Genetic aspects of Multiple Sclerosis
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Chapter 1

General introduction
Multiple sclerosis (MS) is an inflammatory demyelinating disorder of the central nervous system. It is relatively common with a frequency of 0.1-0.2% in Northern European countries. The age at onset is most often between 20 and 40 years. Women are affected more often than men with a female-male ratio between 1.4. and 2.

**Clinical symptoms**

Clinically, MS is characterized by focal neurological symptoms of the optic nerves, spinal cord and brain. The frequency of symptoms at presentation is related to age. The most common initial symptom at any age is sensory, consisting of tingling or numbness. Optic neuritis is much more prevalent as a presenting symptom in patients under 20 than patients over 40 years old. Insidious motor symptoms, typically chronic progressive myelopathy, are characteristic of patients in their forties. Other common initial symptoms are diplopia, vertigo, limb ataxia, impairment of balance or acute motor symptoms.

As the disease progresses additional symptoms may be spasticity, pain, fatigue, dysarthria, disorders of micturition and bowel voiding, sexual disturbances, cognitive dysfunction and paroxysmal phenomena (this list is not limitative). Disability is measured by various scales that all seem to have their own advantages and limitations.

**Disease course**

Most often the initial course is relapsing-remitting (80%), with exacerbations and remissions during which the patient recovers completely or partially. The relapsing phase is followed by a secondary progressive phase in approximately two thirds of the patients after on average 10-15 years. During the secondary progressive phase there is gradually worsening disability in between eventual relapses. However, up to one third of the patients do not develop progressive disability and remain unimpaired for many years (benign MS). A smaller number of patients (10-15%) experiences gradual progression from onset and this course is called primary progressive. Rarely, the disease is rapidly fatal.

**Diagnosis**

The diagnosis of MS is based upon evidence of two or more lesions in the central nervous system (CNS), dissociated both in time and space. Initially, the Schumacher criteria were used to identify patients with clinically definite MS for inclusion in clinical trials. According to these criteria, lesions should be present predominantly in the white matter and disseminated in time and space.
Table 1: The Schumacher criteria

| Evidence on examination or in patient's history of two or more lesions in the CNS |
| Relapsing remitting disease | Two or more episodes separated by at least one month and lasting a minimum of 24 hours |
| Progressive disease | Persistent deterioration for six months |
| Onset between ages of 10 and 50 years |
| No better explanation for the symptoms in the opinion of a physician “competent in clinical neurology” |

In 1983 Poser proposed criteria that incorporated also paraclinical and laboratory findings to be used as support for the diagnosis (Table 2). These criteria were used to include patients in our studies as reported in this thesis.

Table 2: The Poser criteria

<table>
<thead>
<tr>
<th>Category</th>
<th>Attacks</th>
<th>Clinical evidence</th>
<th>Paraclinical evidence</th>
<th>CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Clinically definite MS</td>
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<td></td>
<td></td>
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<tr>
<td>CDMS A1</td>
<td>2</td>
<td>2</td>
<td></td>
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<tr>
<td>CDMS A2</td>
<td>2</td>
<td>1 and 1</td>
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<td>B. Laboratory-supported definite MS</td>
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<td></td>
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<tr>
<td>LSDMS B1</td>
<td>2</td>
<td>1 or 1</td>
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<td>+</td>
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<tr>
<td>LSDMS B2</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LSDMS B3</td>
<td>1</td>
<td>1 and 1</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>C. Clinically probable MS</td>
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<tr>
<td>CPMS C1</td>
<td>2</td>
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<tr>
<td>CPMS C2</td>
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<td>CPMS C3</td>
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<td>Laboratory-supported probable MS</td>
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<td>LSPMS D1</td>
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</table>
In the cerebrospinal fluid (CSF), the presence of abnormally high levels of immunoglobulin G (IgG) is supportive of MS. To exclude the possibility of leakage of IgG through an impaired blood-brain barrier, the concentrations of IgG and albumin in CSF and serum are compared and expressed as the IgG-index.

\[
\frac{\text{IgG in CSF}}{\text{albumin in CSF}} : \frac{\text{IgG in serum}}{\text{albumin in serum}}
\]

CSF and plasma are also examined by isoelectric focussing (IEF). Oligoclonal IgG bands present in CSF and not in serum are strongly supportive of the diagnosis of MS. However, oligoclonal bands can also be found in patients with other diseases like inflammatory and/or infectious diseases of the CNS. Of MS patients, 70% have an IgG index greater than 0.7 and 95% have oligoclonal bands\(^1\). A modestly increased number of white blood cells in the CSF (5-35/mm\(^3\)) is found in about half of MS patients, whereas numbers higher than 35-50/mm\(^3\) are very rare.

Evoked potentials may provide evidence of focal dysfunction within the optic nerve or CNS, even if symptoms are too subtle to be found at clinical examination. Visual, auditory, somatosensory and motor evoked potentials can be investigated. There is, however, only limited information as to the sensitivity and specificity of evoked potentials in MS.

More recently, new criteria incorporating also the results of magnetic resonance imaging (MRI) have been introduced\(^2\).

**Pathogenesis**

In the pathogenesis, autoimmunity is likely to play a major role\(^3\). Proteins that form part of the myelin sheath are suspected to be the target of the immunological reaction. However, some authors examine an alternative hypothesis of pathogenesis, suggesting that MS is a neurodegenerative and metabolic disorder with polygenic influence\(^4\). The heterogeneity of demyelinating lesions at pathological examination leaves room for both theories\(^5\). Patterns showing similarities with T-cell-mediated or T-cell plus antibody-mediated autoimmune encephalomyelitis as well as patterns suggestive of primary oligodendrocyte dystrophy were found.
Etiology
There is evidence for both genetic and environmental factors playing a role in susceptibility to MS. Indications for environmental factors include the correlation between prevalence and geographic localization\(^{16,17}\), migration studies\(^{18-22}\), possible clustering\(^{23-26}\) and reports of specific antibodies in body fluids\(^{27,28}\). The available epidemiologic data were recently reviewed by Marrie\(^{29}\). Indications for genetic factors are the association with specific HLA alleles, increased risk for relatives proportional to the amount of DNA shared, twin studies and racial differences (chapter 2).

Aims and scope of this thesis
Subject of this thesis are the genetic factors playing a role in MS. These factors will be approached from a genetic epidemiological point of view. Major questions in this field are: what is the disease model of MS, regarding the role of genetic and environmental factors? Where are the genetic factors localized within the genome? What is the contribution of each locus? How is their inheritance mode (dominant, recessive, intermediate)? Do loci interact?

Chapter 2 provides an overview of genetic epidemiological studies with emphasis on genome screens. Since a large part of the genome had been excluded for a locus with major contribution to susceptibility, we focussed on the HLA region, the only region that has repeatedly been found to be involved in MS. In our first study (chapter 3) we tried to finemap a locus within the HLA region, using a newly developed method of haplotype sharing analysis. Chapter 4 describes the inheritance mode of the region we finemapped previously. In chapter 5 we review the differences between different types of MS (relapsing-onset and primary progressive) and investigate whether in our population a genetic difference can be found in the HLA region.
References
