77 patients, the outcome improved between short- and long-term follow-up and in 10/77 patients the outcome worsened.

Secondary outcomes related to treatment alteration

In 38 events, treatment alteration took place. Reasons for alteration were side-effects in twelve events (two with >1 side-effect), insufficient improvement or worsening in ten, relapse in eight, change of diagnosis in four and various reasons (such as patient preference) in four events.

Side-effects

In 5/43 (12%) of events in which cyclophosphamide was initiated, treatment was altered because of side-effects (severe liver disorder (n = 1), gastrointestinal (GI) (n = 2), mood disorder (n = 1) and hyperhidrosis (n = 1)). 6/49 (12%) switched from azathioprine or preliminarily stopped treatment because of GI side-effects (n = 5) and hepatic disorder (n = 1). One patient stopped treatment with MMF because of GI side-effects and two stopped treatment with prednisone (palpitations: n = 1, hyperglycaemia and muscle aches, n = 1).

Insufficient improvement or worsening

Insufficient improvement or worsening leading to a treatment alteration was present in ten events: cerebral vasculitis (n = 2), polyneuropathy (n = 2), psychosis (n = 1), transverse myelitis (n = 1), epilepsy (n = 1), apraxia (n = 1), often in combination with cognitive dysfunction. Cognitive dysfunction was the main presentation in two events. In most events (n = 8), insufficient improvement or worsening was observed after induction or during maintenance treatment and treatment was intensified to cyclophosphamide (n = 4) or rituximab (n = 3) or treatment switched to azathioprine (n = 1). Of the 10 events with initial insufficient improvement or worsening, long-

term follow-up showed improvement in 5/10, stable disease in 3/10 and worsening in 2/10.

Relapse

Symptom relapses occurred in eight events. Most relapses occurred during tapering (n = 4) of prednisone treatment, within six months of initiating therapy. NPSLE manifestations in these events were cerebral vasculitis (n = 1), stroke like symptoms (n = 1), cognitive disorder and mood disorder (n = 1) and lupus headache (n=1). In three events, relapse occurred within three months after stopping prednisone induction therapy. Clinical presentations in these events were chorea (n = 1), transverse myelitis (n = 1) and cognitive disorder (n = 1). One individual presenting with headache and lethargy had a relapse during maintenance treatment with azathioprine (n = 1).

Of the events resulting in a relapse (n = 8), long-term follow-up showed improvement in half of the cases, worsening compared to the initial presentation in three cases and for one case, the outcome remained unknown.

Secondary outcome: comparing treatment regimens

The type of therapy prescribed per NPSLE manifestation is provided in *Supplementary Table S2*. At least 50% of all manifestations were treated with a combination of induction and maintenance therapy, with the exception of psychosis (38%). Long-term clinical outcomes of manifestations with induction and maintenance versus other treatment strategies were largely similar (*Supplementary Table S1*). Only 1/24 patients treated solely with induction therapy showed worsening of symptoms, for which treatment was altered.

DISCUSSION

We present our experience of over a decade of treating patients in which NPSLE symptoms were attributed to inflammatory origin and demonstrate that both short- and long-term clinical outcomes are generally good; improvement was observed in around 70% of patients presenting with severe NP symptoms requiring immunosuppressive treatment.

In this study, we show the types of NP manifestations present in 95 patients with 101 events in which inflammatory NPSLE was suspected. In patients with a certain diagnosis of NPSLE, the most common NPSLE manifestations were severe cognitive dysfunction (often in combination with other manifestations), cerebrovascular disease and manifestations not part of the 1999 ACR case definitions for NPSLE. The high number of these 'other' manifestations (23%), such as cerebral vasculitis, is noteworthy and nearly all of these patients responded well to immunosuppressive therapy. This underlines the question whether the current 1999 ACR case definitions still hold or should be updated.[24] In 13 patients, diagnosis altered because of various reasons. In some patients, the lack of response to immunosuppressive therapy contributed to the retraction of the diagnosis. One could argue that by retracting diagnosis in case of a lack of therapy response, refractory NPSLE might have been overlooked and circular reasoning is present. However, in these patients diagnostic uncertainty regarding attribution to SLE was often present before

treatment initiation based on the clinical presentation, most commonly cognitive dysfunction. In some cases, (serological) signs of inflammation were present, but the main reason for treatment initiation was the lack of a clear alternative diagnosis. Treatment was initiated in these cases as proof of principal and to avoid potential damage. Therefore, we deem refractory NPSLE unlikely.

Several treatment recommendations for inflammatory NPSLE exist, based on the limited clinical evidence available.[11,12] Steroids are considered the cornerstone of treatment of inflammatory NPSLE and cyclophosphamide is recommended depending on the severity and type of symptoms. In most severe manifestations, such as aseptic meningitis, myelopathy and acute confusional state, both methylprednisolone and cyclophosphamide were initiated. However, in other severe manifestations, such as psychosis and cerebral vasculitis, (methyl)prednisolone was usually sufficient for a swift recovery and no cyclophosphamide was initiated. This emphasizes the need for large studies to find the optimal treatment for each type of NPSLE manifestation.
Apart from the treatment type, the optimal treatment duration also needs to be further elucidated. In our cohort, most patients received a combination of induction and maintenance therapy, but outcomes were generally favourable with solely induction therapy as well. Seeing the observational design of this study, this might be the result of confounding by indication: shorter treatment regimens in patients with more and quick improvement. It does, however, indicate that even severe manifestations might not always require maintenance therapy over a longer period of time.

Most patients showed an improvement of their NP manifestations over time, usually already at short-term follow-up. No study has previously provided a general overview of outcomes of patients with NPSLE of an inflammatory origin. Observational studies with outcomes after specific immunosuppressive therapies in patients with NPSLE report response rates varying from approximately 30 – 100%, depending on the type of therapy, manifestation and outcome measure.[12] In our cohort, 70% of patients showed clinical improvement, and after excluding patients with retracted diagnoses this was around 75%. This percentage is similar to the previously reported improvement rate of 74% after immunosuppressive treatment in 35 patients with major NPSLE.[25] This study reported improvement of NP symptoms based on disease activity scores (amongst others SLEDAI-2K) rather than outcomes focusing specifically on the NP symptoms; therefore, the results are not directly comparable. Although most patients showed improvement over time in our cohort, complete resolution of symptoms was only present in approximately 25% of all events. Often, minor NP symptoms persisted at follow-up, which patients would mostly observe in case of fatigue or stress. However, some manifestations showed overall lower rates of improvement: seizure disorder, movement disorder, polyneuropathy, cognitive dysfunction and mood disorder. Cognitive dysfunction and mood disorders are often multifactorial, which may lead to limited improvement after immunosuppressive therapy.[26]

Seizure and polyneuropathy may have persisted due to irreversible damage caused by inflammation. Further investigation and larger cohorts are necessary to explain these differences in outcome between NPSLE manifestations.

Future clinical trials to assess immunosuppressive treatment regimens in NPSLE should focus on manifestations that can be diagnosed uniformly in different centres, such as transverse myelitis and cerebral vasculitis. A multicentre trial is clearly required, as our study indicates that <10 patients/year require immunosuppressive treatment for a diffuse range of NPSLE presentations, even in a national tertiary referral centre in a country with 17 million inhabitants. Prioritizing the use and dosage of cyclophosphamide in clinical trials is important, as cyclophosphamide influences fertility and mainly patients of childbearing age suffer from NPSLE. We suggest comparing the lower dosed cyclophosphamide regimen Euro-Lupus to the NIH regimen, which has also been proven successful in lupus nephritis.[27]

Our study has several strengths. This is the largest overview of patients with an inflammatory origin of NP symptoms to date and the first to provide detailed information on clinical outcomes. As the inflammatory origin was attributed in a multidisciplinary setting including reassessment, the patients are well characterized and probably correctly diagnosed.

There are several limitations to this study. First, the attribution of symptoms to major inflammation is subjective. Although we used "the golden" clinical standard, multidisciplinary assessment, imaging, neuropsychological testing and follow-up, there is no definitive attribution and the extend of misclassification cannot be assessed. Second, clinical outcomes were retrospectively obtained from medical files and not uniformly registered during follow-up visits. In addition, long-term follow-up visits did not only take place in the NPSLE clinic, but also at regular rheumatology or neurology consultations. However, by assessing the clinical outcomes by two readers, we reduced subjectivity and increased certainty regarding the clinical outcomes. As no validated outcome tool exists for NPSLE, we used a physician global assessment tool (the Likert scale) to assess clinical outcomes. In the future, the use of a standardized tool would be preferable. Third, not all patients had multiple follow-up visits, and therefore long-term clinical outcome was incomplete. We strongly assume that we have missed favourable rather than unfavourable outcomes, as the referral threshold to our tertiary centre is low and short-term clinical outcomes were generally good in patients with a certain NPSLE diagnosis lacking long-term follow-up assessment (improvement: 15/16 patients). Hence, an underestimation of the long-term clinical outcome is most likely present. Furthermore, long-term follow-up was limited to a maximum of two years because this is the length of regular follow-up in the NPSLE clinic. Relapses after two years may have therefore been missed. In addition, the exact contribution of the immunosuppressive treatment to clinical improvement at follow-up is uncertain due to the study design as well as the presence of concomitant treatment (anti-epileptics, antidepressants) in some patients. Last, as our NPSLE clinic is a tertiary referral centre, only the most severe cases of inflammatory NPSLE may have been observed. Even so, we report improvement in most cases with inflammatory NPSLE.

In conclusion, most patients with inflammatory NPSLE, one of the most severe organ manifestations of SLE, improve after immunosuppressive treatment.

ACKNOWLEDGEMENTS

We thank all patients and physicians that have contributed to the NPSLE clinic in the past fifteen years.

SUPPLEMENTARY MATERIALS

Supplementary Tables 1 and 2 are available through: https://lupus.bmj.com/

REFERENCES

1. Bertsias GK, Ioannidis JPA, Boletis J, et al. EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. *Ann Rheum Dis*. 2008;67(2):195-205.
2. Bertsias GK, Boumpas DT. Pathogenesis, diagnosis and management of neuropsychiatric SLE manifestations. *Nat Rev Rheum*. 2010;6(6):358-67.
3. Bertsias GK, Ioannidis JPA, Aringer M, et al. EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs. *Ann Rheum Dis*. 2010;69(12):2074-82.
4. Clarke DM, Currie KC. Depression, anxiety and their relationship with chronic diseases: a review of the epidemiology, risk and treatment evidence. *MJA*. 2009(190):S54-S60.
5. Hanly JG, Urowitz MB, Su L, et al. Prospective analysis of neuropsychiatric events in an international disease inception cohort of patients with systemic lupus erythematosus. *Ann Rheum Dis*. 2010;69(3):529-35.
6. Magro-Checa C, Zirkzee EJ, Beaart-van de Voorde LJJ, et al. Value of multidisciplinary reassessment in attribution of neuropsychiatric events to systemic lupus erythematosus: prospective data from the Leiden NPSLE cohort. *Rheum (Oxford)*. 2017;56(10):1676-83.
7. Bortoluzzi A, Scirè CA, Govoni M. Attribution of Neuropsychiatric Manifestations to Systemic Lupus Erythematosus. *Front in Med*. 2018;5.
8. Hanly JG, Kozora E, Beyea SD, Birnbaum J. Nervous System Disease in Systemic Lupus Erythematosus: Current Status and Future Directions. *Arthritis Rheumatol*. 2018;71(1):33-42.
9. Stojanovich L, Stojanovich R, Kostich V, Dzjolich E. Neuropsychiatric lupus favourable response to low dose i.v. cyclophosphamide and prednisolone (pilot study). *Lupus*. 2003;12:3-7.
10. Barile-Fabris L. Controlled clinical trial of IV cyclophosphamide versus IV methylprednisolone in severe neurological manifestations in systemic lupus erythematosus. *Ann Rheum Dis*. 2005;64(4):620-5.
11. Magro-Checa C, Zirkzee EJ, Huizinga TW, Steup-Beekman GM. Management of Neuropsychiatric Systemic Lupus Erythematosus: Current Approaches and Future Perspectives. *Drugs*. 2016;76(4):459-83.
12. Papachristos DA, Oon S, Hanly JG, Nikpour M. Management of inflammatory neurologic and psychiatric manifestations of systemic lupus erythematosus: A systematic review. *Semin Arthritis Rheu*. 2021;51(1):49-71.
13. Nikolopoulos D, Fanouriakis A, Bertsias G. Treatment of neuropsychiatric systemic lupus erythematosus: clinical challenges and future perspectives. *Expert Rev Clin Imm*. 2021;17(4):317-30.
14. Govoni M, Hanly JG. The management of neuropsychiatric lupus in the 21st century: still so many unmet needs? *Rheumatology*. 2020;59(Supplement_5):v52-v62.

15. Zirkzee EJ, Steup-Beekman GM, van der Mast RC, et al. Prospective study of clinical phenotypes in neuropsychiatric systemic lupus erythematosus; multidisciplinary approach to diagnosis and therapy. *J Rheumatol*. 2012;39(11):2118-26.
16. Monahan RC, Fronczek R, Eikenboom J, et al. Mortality in patients with systemic lupus erythematosus and neuropsychiatric involvement: A retrospective analysis from a tertiary referral center in the Netherlands. *Lupus*. 2020;29(14):1892-901.
17. Hochberg MC. Updating the American College of Rheumatology Revised Criteria for the Classification of Systemic Lupus Erythematosus. *Arthritis Rheumatol*. 1997;40:1725.
18. Gladman DD, Ibanez D, Urowitz MB. Systemic Lupus Erythematosus Disease Activity Index 2000. *J Rheumatol*. 2002;29:288-91.
19. Gladman DD, Ginzler E, Goldsmith C, et al. The development and initial validation of the Systemic Lupus International Collabarating Clinic/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheumatol*. 1996;39:363-9.
20. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum*. 1999;42:599-608.
21. Cohen JA. A coefficient of agreement for nominal scales. *Educ Psychol Meas*. 1960;20:37-46.
22. Gourley MF, Austin HA, Scott D, et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. *Ann Intern Med*. 1996;125(7):549-57.
23. Klippel JH. Indications for, and use of, cytotoxic agents in SLE. Baillieres Clin Rheumatol. 1998;12(3):511-27.
24. Vivaldo JF, de Amorim JC, Julio PR, et al. Definition of NPSLE: Does the ACR Nomenclature Still Hold? *Front Med (Lausanne)*. 2018;5:138.
25. Bortoluzzi A, Padovan M, Farina I, et al. Therapeutic strategies in severe neuropsychiatric systemic lupus erythematosus: experience from a tertiary referral centre. *Reumatismo*. 2012;64(6):350-9.
26. Barraclough M, McKie S, Parker B, et al. Altered cognitive function in systemic lupus erythematosus and associations with inflammation and functional and structural brain changes. *Ann Rheum Dis*. 2019;78(7):934-40.
27. Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, Garrido EdR, Danieli MG, et al. Immunosuppressive therapy in lupus nephritis: The Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. *Arthritis Rheumatol*. 2002;46(8):2121-31.