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Studies on Neuropsychiatric SLE

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CHAPTER 13

Summary



Systemic lupus erythematosus (SLE) is an autoimmune disease that causes damage in multiple organ systems. Neuropsychiatric symptoms are common in SLE patients and might be a manifestation of involvement of the nervous system, which is associated with worse prognosis, more cumulative damage and an increase in mortality. This thesis describes studies on clinical, pathogenetic and imaging aspects of involvement of the nervous system in patients with SLE.

The first part of **Chapter 1** provides a general introduction to the thesis and describes epidemiology, symptomatology, pathogenesis and therapy of SLE, a chronic autoimmune disease with flares and remissions that predominantly affects females. Current knowledge about nervous system involvement in SLE is summarized in the second part of this chapter. A major difficulty in studying neuropsychiatric SLE (NPSLE) is the lack of a clear definition as there is no single diagnostic test that is specific for SLE-related neuropsychiatric manifestations. NPSLE is usually defined as 'neurological manifestations of the central, peripheral and autonomic nervous system and psychiatric symptoms, observed in patients with SLE in which other causes have been excluded'. The diagnosis of NPSLE is based on expert opinion after careful exclusion of other possible causes of neurologic and psychiatric symptoms. Besides history taking and physical examination, immunoserological testing, brain imaging, and psychiatric and neuropsychological evaluation are used to support or refute the diagnoses. They also form the basis for prospective monitoring of clinical evolution and response to treatment. In 1999 the American College of Rheumatology established case definitions for 19 central and peripheral nervous system syndromes in SLE in order to facilitate research and to allow the comparison of results among studies.

For neuropsychiatric manifestations in SLE different pathogenetic pathways have been proposed, such as protracted inflammatory activity causing chronic damage, antiphospholipid antibody related thrombosis and immune-mediated pathways. It is likely that the pathogenesis of NPSLE is multifactorial and involves autoantibody production, microangiopathy, intrathecal production of proinflammatory cytokines and atherosclerosis. In animal models the importance of a breach in the integrity of the blood-brain-barrier in SLE-related neuropathology is demonstrated.

Cerebral imaging is an important tool in the diagnostic work-up of SLE patients with neuropsychiatric symptoms. Magnetic resonance imaging (MRI) is regarded as the diagnostic imaging technique of choice in the evaluation of neuropsychiatric manifestations in SLE patients and is important in excluding other causes of neuropsychiatric symptoms. In patients with focal neurological symptoms, brain infarctions are frequently detected. However, in SLE patients with diffuse neuropsychiatric manifestations, such as cognitive dysfunction, MRI scan of the brain frequently shows aspecific abnormalities or no abnormalities at all.

Advanced MRI techniques can detect central nervous system (CNS) damage in the absence of abnormalities on conventional MRI. Some of these techniques are promising in the evaluation of SLE patients with neuropsychiatric symptoms.

Magnetization transfer imaging (MTI), diffusion weighted imaging (DWI) and magnetic resonance spectroscopy (MRS) are MRI techniques with higher sensitivity to structural disturbances of the brain than conventional MRI. Furthermore, with these imaging techniques, cerebral damage can be quantified.

MTI quantifies the exchange of protons between water in a bound state within a macromolecule such as cholesterol (found in myelin in the CNS) and those in a free pool of cellular water. Both loss of myelin or accumulation of fluid (due to edema) alters the amount of transfer. This is represented by the magnetization transfer ratio (MTR). MTR histograms represent the integrity of brain tissue. In multiple sclerosis, but also in NPSLE, lower MTR peak heights are reported, indicating loss of macromolecular structure of brain tissue.

DWI is based on the random motion of protons. Acute ischemic lesions result in reduced diffusion of water. The apparent diffusion coefficient (ADC) indicates the amount of diffusion and is a quantitative measure for tissue integrity. DWI helps in discriminating ischemic from inflammatory disease, in which reduction of diffusion is not seen.

Proton (^1H)-MRS allows noninvasive biochemical assessment of brain tissue, using a similar technique as MRI. Reduction of *N*-acetylaspartate (NAA), a metabolite which is abundant in neurons, or reduction in the NAA/creatinine ratio, indicates neuronal damage or dysfunction.

In **Chapter 2** clinical and radiological data in a large cohort of SLE patients with neuropsychiatric manifestations are described. In 102 patients primary NPSLE was diagnosed. The patient group represents the broad range of clinical neuropsychiatric syndromes that is observed in NPSLE. Cerebrovascular disease, cognitive dysfunction, seizures and headache were the most prevalent syndromes and symptoms. In 45% of the patients two or more neuropsychiatric syndromes were present. SLE diagnosis was established at the median age of 27.5 years in NPSLE patients. In 39% of the patients neuropsychiatric manifestations occurred within the first year of diagnosis of SLE. This suggests a role for immune-mediated mechanisms, as the specificity of autoreactive antibodies increases early in the development of SLE. In 47% of the patients, no abnormalities were found on MRI scan of the brain. This might indicate subtle and more diffuse damage of brain tissue in a part of the patients with neuropsychiatric signs and symptoms.

In SLE mouse models, the presence of a subset of anti-dsDNA antibodies resulted in neuronal damage when the integrity of the blood-brain barrier was affected by bacterial lipo-polysaccharide. These studies suggest a possible role of infections in the pathogenesis of neuropsychiatric symptoms in SLE. This theory would be supported if neuropsychiatric manifestations in SLE cluster in seasons, suggesting seasonal exposure to infections that affect the blood-brain barrier. In **Chapter 3** we assessed whether seasonal variation in first occurrences or flares of NPSLE could be established to support the concept that infections might be an inducing factor for neuropsychiatric symptoms in SLE. In a cohort of 48 patients, 61 first manifestations or flares of NPSLE were recorded and distribution over the year was evaluated. No seasonal

variation could be established to support the concept that infections are a contributing factor for neuropsychiatric symptoms in SLE.

The subset of anti-dsDNA antibodies mentioned in chapter 3, cross-reacts with the *N*-methyl-D-aspartate (NMDA) receptor. The NMDA receptor is a glutamate receptor which is important in processes that influence memory and learning and it is recognized by both murine and human anti-dsDNA antibodies. These antibodies mediate apoptotic cell death of neurons *in vitro* and *in vivo*. Antibodies to the NMDA receptor have been demonstrated in the serum of patients with SLE and may be associated with various manifestations of NPSLE, including cognitive dysfunction and depression. Most studies report that these antibodies are detected in 25-30% of all patients with SLE. However, the relationship between anti-NMDA receptor antibodies and NPSLE manifestations in humans has been conflicting. To determine whether anti-NMDA receptor antibodies could be involved in (NP)SLE, these antibodies were measured in SLE patients with and without neuropsychiatric manifestations, their first-degree relatives and unrelated controls in the study described in **Chapter 4**. The anti-NMDA autoantibody reactivity was higher in SLE patients and first-degree relatives, but no difference was found between subjects with or without neuropsychiatric manifestations. These results indicate that the tendency to mount this immune response might be a familial trait, suggesting genetic influences in the pathogenesis of the disease. Furthermore, also in human NPSLE the role of the blood-brain barrier might be important in the development of clinical symptoms in patients with anti-NMDA receptor autoantibodies.

Recent mouse studies suggest that anti-NMDA receptor autoantibodies are associated with cognitive dysfunction and apoptosis of neurons in the hippocampus, only in the presence of blood-brain barrier disruption by bacterial lipopolysaccharide. In a subsequent study with induction of leakage of the blood-brain barrier by epinephrine, neurons in the amygdala were specifically affected in this mouse model of SLE. The animals showed abnormal response in fear-conditioning paradigms. It is possible that also in human patients with SLE, the magnitude and localization of the blood-brain barrier dysfunction in concert with the type and level of the autoantibodies may be determining factors regarding their pathogenicity in the brain. In **Chapter 5** we used a quantitative MRI technique to investigate if selective damage in the hippocampus or amygdala could be demonstrated in NPSLE patients, and whether the presence of anti-NMDA receptor autoantibodies in serum correlated with the observed damage. A group of 37 NPSLE patients, 21 SLE patients and 12 healthy control subjects were analyzed with DWI. The average ADC of NPSLE patients was significantly lower than in healthy control subjects. Although the sample size was small, more severe changes in the amygdala of SLE patients with anti-NMDA receptor autoantibodies were observed as compared to SLE patients without anti-NMDA receptor autoantibodies suggesting that these antibodies are involved in the development of brain damage in particular NPSLE patients. In this study, the amygdala is specifically affected in patients with SLE and anti-NMDA receptor autoantibodies might play

a role in this process. These results also suggest that the animal model in which the blood-brain-barrier is opened, allowing antineuronal antibodies to enter the brain and cause neuronal damage, could be an appropriate reflection of human NPSLE disease.

Although the exact contribution of antiphospholipid antibodies to the pathogenesis of NPSLE is not established, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant and anti- β_2 glycoprotein I antibodies) are often quoted in relation to focal manifestations in NPSLE. Many patients with SLE have antiphospholipid antibodies, and in 20-35% of patients with SLE, symptomatic secondary antiphospholipid syndrome will develop during the course of the disease. **Chapter 6** gives an overview of the antiphospholipid syndrome. This systemic autoimmune disorder is characterized by both arterial and venous thrombosis, adverse outcome in pregnancy, and elevated levels of antiphospholipid antibodies. Cerebral involvement is common in the antiphospholipid syndrome; the most common arterial thrombotic events are stroke, which is the initial clinical manifestation in 13% of patients with the syndrome, and transient ischemic attack in 7%. Cerebral ischaemia, migraine, cognitive dysfunction, seizures, chorea, transverse myelitis, psychosis, depression, and Guillain-Barré syndrome have all been associated with the presence of antiphospholipid antibodies.

Anticardiolipin antibodies are associated with thromboembolic events and macroscopic brain infarctions in NPSLE patients. However, their role in the development of neuropsychiatric symptoms in NPSLE patients without apparent abnormalities on conventional MRI of the brain is less clear. In **Chapter 7** we investigated whether quantitative MTI parameters correlated with the presence of anticardiolipin antibodies in the serum of NPSLE patients in order to evaluate whether microscopic brain damage, as can be detected by MTI, could be a possible explanation for neuropsychiatric symptoms in these patients. Gray and white matter MTR parameters were correlated to the presence of IgM and IgG anticardiolipin antibodies and lupus anticoagulant in a group of 18 SLE patients with a history of NPSLE but without cerebral infarcts on conventional MRI. Lower white matter mean MTR and peak location and gray matter mean MTR were observed in IgM anticardiolipin antibody positive patients as compared to IgM anticardiolipin antibody negative patients. These MTR parameters demonstrated brain damage in anticardiolipin antibody positive SLE patients in the absence of explanatory abnormalities on conventional MRI. Therefore, our results suggest that, apart from giving rise to macroscopic cerebral infarctions, anticardiolipin antibodies may play a role in the pathogenesis of diffuse microscopic brain damage in NPSLE.

Genetic susceptibility is one of the contributing factors in the pathogenesis of SLE. In 2007, mutations in the *TREX1* gene, encoding the major mammalian 3'-5' DNA exonuclease, were identified in 9 out of 417 SLE patients. In addition, mutations in the *TREX1* gene have been reported in vascular and immune-mediated disorders that are associated with cerebral white matter hyperintensities, migraine (-like symptoms), and other manifestations of brain disease.

In the study described in **Chapter 8** a *TREX1* gene mutation is described in a patient with NPSLE for the first time. The genomic DNA of 60 NPSLE patients, with and without cerebral white matter hyperintensities, was scanned for exonic *TREX1* mutations using direct sequencing. A novel p.Arg128His mutation was identified in one out of 60 NPSLE patients. This patient had extensive white matter hyperintensities on MRI scan of the brain, progressive migraine-like headache and other symptoms such as Raynaud's phenomenon and lupus nephritis class IV. These results indicate that *TREX1* could be a potential genetic factor in NPSLE.

Conventional MRI is the diagnostic imaging modality of choice in the diagnostic work-up of NPSLE patients. In **Chapter 9** an inventory was made of cerebral abnormalities on conventional MRI in a large group of patients during their first episode of active primary NPSLE manifestations. The patients were classified according to the '1999 ACR nomenclature and case definitions'. In 74 patients with 15 different NPSLE manifestations, 58% of patients showed one or more abnormalities on MRI and 42% of patients had no visible abnormalities. The most frequently encountered radiological finding was the presence of multiple focal white matter hyperintensities in the periventricular, deep, and subcortical white matter. Such white matter hyperintensities were found in 49% of all patients and in 84% of patients with abnormalities on MRI. A remarkable finding was the high prevalence of cortical gray matter hyperintensities which were observed in 18% of all patients and 30% of patients with MRI abnormalities. Distinct radiological patterns were observed that are suggestive of different NPSLE pathomechanisms: 1) focal, punctate hyperintensities in white and/or gray matter suggestive of vasculopathy or vasculitis; 2) more widespread, confluent hyperintensities in the white matter, suggestive of chronic hypoperfusion due to the same mechanisms; 3) diffuse cortical gray matter lesions suggestive of an immune response to neurons; and 4) absence of MRI abnormalities, despite signs and symptoms of active disease (in 42% of all patients). The different MRI patterns are suggestive of different pathogenetic mechanisms. Therefore, categorization of NPSLE patients based on radiographic manifestations might be useful in further research focusing on the pathogenesis of NPSLE.

With the use of quantitative MRI techniques, diffuse abnormalities have been observed in patients with NPSLE that are invisible on conventional MR sequences. However, for quantitative MRI techniques such as MTI to provide useful surrogate markers of disease activity, it must not only be able to detect abnormalities, but parameters must also change in concordance with changes in disease activity. In **Chapter 10** we investigated whether clinical changes in disease activity in NPSLE patients correlated with MTI parameters. Nineteen NPSLE patients were subjected to MTI on, at least, two separate occasions. A total of 24 pairs of scans were available for evaluation. The peak height of the MTR histograms was used as an estimate of parenchymal integrity. The clinical course was defined as improved, stable or deteriorated. During the course of the paired observations, 4 patients clinically deteriorated and in all clinically deteriorated patients, the MTR peak height decreased. In the 6 patients that showed clinical

improvement, a significant increase of the peak height was observed, while in 14 patients with clinically stable disease, the peak height did not change significantly. The finding that MTR peak height corresponded with changes in the clinical status of individual NPSLE patients suggests that MTI can be a valuable tool in the clinical assessment of these patients.

To use quantitative MRI techniques such as MTI, DWI and MRS as diagnostic tools in NPSLE patients, it is important to know that the observed abnormalities can be attributed to the underlying disease and that results are not confounded by other factors such as medication use. As many NPSLE patients are on corticosteroid medication and treatment with corticosteroids is known to have an effect on the nervous system, it is conceivable that brain abnormalities previously detected by quantitative MRI methods might (partially) be induced by corticosteroid treatment. In **Chapter 11** we investigated the effect of chronic use of low dose oral corticosteroids on MTI, DWI and MRS measurements of the brain in patients with rheumatoid arthritis, a disease that has no known cerebral involvement. Twenty-seven patients, 13 with and 14 without corticosteroid medication and 15 healthy controls were subjected to conventional MRI, whole-brain MTI and DWI and single-voxel MRS. We found no evidence for an effect of low-dose oral corticosteroids on these quantitative MRI measurements of the brain in patients with rheumatoid arthritis. It is therefore unlikely that MTI, DWI and MRS parameters of the brain in NPSLE patients are confounded by the use of low-dose oral corticosteroid medication.

MTI is a quantitative MRI technique with higher sensitivity to structural disturbances of the brain than conventional MRI. Recent studies in NPSLE patients without abnormalities on conventional MRI scan, demonstrated a lower peak height of the MTR histogram of the whole brain compared to control subjects. However, the underlying pathology of these MTI abnormalities is unclear. Furthermore, it is unknown if a correlation with specific neuropsychiatric syndromes or SLE criteria exists. In **Chapter 12** we investigated in (NP)SLE patients whether the MTR histogram parameters correlated with neurochemical findings obtained with ¹H-MRS, a technique that is sensitive in establishing and quantifying neuronal damage. Subsequently it was investigated whether MTR histogram parameters were linked to specific SLE and NPSLE characteristics. Eighteen SLE patients, 34 NPSLE patients and 15 healthy controls underwent MTI and ¹H-MRS.

The MTR peak height was lower in NPSLE patients than in healthy controls, which is in line with previous studies. The MTR peak height was significantly associated with the ratio of *N*-acetylaspartate to creatine ratio as detected by ¹H-MRS, indicating neuronal damage. Furthermore, after correction for age, gender and SLE criteria, MTR peak height was associated with cognitive dysfunction but not with other neuropsychiatric syndromes, suggesting different pathogenetic mechanisms in neuropsychiatric involvement in SLE.

The data presented in this thesis support the hypothesis that autoantibodies (both the antineuronal system antibodies and the antiphospholipid antibodies) are relevant for NPSLE

pathogenesis. However, despite the continuous growth in understanding the mechanisms leading to neuropsychiatric manifestations in SLE, the diagnosis of NPSLE remains a clinical one, based on an expert multidisciplinary team effort, requiring the expertise and communication between different specialists to establish a consensus-based diagnosis. Using this consensus-based diagnosis of NPSLE as a clinical standard, we showed that new quantitative MRI techniques are likely to help this diagnostic process. Moreover, these techniques also enhance the knowledge of disease pathogenesis as shown in chapter 7 to 12 In the future we hope to use quantitative MRI techniques in the routine care of patients with NPSLE

