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ABSTRACT

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

Methods All patients with SLE visiting the Leiden University Medical Centre NPSLE clinic between 2007 and 2021 receiving immunosuppressive therapy for neuropsychiatric symptoms were included. Clinical, immunological and radiological information was collected in as standardised way during a 1-day multidisciplinary assessment. In a multidisciplinary consensus meeting, the presence of NPSLE and 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 out of 398 (24%) patients visiting the NPSLE clinic between 2007 and 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 2 mg/kg daily) (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 out of 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.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Neuropsychiatric manifestations of inflammatory origin in patients with SLE (inflammatory NPSLE) are rare, leading to a lack of knowledge regarding type of manifestations, treatment regimens and clinical prognosis.

WHAT THIS STUDY ADDS

⇒ In this study, we demonstrate that 70% of patients with inflammatory NPSLE show improvement over time after immunosuppressive treatment.

⇒ In addition, we show that the 1999 American College of Rheumatology (ACR) case definitions for NPSLE insufficiently reflect the variety of inflammatory NPSLE manifestations.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study endorses the need to revisit the 1999 ACR case definitions for NPSLE and facilitates communication with patients regarding the treatment and prognosis of inflammatory NPSLE.

INTRODUCTION

Neuropsychiatric SLE (NPSLE) is a complex and heterogeneous 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 hypothesised 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 (eg, 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 standardised 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 and 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 1 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 MRI scan are performed. Furthermore, evaluation of cerebral spinal fluid 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.

Follow-up

In general, follow-up visits take place 6 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 2 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 electronic 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/ischaemic/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, California, USA). Anti-Sm (IgG) and anti-cardiolipin (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 and 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 analysers (Stago, Parsippany, New Jersey, 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 standardised brain MRI scan was performed in all patients using a Philips Achieva 3 T MRI scanner (Philips Healthcare, Best, the Netherlands). The standardised protocol consisted of a T1-weighted, T2-weighted, fluid attenuated inversion recovery, diffusion weighted imaging and susceptibility weighted imaging sequence. The presence of abnormalities on brain MRI was 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 to 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 (IQR 8–9) and 7.75 (IQR 6.5–8.5) for long-term outcomes.

The primary outcome was the average PGA at short-term 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 2 years.

Patient and public statement

No patients were involved in the design, conduct or reporting of this project.

Statistical analysis

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

RESULTS

Study population

Of the 398 patients with SLE referred to the NPSLE clinic between 2007 and 2021, 95 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. Five out of 95 patients received immunosuppressive therapy more than once for NP symptoms (4 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 out of 101 events (42%), immunosuppressive therapy was received for a median duration of 1 month (IQR 0.5–3.0) prior to the NPSLE clinic visit.

In the 101 events, mean ESR was 34 (IQR 14–51) at the 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 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%).

NPSLE manifestations

Attribution to an inflammatory NPSLE flare was present in 70% of events and attribution to a combined flare (inflammation and ischaemia) 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

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 ACR SLE criteria	
Malar rash	32 (34)
Discoid rash	14 (15)
Photosensitivity	38 (40)
Oral ulcers	34 (35)
Non-erosive arthritis	64 (67)
Pleuritis or pericarditis	28 (29)
Renal disorder	27 (28)
Neurological disorder	13 (14)
Haematological disorder	49 (52)
Immunological 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; 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/hour)	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*	12 (12)
Anti-cardiolipin IgM/IgG	14 (14)
MRI	
Brain	
Normal†	17 (17)
WMH	29 (29)
Infarct(s)	37 (37)
Global atrophy	13 (13)
Oedema	5 (5)
Haemorrhage	5 (5)
Myelum	
Myelopathy	6 (6)

Results are presented as n (%), mean±SD or median (IQR).
*Unavailable for 26 events.
†Of which events with diagnosis retraction at follow-up: 2 out of 17.
dsDNA, double-stranded DNA; ESR, erythrocyte sedimentation rate; WMH, white matter hyperintensities; β2-GP1, beta-2-glycoprotein-1.

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 ischaemia, 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, 10 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 ischaemic 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.

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 1 mg/kg/day with tapering scheme of 10 mg/month, methylprednisolone (53%) 1000 mg for 3 days, azathioprine (49%) with a target dose of 2 mg/kg/day for 1 year and intravenous cyclophosphamide (42%) according to the National Institute

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+ischaemic)	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 (%).
ACR, American College of Rheumatology; NPSLE, neuropsychiatric SLE.

Table 4 Immunosuppressive treatment regimens in 95 NPSLE patients with 101 NPSLE events

	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)*
Ciclosporin	*1 (1)*
Concomitant treatment*	
Hydroxychloroquine	66 (65)
Antiplatelet	54 (53)
Anticoagulant	18 (18)

Results are presented as n (%).
*Treatment already present at time of presentation with NP symptoms or started for ischaemic manifestations.
IVIG, intravenous immune globulin; NIH, National Institute of Health; NP, neuropsychiatric; NPSLE, neuropsychiatric SLE.

of Health (NIH) protocol (750 mg/m^2 monthly for 6 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 was 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 online supplemental table S1.

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 out 101 events and demonstrated improvement in most events (resolved: 22%, much improved: 29%, improved: 22%), no change in 21% and

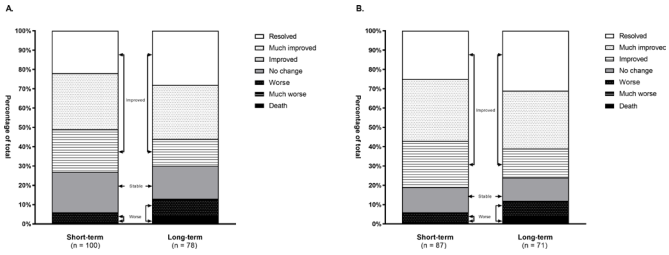

Figure 1 Clinical outcomes of inflammatory NPSLE with immunosuppression: all patients (A) and patients without a retracted diagnosis (B). Short-term outcome was defined as outcome of the induction therapy or 6 months (available for n=100 (A) and 87 (B), respectively); long-term outcome was defined as outcome of the maintenance therapy until 2 years or between 7 months and 2 years (available for n=78 (A) and 71 (B), respectively).

worsening in six events (worse: 5%, much worse: 1%) (see figure 1A).

Long-term follow-up (maintenance therapy/7–24 months) was available for 78 out of 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 with 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-term and long-term clinical outcomes were generally worse. On the short term, worsening was present in 1 out of 13 events, no change in 10 out of 13 events and improvement in 2 out of 13 events. On the long term, worsening was present in 1 out of 13, no change in 5 out of 13, improvement in 1 out of 13 and unknown outcomes in 6 out of 13 events. Outcomes excluding patients with a retracted diagnosis are presented in figure 1B.

Patients with versus 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 out of 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 the Insufficient improvement or worsening section). In others, damage was considered irreversible based on among other 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 out of 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 online supplemental table S2, improvement at short-term 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-term and long-term follow-up

In 77 patients, both short-term and long-term outcomes were available. In 54 out of 77 patients, the outcome did not change between short-term and long-term follow-up (41/54: improvement, 11/54 no change and 2/54 worsening). In 13 out of 77 patients, the outcome improved between short-term and long-term follow-up and in 10 out of 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 12 events (two with >1 side effect), insufficient improvement or worsening in 10, relapse in 8, change of diagnosis in 4 and various reasons (such as patient preference) in 4 events.

Side effects

In 5 out of 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)). Six out of 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 10 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 out of 10, stable disease in 3 out of 10 and worsening in 2 out of 10.

Relapse

Symptom relapses occurred in eight events. Most relapses occurred during tapering (n=4) of prednisone treatment, within 6 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 3 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 with 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 online supplemental 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 (online supplemental table S1). Only 1 out of 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-term 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 emphasises 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% to 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 (among 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. Prioritising 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 characterised 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 standardised 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 2 years because this is the length of regular follow-up in the NPSLE clinic. Relapses after 2 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. Lastly, 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.

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