

**On lupus of the brain : magnetic resonance imaging studies** Emmer, B.J.

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## Chapter 1

Introduction

## Introduction

Systemic lupus erythematosus (SLE) is an inflammatory autoimmune disease with a relapsing-remitting course and symptoms based on the involvement of multiple organs. (1) The disease is nine times more common in women than in men and the prevalence has been reported to be as high as 1 in 2000. (2) The peak of the onset of SLE lies between 15-25 years. Up to 80 percent of SLE patients develop neurological or psychiatric symptoms. (2)

The exact cause of SLE is still unknown, but it is believed that auto-antibodies play an important role in its pathogenesis. One important hypothesis is that clinical disease in SLE is the end stage of a process where normal immunity progresses first to benign autoimmunity then to pathological autoimmunity under the influence of environmental and genetic influences and, when symptoms become manifest, to clinical disease. (1) Recently it has been demonstrated that auto-immune antibodies against self-epitopes are present long before the onset of the disease. These antibodies can be directed against any peptide of the SLE patient. It has been shown that the number of different antibodies directed against various self-epitopes increases close to the onset of the symptoms of SLE. (1) They can interfere with the coagulation pathways, vessel walls, or bind with circulating proteins to form immune complexes. This can cause hypercoagulability, vessel wall damage or altered vessel wall permeability respectively. Recent studies have shown that some auto-antibodies are directed against single or double strands of DNA and are thus potentially harmful to any cell in the body. In addition, some of these anti-DNA antibodies interact with cells to cross react with receptors on the cell surface, blocking or over-exciting neurons. (3)

Neuropsychiatric symptoms in SLE are probably not based on a single pathophysiological process. Different pathomechanisms, triggered by the different types of circulating antibodies, can give rise to signs and symptoms of nervous system dysfunction in SLE. First, such signs and symptoms can be caused by focal ischemia, i.e. infarcts, based on increased coagulability as a consequence of antiphospholipid antibodies interfering with the coagulation system. Second, vessel wall damage caused by deposition of immunecomplexes has been described as a mechanism causing vasculopathy in small vessels and capillaries of the brain. (4) Third, anti-DNA antibodies or antibodies directed against specific proteins of the cells that are present in the central nervous system have recently been shown to be responsible for complex symptoms like epilepsy, psychosis, cognitive and emotional dysfunction. Due to the presence of multiple different antibodies in the same patient, these different pathomechanisms may occur simultaneously and give rise to a complex clinical picture.

NPSLE has been divided into primary and secondary NPSLE. In primary NPSLE neurological complaints in SLE patients are caused by direct damage to the central nervous system through one or more of the mechanisms described above. However, primary NPSLE can only be diagnosed when other causes of neurological complaints are not present. If neuropsychiatric symptoms in SLE patients can be explained by secondary causes such as metabolic derangement based on lupus nephritis, concurrent disease like infection or by medication, they are diagnosed with secondary NPSLE.

Due to the various ways in which auto-antibodies can interfere with the functioning of the central nervous system, neurological symptoms in NPSLE can be diverse. For research purposes these neuropsychiatric symptoms have been categorized into focal and diffuse symptoms. Focal neurological symptoms, like paralysis or sensory deficits, have been categorized as focal NPSLE. Focal NPSLE symptoms have been associated with the occurrence of thrombo-embolic events. (5) Other more diffuse symptoms like cognitive dysfunction, headache or psychosis have been categorized as diffuse NPSLE.

In general, the diagnosis of diffuse NPSLE is more difficult to make than focal NPSLE. Often, in patients with diffuse NPSLE, no abnormalities that provide an explanation for the clinical signs and symptoms can be found on MRI. This radiological-clinical paradox triggered the application of quantitative MRI techniques in NPSLE, since in other diseases with a similar paradox such techniques have proven to be useful based on their increased sensitivity for the presence of subtle tissue changes. Previously, Bosma and co-workers, using quantitative MRI, were able to detect brain changes in SLE patients with acute and chronic neuropsychological symptoms who lacked visible changes on conventional MR images that could explain the clinical picture. (6) Steens and co-workers demonstrated that these quantitative techniques were robust and that the abnormalities found were more pronounced in the gray matter than in the white matter. (7) Despite these studies numerous questions remain unanswered.

The first unresolved problem pertains to the evolution of abnormalities detected by quantitative MRI over time. Previous studies have shown that magnetization transfer imaging (MTI) is dependent on the integrity of macromolecules in general, and, in the brain, of myelin in particular. It has been shown that MTI can be used to detect abnormalities in NPSLE. (6) However, since MTR studies in NPSLE have been cross sectional in design so far, it is unclear whether these changes reflect irreversible damage or reversible, fluctuating chances as well.

The second unresolved problem pertains to the role of direct auto-antibody-mediated damage in SLE patients. Studies in mouse models of SLE have suggested that neuropsychiatric symptoms can be caused by direct antibody-mediated damage. (3) This was not an obvious pathomechanism since the brain is presumed to be an immune privileged organ with a blood-brain barrier protecting it from external assaults. However, Diamond and co-workers showed that the blood-brain barrier can be breached at specific locations under the influence of infection or stress. These studies also demonstrated that the symptoms caused by auto-antibodies directed against CNS components depend on the location of the breach of the blood-brain barrier. (8;9) However, the role of direct auto-antibody mediated damage in human SLE patients remained unclear. The fact that anti-neuronal antibodies are associated with abnormalities found in specific locations of the brain of human SLE patients with advanced MRI techniques, would support the hypothesis that antibodies can directly cause neuronal damage in human SLE.

Third, the histological substrate of the quantitative MR abnormalities observed by Bosma and Steens is still unknown. (6;7) MTI changes are presumed to reflect demyelination, with the loss of macromolecules in myelin leading to the loss of magnetization transfer of the tissue. (10) However, in postmortem studies on cerebral changes in NPSLE patients demyelination has not been reported as a striking feature of the disease. (4) Magnetic resonance spectroscopy (MRS) has been used in the past to detect reversible neurochemical abnormalities in NPSLE. (11) So far, the underlying neurochemical changes of MTI abnormalities in SLE patients are poorly understood. The association of neurochemical changes with abnormalities detected on quantitative MRI techniques such as MTI, would enhance the understanding of the pathophysiological changes underlying neuropsychiatric changes in NPSLE.

Fourth, possible changes in the cerebral metabolism under the influence of circulating cytokines like TNF alpha have so far not been investigated. Recent evidence suggests that circulating systemic cytokines can also influence the cerebral immune system. (12) The influence of cytokines in NPSLE is likely to be obscured due to the multi-factorial etiology of neuropsychiatric symptoms. Rheumatoid arthritis (RA) is an another systemic autoimmune disease predominantly characterized by synovial inflammation and increased circulating pro-inflammatory cytokines, in particular TNFα. (13) Although RA does not have a pervasive direct autoimmune attack on the central nervous system (CNS), as has been implicated in systemic lupus erythematosus (SLE), nonspecific neurological complaints like mood disorders, sleep disturbances and fatigue play an important role in the perception of RA patients. (14) This suggests that RA is a good model to study the influence of circulating cytokines on the CNS.

Fifth, as mentioned earlier, the role of ischemia in NPSLE patients without infarcts on conventional neuro-imaging studies is still unclear. Perfusion weighted MR imaging is a technique that can evaluate the perfusion characteristics of cerebral tissue and detect and quantify subtle changes in the amount of blood flow and blood volume of brain tissue. So far this technique had not been used in SLE patients, although it could provide insight into the contribution of ischemia to NPLSE.

Finally, although using volumetric quantitative MRI techniques it has been convincingly demonstrated that changes occur in the brain's white and gray matter, it is still unknown how these changes are distributed over the brain within the gray and white matter compartments. (7) Using image analysis software and statistical techniques that have recently become available, our insight into the distribution of the changes detected by quantitative MRI techniques in NPSLE patients could increase. Such insight could help increasing our understanding of the etiology of NPSLE.

In this thesis we describe our research that was aimed at addressing the questions mentioned above. Our specific aims were:

- 1. To evaluate whether parameters based on quantitative MRI techniques correspond to changes in clinical status in NPSLE patients.
- 2. To investigate the role of anti-neuronal antibodies in the etiology of neuropsychiatric signs and symptoms in SLE patients.
- 3. To assess the metabolic substrate of changes in parameters based on quantitative MRI techniques in patients with NPSLE.
- 4. To study the influence of circulating systemic cytokines, like TNF Alpha, on cerebral metabolism.
- 5. To study the role of ischemia in NPSLE patients without obvious infarction using perfusion weighted MR imaging.
- 6. To assess the distribution of white matter changes detected by quantitative MRI in patients without obvious brain changes on conventional MR imaging.

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