Lifting the fog of neuropsychiatric lupus

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General introduction

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease, characterized by the loss of tolerance against self-antigens, inducing the production of autoantibodies and deposition of immune complexes in tissues.[1] Genetic factors, environmental factors and hormonal factors interplay in the development and activity of SLE.[2] The estimated incidence rate of SLE is 1-10 per 10000 person years and the estimated prevalence rate ranges from 20-70 per 10.000 persons.[3] The disease is strongly female predominant, with an average female-to-male ratio of approximately 9:1, which fluctuates with age.[4] The incidence of SLE is higher in black, Asian, and Hispanic persons.[4] In these persons, disease activity and severity are often higher, leading to an increased morbidity and mortality.[5] As SLE can affect nearly any organ in the body, clinical manifestations and patterns of organ involvement are extremely diverse.[1] Both the central and peripheral nervous system may be affected in patients with lupus, leading to a myriad of neuropsychiatric manifestations.

Neuropsychiatric manifestations in systemic lupus erythematosus

The first description of neuropsychiatric (NP) involvement in SLE dates back to 1872, in which a patient was presented who showed "impaired consciousness with continuation into coma".[6] In the following decades (1895-1903), multiple articles were published in which NP manifestations were mentioned as part of systemic involvement of SLE.[7-9] It was hypothesized that these manifestations were the result of vasculitis of the nervous system.[10] Although this hypothesis was later partially refuted by neuropathological studies[11], these articles demonstrate the early recognition of NP symptoms as manifestations of SLE. This recognition is also reflected by the development of the first classification criteria for SLE in 1971, where several NP manifestations (seizures and psychosis) were already considered part of the criteria.[12] Concerns were later expressed that many neurologic manifestations specific for SLE were omitted.[13] In 2012, additional neurological manifestations were included in new classification criteria: mononeuritis multiplex, myelitis, peripheral or cranial neuropathy and acute confusional state.[13] Interestingly, in the most recent classification criteria published in 2019, initially none of the individual NP items made the inclusion threshold.[14] Nevertheless, the importance of NP manifestations of SLE was emphasized by experts and patient representatives, which led to the inclusion of a composite central nervous system criterion: seizure, psychosis and acute confusional state.[15] It is unclear how these criteria were created and if other manifestations were considered as well.[14,16] Whether the 2019 classification criteria correctly classify patients with SLE and neuropsychiatric symptoms, therefore remains to be elucidated.

Challenges in diagnosing NPSLE

Defining which NP disorders are a clinical manifestation of SLE, and could therefore be included as classification criteria, is complex. Although some manifestations may be directly related to SLE activity (NPSLE), there are many other potential underlying causes for NP symptoms in patients with SLE.[17,18] First, NP symptoms might be the consequence of immunosuppressive treatment, such as prednisone-induced psychosis or infections of the nervous system. Secondly, major organ involvement, such as renal dysfunction, may cause metabolic and electrolyte disturbances which may lead to NP symptoms, such as weakness and seizures. Thirdly, the burden of having a chronic illness may predispose to anxiety and depression.[19] Lastly, specific

symptoms, such as headache, are common in the general population and are most likely linked to other disease mechanisms. All these examples demonstrate causes of NP symptoms in patients with SLE, without being directly caused by the underlying pathomechanisms of SLE. As no clear biomarker exists to identify NP manifestations truly caused by SLE, diagnosing and studying NPSLE remains extremely difficult.

An attempt to facilitate and enhance clinical research was made by the American College of Rheumatology (ACR) in 1999, which developed nineteen case definitions of NP syndromes and symptoms in SLE.[20] Of these case definitions, twelve are disorders of the central nervous system (CNS) and seven of the peripheral nervous system. Of the CNS manifestations, eight are neurological and four psychiatric, and the manifestations are further divided into diffuse and focal abnormalities (see *Table 1*). The 1999ACR definitions include diagnostic criteria, specific diagnostic tests and criteria for exclusion for these nineteen manifestations.[20] The clinical usefulness of these criteria, however, is limited due to several reasons. First, certain case definitions lack specificity: headache, anxiety disorders, mild depression and mild cognitive dysfunction are equally common in SLE patients as in the general population.[21] Second, considerable room for interpretation is left, which has resulted in a great variation in the reported prevalence of NPSLE: 12-95%.[22] Last, the case definitions are not exhaustive, as many other neurological manifestations are reported in patients with SLE, such as thin fiber neuropathy and cerebral vasculitis. In recent years, the limitations of the 1999ACR definitions have been discussed.[23] The value of these case-definitions as first step towards a uniform approach to NPSLE is acknowledged, but it is thought that more comprehensive models are necessary to facilitate diagnosing and researching NPSLE.[23]

Table 1 Neuropsychiatric syndromes according to the 1999 American College of Rheumatology (ACR) case definitions[20]

Central nervous system	
Neurological syndromes (focal)	**Psychiatric or neuropsychological syndromes (diffuse)**
Aseptic meningitis	Acute confusional state
Cerebrovascular disease	Anxiety disorder
Demyelinating syndrome	Cognitive dysfunction
Headache	Mood disorder
Movement disorder	Psychosis
Myelopathy	
Seizure disorders	
Peripheral nervous system	
Autonomic neuropathy	
Cranial neuropathy	
Guillain-Barré syndrome	
Mononeuropathy	
Myasthenia gravis	
Plexopathy	
Polyneuropathy	

To this end, different alternatives have been proposed in the past decades. An important contribution to the diagnosis of NPSLE was made by the Systemic Lupus International Collaborating Clinics (SLICC). In 2007, SLICC created decision rules for attributing NP events to SLE.[24] In the decision rules, the following aspects are taken into account: temporal relationship, exclusion of other diagnoses, evaluation of 'non-SLE factors' and consideration of specificity of symptoms for SLE. A longer time between NP symptoms and diagnosis of SLE reduces the likelihood that the symptoms are the result of SLE: symptoms that commenced ≥6 months before SLE diagnosis are considered to be unrelated to SLE. Furthermore, other diagnoses, such as infections, metabolic disorder and side-effects of medication have to be excluded before the diagnosis of NPSLE can be made. In addition, the presence of, for example, a family history of certain neurological or psychiatric conditions argues against a relationship between the NP symptom and SLE. Lastly, NP syndromes that are also common in the general population, such as headache and mild anxiety and depression disorders are unlikely to be the result of SLE.[21] Using these SLICC decision rules, 19-38% of NP symptoms in SLE patients are attributed to NPSLE and NPSLE occurs in 6-12% of newly diagnosed SLE patients.[24]

The second significant contribution to facilitate the diagnosis of NPSLE was an attribution model developed in 2015, in which weights are assigned to the decision rules generated by SLICC.[25] In addition, points are to be awarded for factors that make the diagnosis of NPSLE more likely, such as an increased general disease activity (see *Table 2*). A score of ≥7 points generated a positive predictive value of 100% in the original study cohort and 86% in a replication cohort, whereas a score of ≤3 generated a negative predictive value of 94% and 86% respectively.[25] Although this model is a valuable asset, it does not replace the doctor's diagnosis. Because of the complexity and heterogeneity of NP symptoms in patients with SLE, multidisciplinary consultation and decision-making remains the most accurate approach of diagnosing NPSLE in clinical practice.[26]

Table 2 Neuropsychiatric syndromes according to the 1999 American College of Rheumatology (ACR) case definitions[20]

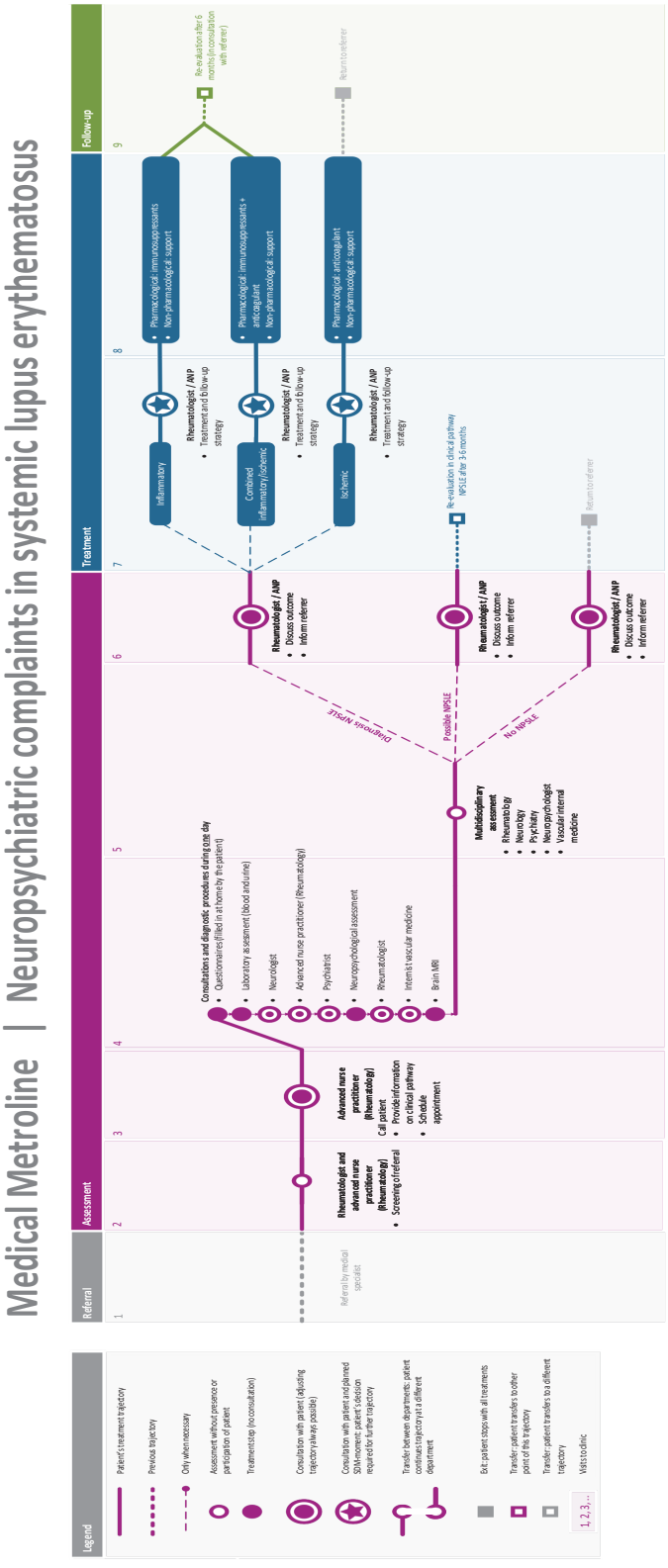
	Score
Item 1. Time of the onset of NP event with respect to SLE clinical onset	
Before (>6 months before SLE onset)	**0**
After (6 months after SLE onset)	**2**
Concomitant (within six months of SLE onset)	**3**
Item 2. Minor or non-specific NP events as defined by Ainiala *et al*[21]	
Present (i.e. minor or common NP events as proposed by Ainiala *et al*[21, a])	**0**
Absent (i.e. NP events other than those proposed by Ainiala *et al*[21, a])	**3**
Item 3.[b] Confounding factors or not SLE-related associations as defined by the ACR glossary[20]	
Present (more than one confounding factor)	**0**
Present (one confounding factor)	**1**
None or not applicable	**2**
Item 4.[b] Additional (or favoring) factors	
None or not applicable	**0**
Present (one additional or favoring factor)	**1**
Present (more than one additional or favoring factor)	**2**

[a]NP presentations deemed as minor or known to occur frequently in the normal healthy population: headaches, anxiety, mild depression, mild cognitive impairment and polyneuropathy without electrophysiological confirmation. [b]The list of confounding and favoring factors are provided in supplementary Table S1 and S2 of the original article are available at *Rheumatology* online. *NP* = neuropsychiatric.

Leiden NPSLE clinic

The NPSLE clinic of the Leiden University Medical Center (LUMC) in the Netherlands uses this approach of multidisciplinary evaluation to attribute NP symptoms to SLE. It is a tertiary referral center for patients with the (suspected) diagnosis of SLE and NP symptoms. The diagnostic work-up of patients visiting the NPSLE clinic is shown in *Figure 1*. In summary, patients are referred to the NPSLE clinic from all over the Netherlands, mainly by rheumatologists, internists and neurologists. During one day, an extensive evaluation takes place, which includes consultations by an advanced nurse practitioner, neurologist, psychiatrist, neuropsychologist, rheumatologist and internist of vascular medicine. In addition, laboratory assessment and a brain magnetic resonance imaging (MRI) scan take place on this same day. In a multidisciplinary assessment, scheduled 2-3 weeks after the assessment day, the obtained information is discussed and weighed and a consensus is reached on whether the symptoms can be attributed to SLE (NPSLE).[27] If NPSLE is considered present, the suspected underlying pathomechanism and hence the most suitable treatment for the NPSLE manifestation is discussed. These findings are communicated with the patient and referring physician. The referring physician remains in charge of the actual treatment of the patient. If deemed necessary, a follow-up for further evaluation or treatment evaluation is proposed. In some cases, this leads to an alteration of treatment regimen or even initial diagnosis. For this reason, the NPSLE diagnosis at follow-up is considered the gold standard.[26] All patients included in this thesis are part of the Leiden NPSLE clinic.

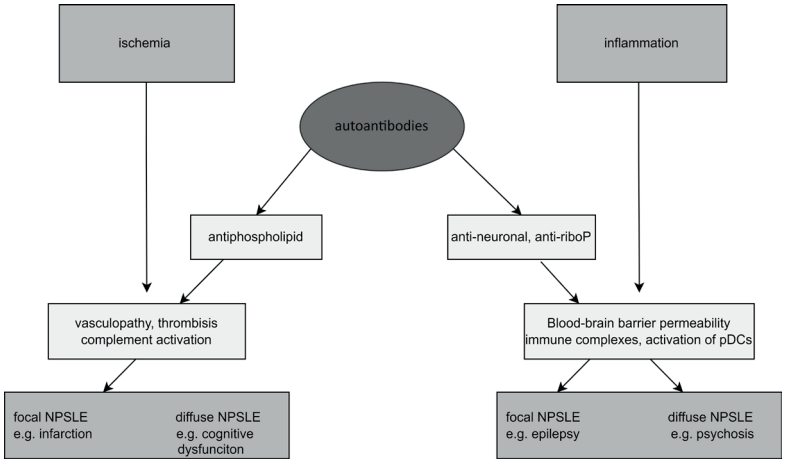
Figure 1 Evaluation procedure of patients visiting the Leiden NPSLE clinic



Pathophysiology of NPSLE

The multidisciplinary consensus meeting seeks to identify the suspected underlying pathomechanism of the NP manifestations. Although the pathophysiology of NPSLE is not fully elucidated, it is generally thought that there are two different causes of nervous system involvement in SLE: inflammatory and ischemic, as shown in *Figure 2*.

Figure 2 Different pathomechanisms may lead to NPSLE: ischemia and inflammation



A summary of different disease mechanisms leading to NPSLE. Autoantibodies play a central role in both ischemic and inflammatory manifestations. This figure is based on [28] *Anti-riboP* = antiribosomal-P; *pDCS* = plasmacytoid dendritic cells

Inflammatory NPSLE

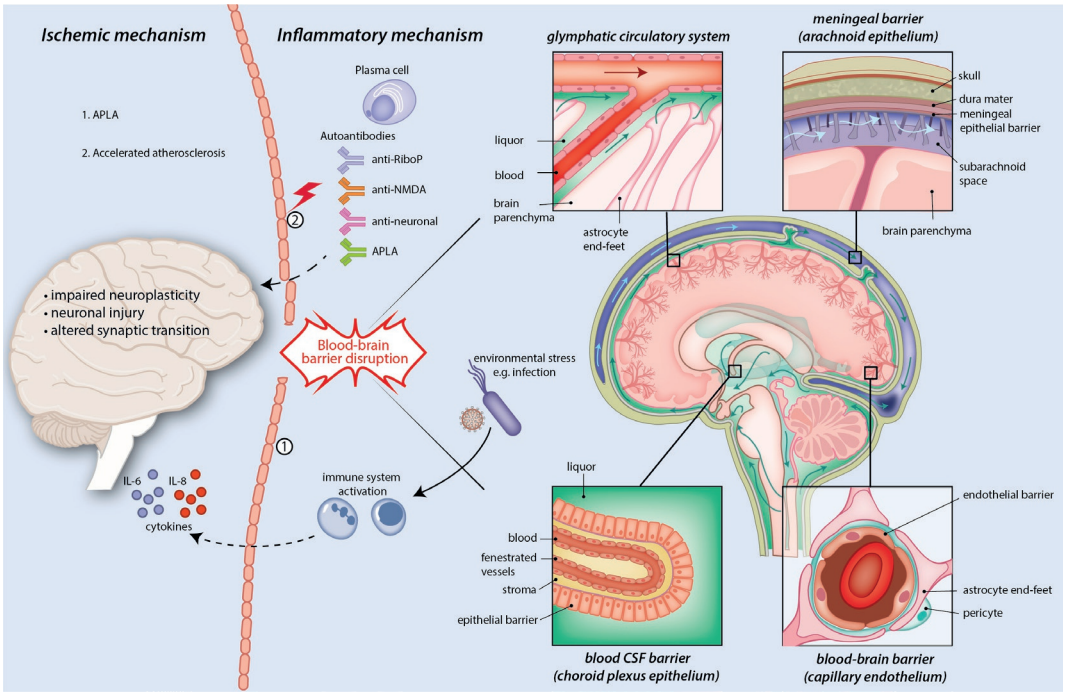
Autoantibodies are thought to play a central role in inflammatory NPSLE. Antibodies directed against many different autoantigens have been described in patients with SLE and NPSLE, but none are sensitive or specific enough to serve as a biomarker.[22,28,29] The most commonly described antibodies in the context of inflammatory NPSLE are a subgroup of anti-double stranded DNA (anti-dsDNA) antibodies and anti-ribosomal P (anti-riboP) antibodies. It has been shown that cross-reactivity between the subset of anti-dsDNA autoantibodies and parts of the N-methyl-D-aspartate receptor (NMDAR) is possible.[30] Binding of these antibodies results in neuronal damage due to an increased influx of calcium into neurons, such as in glutamate excitotoxicity. Anti-riboP antibodies can also cross-react, but with the neuronal surface P antigen (NSPA).[31] NSPA is involved in synaptic transmission and hippocampal plasticity linked to memory, which might be affected by antibody binding.

Although it has been demonstrated that autoantibodies in the serum of patients with SLE have the potential to cause damage, the question remains how these autoantibodies are able to reach the CNS. Under normal circumstances, the brain has an 'immune privilege', as the blood brain barrier enforces tight control, preventing passive diffusion of immune mediators to the CNS.[32] Based on mouse models, it is hypothesized that the blood-brain barrier may become permeable through triggers such as infection, stress and activation of endothelial cells. This may

result in the leakage of autoantibodies from patients' serum to the CNS, which has the potential to cause brain alterations and thereby cause NPSLE.[22,33] This hypothesis is supported by the increased cerebrospinal fluid (CSF)/plasma albumin ratio that has been described in patients with NPSLE.[34] The blood-brain barrier, however, is not the only location where serum and CNS may interact: other potential places of interaction are the meningeal barrier, the glymphatic circulatory system and the choroid plexus[22,33], as shown in *Figure 3*. An alternative hypothesis is that intrathecal production of autoantibodies takes place, which is supported by the presence of an elevated immunoglobulin G (IgG) index and oligoclonal bands in the CSF of NPSLE patients.[35]

Apart from the CNS, the peripheral nervous system may also be affected in patients with SLE, although this is rare and only accounts for 2-10% of all NP manifestations.[36] Autoantibodies and cross-reactivity are, as in CNS involvement, also thought to play a role in the autoimmune response against nerves. Furthermore, pro-inflammatory cytokines such as interleukin (IL) 1-B and IL-6 are found in nerve biopsies (direct immunohistochemical staining) of patients with SLE and painful neuropathies. Nociceptors can release neuropeptides that provide vasodilation and increased vascular permeability. In addition, mediators secreted by sensory neurons can attract and activate immune cells. These factors probably contribute to a chronic pain sensation.[36] However, these mechanisms describe a general process of neurogenic inflammation rather than a specific process in NPSLE patients.

Figure 3 Hypothesized pathomechanism of NPSLE



Hypothesized pathophysiology of ischemic and inflammatory NPSLE.

Ischemic NPSLE may result from APLA and increased atherosclerosis in patients with SLE. In inflammatory NPSLE, autoantibodies may reach the brain through different neuroimmune interfaces, where they can cause neuronal injury (including impaired neuroplasticity and altered synaptic transmission). In order to gain access to the brain, a disruption of the brain-barrier is required, which may be the result of external factors (such as infection) or internal factors (such as cytokines). The different brain-barriers are the glymphatic circulatory system, the meningeal barrier, the blood-CSF barrier and the blood-brain barrier. The glymphatic system consists of perivacular tunnels formed by astroglial cells and has several roles, including waste clearance and transport of nutrients and signaling molecules. It transports CSF and is connected downstream to a lymphatic network.
APLA = antiphospholipid antibodies, *Anti-NMDAR* = anti-N-methyl-D-aspartate receptor, *Anti-riboP* = antiribosomal P, *CSF* = cerebrospinal fluid; *IL* = interleukin; *SLE* = systemic lupus erythematosus.
This figure was based on [86] and [33] and developed by medical illustrator *Ron Slagter*, to whom we are very grateful.

Ischemic NPSLE

Different mechanisms are thought to lead to ischemic NPSLE: damage to small and large blood vessels, mediated by antiphospholipid antibodies (APLAs), immune complexes and leucoagglutination.[37] Non-inflammatory microangiopathy associated with ischemic stroke is the most frequent finding in the few neuropathological studies conducted in NPSLE patients.[38,39] The incidence of ischemic stroke in patients with SLE is estimated to be between 3-20%.[40] Some of these ischemic strokes can be attributed to conventional risk factors, such as hypertension and smoking. In the absence of clear risk factors, ischemia is generally considered a presentation of NPSLE, especially in the presence of APLAs.

APLAs are the most established antibodies in NPSLE and associate with focal manifestations, such as ischemic stroke and epilepsy. The most important APLAs are anticardiolipin, anti-B2-glycoprotein-I and lupus anticoagulant. Although the exact mechanism of thrombosis through APLAs has not been fully elucidated, APLAs are known to affect various aspects of the coagulation cascade.[41] APLAs can activate platelets, monocytes and endothelial cells; they can influence factors of the coagulation cascade, such as protein C, and they can trigger the complement system and interfere with the fibrinolytic system.[41] All these factors ultimately lead to an increased risk of thrombosis and thus the risk of cerebral infarction.

Combined NPSLE

In some patients, both inflammation and ischemia may be present. This can either be through the different mechanisms described previously, or through ischemia as a secondary result of inflammation, such as vasculitis.

Treatment of neuropsychiatric manifestations in SLE

The treatment of patients with NPSLE depends on the suspected underlying pathomechanism. A summary of the current treatment modalities is shown in *Figure 4*.

Inflammatory NPSLE

When an inflammatory origin of NPSLE is suspected, immunosuppressive therapy is initiated. Only one randomized controlled trial (RCT) has been conducted in patients with NPSLE, which demonstrated a benefit of a combination of cyclophosphamide and methylprednisolone for the treatment of severe NPSLE.[42] Due to the lack of RCTs, immunosuppressive treatment is mainly based on the limited clinical

experience available. To date, corticosteroids are the cornerstone in the treatment of inflammatory NPSLE because of their rapid onset of action. However, as treatment with corticosteroids has both short and long-term side effects, corticosteroid-sparing medication such as azathioprine is usually started after the initial treatment phase.[43] No official guideline regarding treatment duration exists. Severe NPSLE manifestations are usually treated with a high-dose immunosuppressant therapy for a short interval, followed by maintenance treatment for 1-2 years. Rare cases of refractory NPSLE have reportedly been treated with plasmapheresis, immunoglobulins and stem-cell therapy.[43-45] In addition, rituximab has been shown to be effective in small non-controlled trials in patients with refractory NPSLE.[46] In the future, biologicals might be more generally used in the treatment of NPSLE.[47] More knowledge regarding optimal treatment of patients with inflammatory NPSLE is necessary.

Ischemic NPSLE

The treatment of ischemic NPSLE mainly depends on the presence or absence of the antiphospholipid syndrome (APS). In the absence of APS, treatment should conform to the standard guidelines of transient ischemic attacks and cerebral infarcts, initiating antiplatelet therapy.[48] In the presence of APS, vitamin K antagonists with or without antiplatelet therapy should be initiated.[49]

Treatment of other neuropsychiatric manifestations

The treatment of non-NPSLE or non-severe NPSLE manifestations depends on the symptoms present. Examples of therapeutic options are anti-epileptics for seizures and antidepressants and psychological interventions for depressive disorders.

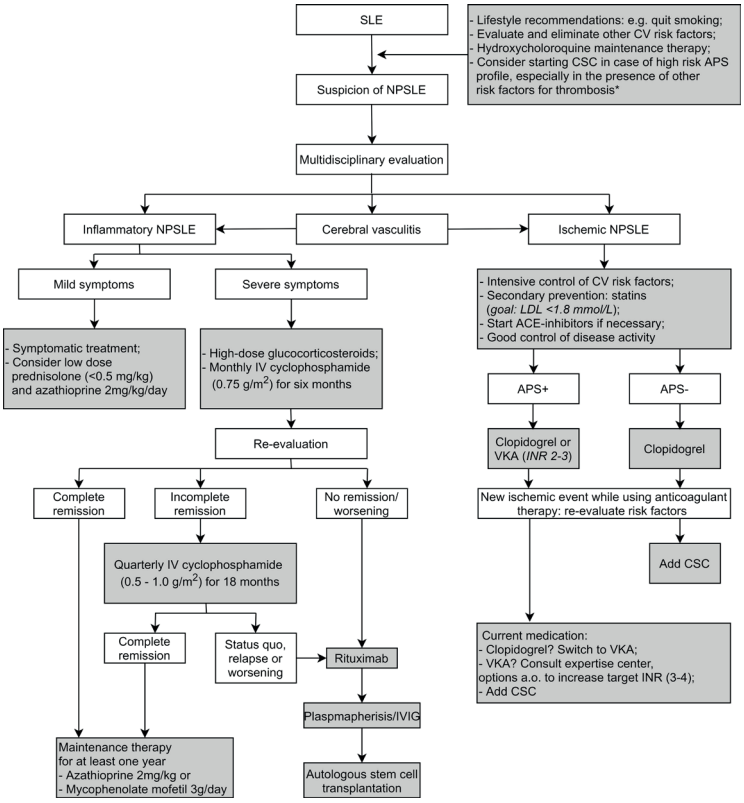
Treatment dilemmas

In clinical practice, dilemmas may arise whether immunosuppressive treatment should be initiated. As patients with a prior diagnosis of SLE might have had (intensive) immunosuppressive treatment in the past, an underlying (opportunistic) infection may be present. Seeing the potential detrimental effect of immunosuppressive treatment in this case, this possibility should be fully excluded before immunosuppressive treatment is initiated. Furthermore, as immunosuppressive therapy has many potential side-effects, it is essential to determine whether this type of therapy is truly required for the NP presentation. For example, in some patients, clear neurological symptoms such as signs of spinal cord dysfunction are present, but no objective abnormalities are found with additional investigations. How these patients should be approached and whether they benefit from immunosuppressive therapy, remains to be elucidated.

Another treatment dilemma is the use of anticoagulant treatment in the presence of both inflammation and ischemia, as inflamed tissue might increase the risk of bleeds and even more so in the presence of anticoagulant treatment. In these cases, the potential benefits and risks have to be weighed for each individual patient.

These are only a few of the treatment dilemmas that may present. They reflect some of the challenges in NPSLE and underline the need for a multidisciplinary approach to identify the best treatment for each individual patient.

Figure 4 Current therapeutic approach for patients with NPSLE. This figure has been adapted from [43].



ACE = angiotensin-converting enzyme; *APS* = antiphospholipid syndrome; *CV* = cardiovascular; *LDL* = low-density lipoprotein; *VKA* = vitamin K antagonist; *CSC* = carbasalate calcium

Clinical outcomes in patients with SLE and neuropsychiatric symptoms

It is clear that more information regarding therapeutical interventions in patients with SLE and NP symptoms is warranted. In order to evaluate therapeutic interventions, it is important to identify relevant clinical outcome measures. This topic poses yet another challenge, as validated outcome instruments are currently lacking. A systematic review demonstrated a great diversity in outcome measures used to assess NPSLE.[50]

Methods to improve outcome measures are available and since 1992 initiatives in rheumatological diseases have been led by OMERACT, an international organized network.[51] OMERACT has proposed a framework, in which all measurable aspects of health conditions are split over two concepts, namely pathophysiology and impact (see *Supplementary Figure 1*).[52] These two concepts are further divided into four core areas: manifestations/abnormalities (e.g. disease activity or laboratory markers), death/lifespan (mortality), life impact (e.g. well-being, participation) and societal/resource use (e.g. health care utilization).[52] In this thesis, aspects of the first three core areas will be addressed.

Death/Life span

It is generally assumed that the presence of NP symptoms in SLE leads to an increased mortality and morbidity, but whether the underlying cause matters ('true' NPSLE versus other causes), is unknown.

A meta-analysis encompassing studies performed between 1960-2010 demonstrated that NP damage was a negative predictor for 5 and 10-year overall survival.[53] In addition, a study in NPSLE patients between 1989-2012 reported a strongly increased mortality compared to the general population.[54] However, not all studies have demonstrated increased mortality in patients with SLE and NP involvement.[55,56] As some progress has been made in our understanding and treatment of NPSLE in the past decade, identifying the current influence of NP involvement on mortality is necessary.

Life impact

In studies assessing treatment effect in patients with NPSLE, physician global assessment (PhGA) is frequently used as outcome measure.[50] Although this provides a useful clinical summary of the patient's condition, it does not necessarily portray the patient's experience. Therefore, patient-reported outcome measures (PROMs) are increasingly used in research to assess different aspects of disease burden.[57] PROMs are defined as "a report coming directly from patients about how they feel or function in relation to a health condition and its therapy without interpretation by healthcare professionals or anyone else".[58] An important PROM and assessor of life impact is health-related quality of life (HRQoL), which can be defined as an individual's or a group's perceived physical and mental health.

It is known that SLE has a significant impact on HRQoL and there is evidence for the influence of NP events on HRQoL.[59,60] Although QoL has been studied in NPSLE to some extent, many other available PROMs have not been explored. For future clinical trials, it is important to define which PROMs are most suited. Before this can be done, it is crucial to obtain information regarding the general function and wellbeing of patients when initially presenting with NP symptoms. In this way, the most important contributors to life impact according to patients can be assessed in future interventions.

Life impact: examples

Fatigue is known to be an important contributor to morbidity in patients with SLE.[61] Although fatigue occurs in many chronic illnesses, it appears to be especially incapacitating in patients with SLE. It is thought that disease activity may cause fatigue, but also comorbidities such as anxiety and depression have been proposed as important contributors.[62] The pathomechanism and therapeutical approach to fatigue remain to be further elucidated.

Apart from fatigue, cognitive dysfunction is also considered to be an important contributor to morbidity in patients with lupus.[63] The term "lupus fog" is often used in the context of cognitive problems, although no clear definition of this term exists. An influence of cognition on QoL

has been suggested in some studies, but limited information is available.[64] Interestingly, a large discrepancy between perceived cognitive deficits versus objective cognitive deficits in patients with SLE has been observed.[65] Taking this knowledge into account, cognition should probably be assessed in intervention studies both subjectively as a life impact factor as well as by performing (objective) neuropsychological assessment.

Manifestations/abnormality

Cognitive field: neuropsychological assessment

Studies have reported a prevalence of cognitive dysfunction in patients with lupus ranging from 3-81%.[66] Naturally, cognitive dysfunction is considered a NP symptom, but like other NP manifestations is not necessarily directly caused by SLE.

Cognition is a complex concept and has many definitions, but is usually described as different aspects of thinking, including perception, learning, problem solving, judgment, and memory.[67] Neuropsychological tests aim to capture the cognitive function of an individual by assessing one or more specific cognitive domains. In the 1999ACR case definitions for NPSLE, a one-hour neuropsychological test battery was proposed.[20] Most research groups have used this as guideline for testing cognition in patients with SLE and the specific tests most commonly used are provided in *Supplementary Table 1*.[66]

Regardless of overt NP involvement, SLE is associated with deficits in visual attention, cognitive fluency, immediate visual memory and visual reasoning.[68] In addition, a gradient of cognitive disturbance in SLE with significantly greater cognitive impairment in NPSLE patients relative to non-NPSLE patients has been demonstrated. The following domains have been found to be more impaired in NPSLE patients than non-NPSLE patients: visuomotor coordination, attention, executive function, visual learning and memory, and phonetic fluency.[69]

Different studies have used cognition as outcome measurement, amongst others in therapeutic interventions.[50] In addition, there are currently several trials ongoing to improve cognition. [70,71] Although this shows that the importance of assessing and treating cognitive problems in SLE is recognized, the underlying pathophysiological processes currently remain insufficiently clear. Understanding the cause(s) of cognitive dysfunction in patients with (NP)SLE might aid in finding targeted therapy.

Instrumental marker: neuroimaging

Brain MRI is routinely used in the evaluation of SLE patients with NP manifestations, especially for ruling out other conditions. Abnormalities frequently found in patients with SLE are white and gray matter lesions and regional cerebral atrophy. However, few correlations have been found yet between MRI abnormalities and NP manifestations, other than cerebral strokes.[37] About half of the patients with NPSLE have a normal brain MRI and in those with abnormalities, the most common findings are white matter hyperintensities (WMHs).[72] WMHs can also be present in SLE patients without NPSLE and are also found in, amongst others, patients with diabetes, hypertension and old age.[73] The meaning of these WMHs is therefore unclear and the

association between alterations in brain structures and clinically relevant symptoms, such as cognitive dysfunction, needs further investigation.

Several research groups are working on imaging techniques in relation to the pathogenesis and diagnosis of NPSLE, as well as evaluating its use as outcome measure. For this, different imaging modalities are used, such as advanced MRI techniques that have a higher sensitivity of detecting brain changes than conventional brain MRI. Examples are diffusion tensor imaging and voxel-based morphometry, which are being studied to gain insight into the brains' microstructure and to unravel differences in brain anatomy (such as cortical thickness) between SLE and NPSLE patients.[74] Other techniques used in research are positron emission tomography and single photon emission computed tomography (SPECT). SPECT contributes to the evaluation of brain perfusion by detecting the presence of a radioisotope in vital neurons based on their metabolic activity and blood flow. As most neuroimaging techniques reveal abnormalities in both SLE and NPSLE patients and are not available in every clinic, none of these techniques are used (yet) in clinical practice for the diagnosis of NPSLE. However, several studies have used neuroimaging techniques as (indirect) evaluation of treatment.[50] A small magnetization transfer imaging study demonstrated that patients with inflammatory NPSLE have lower histogram peak heights (HPHs) and that the HPHs change after immunosuppressive treatment. If these findings are confirmed, HPHs can potentially serve as a neuroimaging outcome measure.[75] Another small study assessed the difference in the presence of abnormalities on conventional brain MRI between responders and non-responders to NPSLE treatment, but did not find a difference.[76] In conclusion, although neuroimaging may serve as biomarker for the diagnosis of NPSLE and as outcome in clinical trials in the future, its current value for NPSLE or specific manifestations, such as cognitive dysfunction, is limited.

Laboratory markers

Autoantibodies are thought to play an important role in NPSLE; therefore it seems evident to also explore this research field for potential biomarkers. As mentioned previously, the most studied antibodies in NPSLE, namely cross-reactive anti-dsDNA and anti-riboP, are not sensitive or specific enough for clinical use.[77] Many other antibodies have also been studied, but none are currently suited for diagnostic or research purposes.[29] It is possible that antibodies that may serve as accurate biomarkers, are yet to be identified. Breakthroughs in other disorders might give insights, such as the discovery of antibodies against post-translation modifications in rheumatoid arthritis[78] and the discovery of the specific autoantibody marker for neuromyelitis optica.[79]

Apart from antibodies, many other laboratory measurements have also been studied in NPSLE, both as biomarker for NPSLE diagnosis and as outcome measurement.[50] Potentially interesting candidates are complement factors, as the complement cascade is known to play a significant role in SLE.[80] The complement cascade is an important factor of the innate immunity and functions include the promotion of inflammatory processes, clearance of immune complexes, and clearance of cellular and apoptotic debris.[81] In addition, complement plays a role in normal brain development and has been demonstrated to contribute to the pathology of inflammatory CNS

and neurodegenerative diseases.[82] In normal circumstances, complement in the CNS regulates neurogenesis, contributes to neuronal migration in the developing brain and aids synaptic pruning.[83] It is thought that in pathological conditions, complement factors can occur in the CNS either through direct expression by brain cells after CNS injury or through passive transfer to the brain when the blood-brain barrier is compromised.[84] A study in SLE patients demonstrated elevated levels of C3 in the CSF of NPSLE patients.[85] The potential role of complement in the pathophysiology of NPSLE and its potential as biomarker needs further exploration.

AIMS AND OUTLINE OF THIS THESIS

It is clear that many different aspects of NPSLE, from bench to bedside, remain to be elucidated. The lack of clarity regarding the pathophysiology of NPSLE and the absence of biomarkers leads to difficulty in diagnosing NPSLE; hence the type of patients included in NPSLE studies varies greatly. Well-characterized and homogenous study populations, as well as suitable clinical outcome measures are essential for performing clinical trials, which in turn are important for reducing morbidity and mortality in patients presenting with SLE and neuropsychiatric symptoms. The Leiden NPSLE clinic provides well-characterized phenotypes of neuropsychiatric manifestations in SLE. The ultimate goal is to improve diagnosis, treatment and clinical outcome in patients with SLE and neuropsychiatric symptoms. This thesis aims to lay stepping stones for this ultimate goal by using the clinical experience of the Leiden NPSLE clinic.

In **Part I** of this thesis, clinical experience from the NPSLE clinic will be shared in order to address two different study aims. First, the accuracy of the new SLE classification criteria will be assessed in patients of our NPSLE clinic. Second, the effect of (immunosuppressive) treatment will be assessed and last, the need for immunosuppressive treatment in specific clinical presentations will be addressed.

As pointed out previously, there is a strong need for clinical trials in patients with SLE and neuropsychiatric symptoms. Trials tend to solely include patients that meet specific classification criteria for SLE. It is therefore important that patients with SLE and NP symptoms are correctly classified as SLE. Therefore, in **Chapter 2** a comparison is made between the clinical diagnosis of SLE and SLE according to new classification criteria (2019), as well as other criteria. Furthermore, there is a need to understand which patients and interventions should be studied in clinical trials. For this, empirical evidence for the type of interventions currently used and their effects is desired. Therefore, we aimed to study the effect of immunosuppressive treatment in patients with different presentations of NPSLE. In **Chapter 3**, an overview is provided of all patients treated with immunosuppressive therapy in the NPSLE clinic between 2007-2021. In addition, information regarding treatment outcomes in these patients is provided. In **Chapter 4**, the need for immunosuppressive treatment in patients with psychiatric disorders in SLE explored. **Chapter 5** addresses the diagnostic challenges of patients with SLE that present with transverse myelitis without MRI abnormalities and focuses on the specific treatment and clinical outcomes in these patients.

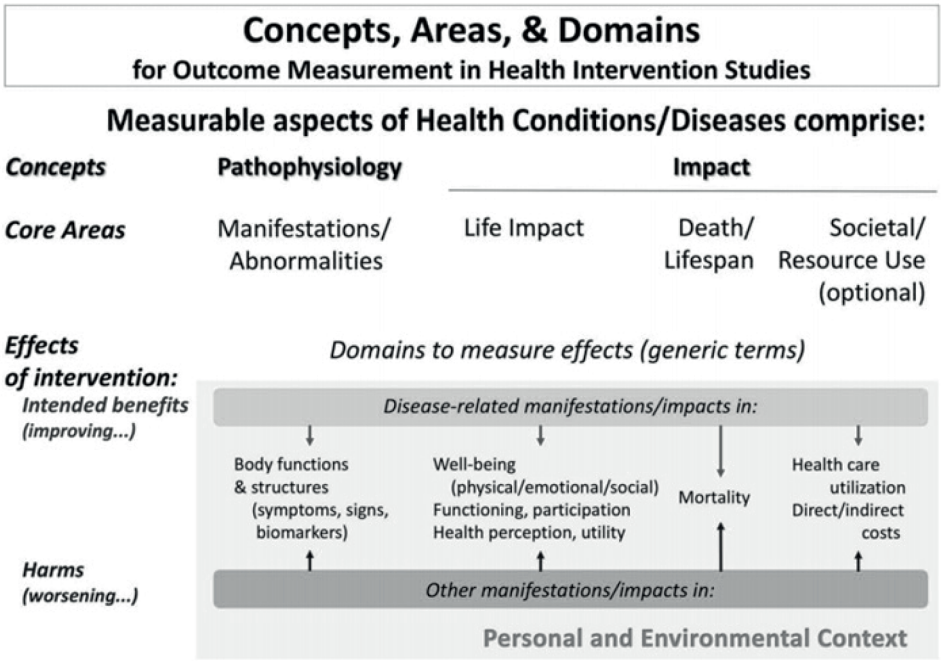
Part II of this thesis focuses on clinical outcomes in patients with SLE and neuropsychiatric symptoms, and addresses both morbidity and mortality. For the assessment of morbidity, patient-reported outcome measures are used, which capture a person's perception of their own health through questionnaires. This information is vital, as interventions should aim to improve disease burden. In **Chapter 6**, the impact of neuropsychiatric symptoms on quality of life in patients with lupus is assessed. **Chapter 7** zooms in on a specific neuropsychiatric symptom, namely cognition, and studies its association with quality of life. A symptom that is considered extremely burdensome by patients with lupus is 'lupus fog', which has been related to cognition. As an exact definition is lacking to date, **Chapter 8** explores the concept of fog in patients with lupus in relation to dissociation and dissociative fog. **Chapter 9** focuses on fatigue, one of the most mentioned and invalidating symptoms in patients with SLE. The association between inflammation, but also psychiatric symptoms and fatigue is explored. As it is unclear to what extent neuropsychiatric presentations in SLE lead to an increased mortality and whether the underlying origin of neuropsychiatric symptoms influences mortality, this topic is addressed in **Chapter 10**.

In **Part III**, the last study aim is addressed: to find biomarkers for NPSLE or specific NPSLE manifestations. Identifying biomarkers is of importance as this might facilitate NPSLE diagnosis. As neuroimaging is an important modality in NPSLE, it is interesting to explore its potential use as biomarker. In **Chapter 11**, the hypothesis that specific brain changes influence cognitive function in patients with SLE, and might therefore serve as biomarker, is explored. Not only neuroimaging, but antibodies might also be able to serve as biomarker for NPSLE in the future. As antibodies against post-translationally modified antigens have been demonstrated to play an important role in other rheumatological diseases, **Chapter 12** explores their association with NPSLE and brain volumes.

Lastly, a summary and general discussion on the findings that are presented in this thesis are provided in **Chapter 13**. In addition, a Dutch summary of this thesis can be found in **Chapter 14**.

SUPPLEMENTARY MATERIALS

Supplementary figure I OMERACT filter 2.1 framework[52]



Supplementary Table I Tests commonly used to assess specific cognitive domains in patients with SLE[66]

Cognitive domains	Tests
Simple attention	Digit Vigilance Test Paced Auditory Serial Addition Test
Complex attention	Trail making test, Digital span, Paced Auditory Serial Addition Test, Category test
Memory Learning Recall	Learning Component Story Memory Test Learning Component-Figure Memory Test California Verbal Learning Test-II (CVLT-II) Delayed Component Story Memory Test Delayed Component-Figure Memory Test The Rey Complex Figure Test (recall trials)
Visual-spatial processing	Facial recognition test, THE Judgment of Line Orientation test short form, Hooper visual organization test, The Rey Complex Figure Test (copy trial)
Language	Complex Material subtest from Boston Diagnostic Aphasia Exam Reading Comprehension subtest from Peabody Individual Achievement Test
Reasoning/problem solving Processing speed, psychomotor speed Executive function	Wechsler Adult Intelligence Scale-Revised (WAIS-R/ III), Ruff Figural Fluency Test Trail Making Test, WAIS-R/III Digit Symbol Substitution Test, Simple Reaction Time The Delis-Kaplan Executive Function Test (DKEFS) color-Word Inhibition test, DKEFS Card-Sorting Test, DKEFS Trail-Making Test, Stroop Color-Word Test, Controlled Oral Word Association Test (COWAT)

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