DIAGNOSIS AND EARLY PROGNOSIS IN MULTIPLE SCLEROSIS
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Diagnosis and early prognosis of Multiple Sclerosis

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door

Jessica Mirella Nielsen

geboren te Amsterdam
promotoren: prof.dr. C.H. Polman
prof.dr. B.M.J. Uitdehaag

copromotor: prof.dr. F. Barkhof
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CHAPTER 1:

GENERAL INTRODUCTION
Epidemiology

Multiple Sclerosis is the most common disabling condition affecting young adults (Confavreux et al. 1430-38). In the Netherlands the prevalence is estimated to be about 100 patients per 100,000 inhabitants. Every week 3 new MS patients are being diagnosed in the Netherlands. The mean age at onset is approximately 30 years. Females are twice as frequently affected as men (Compston and Coles 1502-17). The incidence varies widely worldwide depending on both genetic and geographical factors; in general the highest incidence is found at a larger distance from the equator.

Clinical presentation

The majority of patients present with a first acute or sub-acute episode of symptoms, a presentation that is called a ‘clinically isolated syndrome’ (CIS). The most frequently involved areas are the optic nerve, spinal cord and/or brainstem, respectively causing decreased vision, pareses and/or sensory disorders in the limbs and diplopia. In patients with a CIS, around 30-70% develop MS and have the relapsing / remitting type of the disease (RR-MS) (Fisniku et al. 808-17). This disease type is characterized by subsequent episodes of symptoms or ‘relapses’ with usually full or partial, but sometimes no recovery. The duration of the periods in between symptoms is highly variable and there is no clinical disease progression between relapses. Eventually, the majority of these patients will also gradually worsen in between relapses. This stage of the disease with gradual worsening, in combination with relapses, is called secondary progressive multiple sclerosis (SP-MS) (Lublin and Reingold 907-11) (Figure 1).
Ten to fifteen percent of patients never experience a relapse and present with slowly evolving progressive disease, usually consisting of spinal cord symptoms. These patients have the primary-progressive type of MS (PP-MS) (Wolinsky 145-52).

**Genetic background**

MS is most likely caused by a combination of genetic and environmental factors. The disease is more prevalent amongst Western Europeans, and as mentioned before, prevalence increases with the distance from the equator. However, some ethnic groups seem to be resistant to the disease even though they live in areas of high prevalence. Also, migration during childhood from areas with a high to areas with a low incidence is associated with a reduced risk. Genetic factors are further demonstrated by the familial occurrence of MS. 15-20% of patients report a family history of MS, which is higher than would be expected by chance (Sawcer 3118-31). The disease is more frequent in siblings, who have a 5% chance of the disease, as opposed to for example 1% chance in third degree relatives. A consistent association has been shown between MHC alleles DR15, DQ6 and MS. Due to the high prevalence of these
alleles in the general population however, it is not possible to apply this knowledge in clinical practice (Compston and Coles 1502-17; Rejdak, Jackson, and Giovannoni 79-104).

**Pathophysiology**

Multiple sclerosis is a multifocal demyelinating disease affecting white as well as grey matter. The disease is characterized by lesions with inflammation, demyelination and axonal loss. In the initial phase in the disease there is probably migration of auto reactive lymphocytes across the blood brain barrier. In combination with local regulatory failure, plaques are being formed in localized areas in the brain and the spinal cord. It is unclear what the antigen specificity of the involved immune responses is. Locally different inflammatory cells gather and pro inflammatory cytokines enhance inflammation by activating microglia, which in turn contact oligodendrocytes. In acute lesions a heterogeneous pathology is observed with astrocytes, activated phagocytic macrophages, T-cells, transected axons and myelin degradation products. These myelin degradation products are positive for myelin oligodendrocyte glycoprotein (MOG) and myelin associated glycoprotein (MAG) initially, and later for major myelin proteins such as myelin basic protein (MBP) and proteolipid protein (PLP). Acute lesions are encountered chiefly in patients with relapses. In chronic not actively inflamed lesions, an inactive center is surrounded by an edge of activated macrophages, microglia and very few myelin degradation products. These lesions are observed especially in patients with progressive disease (Hu and Lucchinetti 439-53).

**Therapy**

Currently, there is no cure for MS. However, several drugs are available that suppress disease activity, and some of these have also been shown to slow disease progression. Most frequently used medication includes interferon β which has been shown to delay the second clinical event in CIS patients (Kappos et al. 1242-49) (Comi et al. 1576-82; Jacobs et al. 898-904), to decrease the number and severity of relapses in patients with RR-MS, and seems to delay clinical disability (Kappos et al. 389-97).
Interferon β requires the patient to self-inject on at least a weekly basis. A comparable regularly used first line drug is **glatiramer acetate**. Further medication includes **natalizumab**, a monoclonal antibody against α4 integrin that is more effective than interferon (Rudick et al. 911-23). It is used as second line drug due to the occurrence of progressive multifocal encephalopathy (PML), a rare but potentially fatal side effect that occurs in 1 out of every thousand patients treated with the drug. Natalizumab is administered as monthly intravenous infusions. Other second line drugs include Mitoxantrone. Presently new drugs are emerging. Among them the orally administered Fingolimod (Cohen et al. 402-15) and Cladribine (Giovannoni et al. 329-37). None of these drugs have been shown effective in the progressive phase of the disease, for which presently no disease modifying therapy is available.

### 1.2 Diagnosis

Presently, no single diagnostic test for MS exists. Therefore diagnostic guidelines have been defined. A definite diagnosis of MS requires evidence of dissemination in space and time in terms of central nervous system lesions (Schumacher GA et al. 552-68). Initially such evidence was based almost entirely on clinical findings, and to a lesser extent, on the results of paraclinical evidence, at that time principally cerebrospinal fluid (Poser et al. 227-31). Classically, to diagnose MS, at least two relapses (“dissemination in time”, DIT) are required, including objective clinical evidence of more than one separate lesion in the CNS (“dissemination in space”, DIS); this is called clinically definite MS (CDMS). Whether (para)clinical evidence can best be explained by one or by more underlying anatomical lesions, and thus provide evidence for dissemination in space, was not defined further and left to the diagnosing physician. The most sensitive paraclinical test is Magnetic Resonance Imaging (MRI), showing abnormalities in approximately 95% of patients with CDMS and valuable in ruling out other neurological diseases. With detailed MRI criteria (Barkhof et al. 2059-69; Tintore et al. 702-06) requiring an MRI to show a minimum number of lesions located at MS specific locations and showing specific activity, it was possible to substitute part of the clinical evidence and consequently provide additional evidence for DIS (table...
1) and DIT. With these MRI criteria, the second relapse was no longer required in a substantial number of patients; the diagnosis could now be made after the first relapse.

Diagnostic tests: sensitivity and specificity

**Specificity** is the proportion of patients without the disease who have a negative test result.

**Sensitivity** is the proportion of patients with the disease who have a positive test result (i.e. the percentage of sick people who are correctly identified by the test as having the condition).

Sensitivity and specificity are independent of the prevalence of the disease in the studied population. For example positive and negative predictive value, in contrast, are dependent of the prevalence of the disease in the studied population. A diagnostic test with high specificity is valuable to confirm a diagnosis, whereas a test with high sensitivity is important for ruling out the disease.

Box 1. Explanation of sensitivity and specificity

In 2001 (McDonald et al. 121-27) these detailed Magnetic Resonance Imaging criteria were incorporated to improve diagnostic accuracy and to allow for an earlier diagnosis (Table 2). It was then shown that the majority of MS patients have spinal cord lesions on MRI, whereas patients with other neurological diseases seldom have such lesions (Bot et al. 46-56). Another study (Dalton et al. 673-76) demonstrated that a new T2 lesion on an MRI made on an average of 5 weeks after disease onset, was sufficient proof for the dissemination in time criterion. To incorporate the use of spinal cord and DIT criterion, and clarify original definitions, the
diagnostic guidelines were again revised in 2005 (Polman et al. 840-46). Dissemination in time could now be established by the presence of a new T2 lesion on an MRI made at least 1 month after disease onset.

Table 1. Magnetic Resonance Imaging Criteria for Brain Abnormality
Three of four of the following

1. One gadolinium-enhancing lesion or nine T2-hyperintense lesions if there is no gadolinium enhancing lesion
2. At least one infratentorial lesion
3. At least one juxtacortical lesion
4. At least three periventricular lesions

Note: One spinal cord lesion can be substituted for one brain lesion. Data from Barkhof et al and Tintoré et al.

In spite of the increasing role for MRI in diagnosing MS, clinical data remain essential. Whereas rules for the interpretation of MRI data are defined in detail, no such clinical classification existed. The need for additional paraclinical investigations such as MRI, depends on the available clinical information. As more evidence for DIS and DIT can be assessed clinical, less paraclinical information is needed. In order to accomplish dissemination in space criteria clinically for example, there has to be objective evidence of 2 or more clinical lesions (McDonald et al. 121-27). Whether symptoms and signs can be explained by 2 or more clinical lesions however, is left to the diagnosing physician and has been shown to vary widely (Uitdehaag et al. 227-31). Additionally, knowledge of factors that predict disease progression, especially in the early stages of the disease, is limited but of increasing importance as more therapy becomes available that may be beneficial in the early disease stages. A clinical classification system to define dissemination in space in more detail (Figure 2) was proposed to provide further guidance on this subject. In chapter 3.1 and 3.2 we evaluated the relation between this clinical classification (Uitdehaag et al. 227-31) and MS related abnormalities on brain MRI. This clinical classification system defines disease onset as
monofocal (clinical evidence of one lesion in the central nervous system) or multifocal (clinical evidence of more than one lesion). Besides its diagnostic value, such a classification system might also have prognostic value.

1.3 Prognosis

Multiple sclerosis is a progressive disease where accumulation of disease activity will be present in most patients after years as physical and/or cognitive impairment. After 2 years of follow up, approximately 50% of CIS patients meet the diagnostic criteria for MS. After 20 years this is more than 80% (Fisniku et al. 808-17). Although the majority of patients will consequently be diagnosed with MS, a minority of patients will remain CIS. As disease modifying agents have repeatedly proven to delay a second relapse (Comi et al. 1576-82;Comi et al. 1503-11;Jacobs et al. 898-904;Kappos et al. 1242-49;Polman et al. 899-910), it is often recommended to start disease modifying therapy after the first relapse. However, as a minority of patients have little or no further disease progression after their first relapse (thus remain CIS patients) without therapy, it would be useful to be able to identify either such patients, or, vice versa, patients who have progressive disease activity. However, few clinical prognostic factors have been described.

1.4 Outline of this thesis

Chapter 2 focuses on specificity of diagnostic criteria for MS. First (2.1) the differentiating value between MS and other neurological diseases of the MRI criteria for DIS as incorporated in the 2001 McDonald diagnostic criteria for dissemination in space are compared to the AAN proposed criteria and then (2.2) to the criteria as proposed by Swanton et al. along with the 2005 revisions of the McDonald criteria, in a group of patients initially suspected of MS who were eventually diagnosed with another disease. Chapter 2.3 describes the frequency of a neurological diagnosis 7 years after initial referral for a possible MS diagnosis in patients in whom no definite diagnosis was initially made. Chapter 2.4 describes a case report which illustrates the importance of a careful interpretation of
Table 2. Diagnostic Criteria (McDonald et al. 121-27)

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Additional Data Needed for MS Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two or more attacks; objective clinical evidence of 2 or more lesions</td>
<td>None⁷</td>
</tr>
</tbody>
</table>
| Two or more attacks; objective clinical evidence of 1 lesion | Dissemination in space, demonstrated by MRIᵇ  
or  
Two or more MRI-detected lesions consistent with MS plus positive CSFᶜ  
or  
Await further clinical attack implicating a different site |
| One attack; objective clinical evidence of 2 or more lesions | Dissemination in time, demonstrated by MRIᵈ  
or  
Second clinical attack |
| One attack; objective clinical evidence of 1 lesion (monosymptomatic presentation; clinically isolated syndrome) | Dissemination in space, demonstrated by MRIᵇ  
or  
Two or more MRI-detected lesions consistent with MS plus positive CSFᶜ  
and  
Dissemination in time, demonstrated by MRIᵈ  
or  
Second clinical attack |
Insidious neurological progression suggestive of MS

Positive CSF

\(\text{and}\)

Dissemination in space, demonstrated by 1) Nine or more T2 lesions in brain or 2) 2 or more lesions in spinal cord, or 3) 4–8 brain plus 1 spinal cord lesion

\(\text{or}\)

abnormal VEP\(^a\) associated with 4–8 brain lesions, or with fewer than 4 brain lesions plus 1 spinal cord lesion demonstrated by MRI

\(\text{and}\)

Dissemination in time, demonstrated by MRI\(^d\)

\(\text{or}\)

Continued progression for 1 year

If criteria indicated are fulfilled, the diagnosis is multiple sclerosis (MS); if the criteria are not completely met, the diagnosis is “possible MS”; if the criteria are fully explored and not met, the diagnosis is “not MS.”

\(^a\)No additional tests are required; however, if tests [magnetic resonance imaging (MRI), cerebral spinal fluid (CSF)] are undertaken and are negative, extreme caution should be taken before making a diagnosis of MS. Alternative diagnoses must be considered. There must be no better explanation for the clinical picture.

\(^d\)MRI demonstration of space dissemination must fulfill the criteria derived from Barkhof et al and Tintore et al (see Table 1).

\(^c\)Positive CSF determined by oligoclonal bands detected by established methods (preferably isoelectric focusing) different from any such bands in serum or by a raised IgG index.

\(^d\)MRI demonstration of time dissemination must fulfill the criteria listed in Table 2. Abnormal visual evoked potential of the type seen in MS (delay with a well-preserved wave form).
step 1

Tick symptoms as reported by patient:

- optic nerve dysfunction
- other cranial nerve dysfunction; specify
- oculomotor
- trigeminal nerve
- facial nerve
- other
- motor dysfunction extremities
- right upper
- left upper
- right lower
- left lower
- sensory dysfunction extremities
- right upper
- left upper
- right lower
- left lower
- coordination dysfunction extremities
- right upper
- left upper
- right lower
- left lower
- Lhermitte’s sign
- bladder / bowel dysfunction
- cognitive dysfunction
- other, specify, ...

step 2

Interpretation of symptoms ticked at step 1, location of corresponding lesions.
Tick as few as theoretically possible to explain all symptoms (consider ‘strategically located lesions’).

- optic nerve
- brainstem / posterior fossa
- spinal cord
- other, specify...
- other, unspecified

step 3

Signs at neurological examination (Functional Systems):

- visual FS score: ... if >0, new compared to step 2? 0 yes 0 no
- brainstem FS score: ... if >0, new compared to step 2? 0 yes 0 no
- pyramidal FS score: ... if >0, new compared to step 2 or previous FS? 0 yes 0 no
- cerebellar FS score: ... if >0, new compared to step 2 or previous FS? 0 yes 0 no
- sensory FS score: ... if >0, new compared to step 2 or previous FS? 0 yes 0 no
- blad/bowel FS score: ... if >0, new compared to step 2 or previous FS? 0 yes 0 no
- cerebral FS score: ... if >1, new compared to step 2 or previous FS? 0 yes 0 no

step 4

To obtain minimum number of lesions required to explain symptoms and signs:

add number of ticks at step 2 and number of ‘yes’ ticked at step 3

Figure 2. Standardize stepwise evaluation schema (Uitdehaag et al. 227-31)
medical history and physical examination in order to distinguish MS from other diseases. **Chapter 3** focuses on a previously described clinical classification system (fig 2), which translates signs and symptoms into underlying lesions in a standardized way in patients who present with a first episode suggestive of MS. This classification system was studied in patients included in the BENEFIT (Betaferon in Newly Emerging Multiple Sclerosis for Initial Treatment) trial, a double blind placebo controlled multicenter study designed to study the efficacy, safety and tolerability of interferon beta-1b. Four hundred and eighty seven patients were randomized in this trial, and randomly assigned in a 5:3 ratio to either interferon beta-1b or placebo. At study entry each patient was classified centrally as mono or multifocal according to the above mentioned classification system. Patients were scheduled to receive treatment with placebo or interferon for two years or until CDMS according to the modified Poser criteria. After completing the two year double blind study, all patients were eligible to enroll in a single arm (interferon beta-1b) follow up study with a 3 year extension (and thus 5 years total duration) designed to explore the longer term impact of early versus delayed treatment with interferon beta-1b (Kappos et al. 1242-49). In **chapter 3.1** we first concentrate on the meaningfulness of this classification system by relating it to MRI measures for disease progression. In **chapter 3.2** the prognostic value of this classification system for CDMS is assessed and compared to MRI abnormalities that are a risk factor for CDMS.
Reference List


DIAGNOSTIC GUIDELINES:
DIFFERENTIATING MS FROM OTHER NEUROLOGICAL DISEASES
CHAPTER 2.1

OVERDIAGNOSIS OF MULTIPLE SCLEROSIS AND MAGNETIC RESONANCE IMAGING CRITERIA

Jessica M Nielsen,
Tijmen Korteweg,
Frederik Barkhof,
Bernard MJ Uitdehaag and
Chris H Polman

Abstract:

Retrospectively, we assessed the specificity of two proposed magnetic resonance imaging (MRI) criteria for multiple sclerosis (MS) in patients suspected of MS but who ultimately receive another diagnosis. Brain MRIs of 28 patients mixed with 28 MRIs of MS patients from the same cohort of 377 consecutively referred patients were scored by a neuroradiologist masked for the final diagnosis. The criteria for dissemination in space incorporated in the McDonald International Panel criteria showed good specificity (89%). However, the more sensitive criteria proposed by a Subcommittee of the American Academy of Neurology resulted in a lower specificity (29%), indicating an increased risk of a false positive diagnosis.
Introduction:

In recent guidelines for diagnosing multiple sclerosis (MS) as proposed by the McDonald International Panel (IP) (McDonald et al. 121-27) magnetic resonance imaging (MRI) findings were given a critical role, mainly to allow for an earlier diagnosis of MS. MRI is the most sensitive paraclinical diagnostic test for MS (Gebarski et al. 469-74; Paty et al. 180-85) but white matter abnormalities are known to be present in many other diseases as well. They have been reported in 40-95% of patients with other neurological diseases (Bot et al. 46-56; Offenbacher et al. 905-09) and even in 44% of elderly asymptomatic patients (Fazekas et al. 1822-25).

The MRI criteria as incorporated in the IP guidelines are based on a series of studies (Barkhof et al. 2059-69; Fazekas et al. 1822-25; Paty et al. 180-85; Tas et al. 259-64) in which the predictive value of different characteristics of white matter lesions for conversion from a clinically isolated syndrome (CIS) suggestive for MS to clinically definite MS (CDMS) according to previous criteria (the Poser criteria) was evaluated. Since their publication several studies (Dalton et al. 47-53; Tintore et al. 27-30) have evaluated the IP guidelines and found a sensitivity of 74 to 83%. The specificity in these studies was reported to be 83 to 85%. However, the relevance of the latter percentages may be questioned because all studies were performed in highly selected patient groups. Patients were usually recruited in tertiary referral centres and had a typical presentation of CIS and a restricted age and disease duration. Moreover patients in whom (ultimately) another diagnosis was made, were typically excluded from analyses. Such populations are useful to address the issue of sensitivity but are of limited value to determine specificity. Because most patients from these selected populations have a second event over years (Brex et al. 158-64), these diagnostic criteria may be perceived as a parameter for disease prognosis rather than as an instrument to diagnose difficult cases.

A systematic analysis of studies resulted in a consensus report of the Therapeutics and Technology Assessment Subcommittee of the AAN (Frohman et al. 602-11) on the use of MRI in the diagnosis of MS. It was argued that three white matter lesions in patients with CIS represent...
a more sensitive predictor of the subsequent development of CDMS, without affecting specificity. This assumes a population in which the prior chance of not having the disease is negligible, which is probably true for the populations in the published studies but may not be the case in a more general clinical setting.

To approximate the specificity of these two MRI criteria for dissemination in space in clinical practice, we studied a group of patients in whom their own neurologist suspected a diagnosis of MS but after second opinion another diagnosis was made.

**Patients and methods:**

From the 754 consecutive cases referred to our MS Centre for a second opinion in the last 3 years before implementation of the IP criteria (between January 1998 and January 2001) the purpose of the referring neurologist was a confirmation or rejection of a suspected diagnosis of MS in 377 patients. In this group the following diagnoses were made using the Poser criteria for MS (Poser et al. 227-31): 195 definite MS (51.7%), 58 probable MS (15.4%), 5 other demyelinating disease (1.3%), 29 other neurological diseases (OND; 7.7%), 3 both MS and another neurological disease (0.8%). In 87 (23%) cases no certain diagnosis could be made. In four cases essential parts of the medical files could not be retrieved.

Of 29 OND patients 17 were diagnosed with ischemic cerebrovascular disease (ICVD), 4 with angiitis/vasculitis due to systemic inflammatory disease, 3 with multiple system atrophy and in 5 other single diagnoses were made. In order to determine ‘true’ specificity of diagnostic criteria we focused on patients in whom another diagnosis was positively made (OND). Patients in whom a diagnosis of MS could not (yet) be made were not included in the analysis to avoid circular reasoning and thus overestimating the specificity of the IP criteria. Diagnoses were always based on the combination of clinical, laboratory and (additional) radiological data, in a few patients including tissue biopsy, wherever possible in accordance with accepted diagnostic guidelines.

The original brain MRI on which the diagnosis of MS was suspected was available for 28 of these 29 patients. To mask the radiologist for
the ultimate diagnosis we mixed these scans with 28 scans of randomly selected patients from the same cohort in whom the diagnosis of definite MS according to the Poser criteria was confirmed. Thus, 56 patients were included in the analysis. The scans were presented in random order to an experienced neuroradiologist who scored the scans according to the MRI characteristics as incorporated in the different diagnostic criteria that then were specified as either fulfilling or not fulfilling the criteria for dissemination in space as incorporated in the IP guidelines and the criterion of three or more lesions as proposed by the AAN Subcommittee.

Specificity (true-negative rate) and sensitivity (true-positive rate) and 95% confidence intervals (CIs) were calculated for both the IP MRI criteria and the AAN criterion using CIA software (version 2.0.0 Trevor Bryant, University of Southampton). Additional statistical tests were performed using SPSS software (version 11.0). Reported $p$ values are based on two-tailed significance tests with a threshold of 0.05.

**Results:**

Patient characteristics are summarized in Table 1. Patients with OND were older than MS patients ($p=0.002$), but had comparable sex distribution and disease duration. Imaging characteristics and univariate OR for different MRI characteristics are displayed in Table 2.

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Other neurological diseases (N=28)</th>
<th>MS (N=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>49.8 (SD 9.5)</td>
<td>41.6 (SD 8.7)</td>
</tr>
<tr>
<td>Gender** (female: male)</td>
<td>17:11</td>
<td>20:8</td>
</tr>
<tr>
<td>Disease duration***</td>
<td>2.6 (3.7) years</td>
<td>1.9 (2.6) years</td>
</tr>
<tr>
<td>Type of MS</td>
<td>20 (71.4%) RR****</td>
<td>5 (17.9%) PP****</td>
</tr>
<tr>
<td></td>
<td>3 (10.7%) SP****</td>
<td></td>
</tr>
</tbody>
</table>

*mean value and standard deviation; difference significant ($p=0.002$).
** difference not significant
*** median and interquartile range; difference not significant
****(Lublin and Reingold 907-11)
Three of the 28 OND patients fulfilled the IP MRI criteria. These patients (one case of vasculitis and two of ICVD) all had more than 35 T2 lesions. By contrast, 20 OND patients fulfilled the AAN criterion. This results in a specificity of 89% (95% CI: 73-96%) for the IP MRI criteria and 29% (95% CI: 15-47%) for the AAN criterion (Table 3). The sensitivity in the random sample of 28 MS patients was 64% (95% CI 46-82%) and 93% (95% CI 77-98%) respectively.

**Discussion:**

We addressed the utility of different MRI criteria for MS for the first time in a sample where diagnostically difficult cases are over represented rather than excluded. The specificity of diagnostic criteria in clinical practice is more reliably estimated using such a population compared to a population in which all other diagnoses are excluded.

<table>
<thead>
<tr>
<th>Imaging findings</th>
<th>OND (n=28)</th>
<th>MS (n=28)</th>
<th>Odds ratios MS vs OND (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 9 T2 lesions</td>
<td>14 (50%)</td>
<td>22 (79%)</td>
<td>3.7 (1.1-11.8)</td>
</tr>
<tr>
<td>Infratentorial lesion present</td>
<td>7 (25%)</td>
<td>18 (64%)</td>
<td>5.4 (1.7-17.1)</td>
</tr>
<tr>
<td>Juxtacortical lesion present</td>
<td>4 (14%)</td>
<td>15 (54%)</td>
<td>6.9 (1.9-25.2)</td>
</tr>
<tr>
<td>3 periventricular lesions present</td>
<td>5 (18%)</td>
<td>21 (75%)</td>
<td>13.8 (3.8-50.2)</td>
</tr>
<tr>
<td>≥ 3 T2 lesions</td>
<td>20 (71%)</td>
<td>26 (93%)</td>
<td>5.2 (1-27.2)</td>
</tr>
</tbody>
</table>

OND = other neurological disease, CI = confidence interval

<table>
<thead>
<tr>
<th>Imaging criteria</th>
<th>OND (n=28)</th>
<th>Specificity (CI)</th>
<th>MS (n=28)</th>
<th>Sensitivity (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IP MRI criteria positive</td>
<td>3 (11%)</td>
<td>89% (73-96)</td>
<td>18 (64%)</td>
<td>64% (46-82)</td>
</tr>
<tr>
<td>AAN criterion positive</td>
<td>20 (71%)</td>
<td>29% (15-47)</td>
<td>26 (93%)</td>
<td>93% (77-98)</td>
</tr>
</tbody>
</table>

OND = other neurological disease, IP = International Panel, AAN = American Academy of Neurology, CI = confidence interval
Ideally such a study would be carried out prospectively; however, as the IP criteria have become a worldwide standard for the diagnostic process for MS, this remains a difficult task. Furthermore, we tried to optimise generalizability by selecting all patients referred by a neurologist for a second opinion regarding a possible diagnosis of MS, without any restrictions on age, typical presentation or maximum disease duration, even though the referral to a specialised MS centre does involve referrals of unusual cases and possibly to some extent cases that were not yet completely evaluated before referral.

The difference in age between the OND and the MS group expresses the average older age of onset of ICVD, neurodegenerative disease and age-related white matter changes as opposed to MS. However, although distinctive at a group level, this showed not to be valuable for an individual patient as illustrated by the large overlap between the groups.

The sensitivity of the IP MRI guidelines in this study (64%) was comparable to sensitivities of 69% and 71% reported before in CIS patients (Dalton et al. 47-53; Tintore et al. 702-06). The AAN criterion indeed had a higher sensitivity (93%), which is especially valuable to prevent false negative diagnosis. However, for the confirmation of the diagnosis, a test with a high specificity is needed. In the studies performed so far, specificity was defined in relation to risk for conversion to clinically definite MS rather than to misdiagnosis. In this study, the specificity of the IP MRI criteria was shown to be higher compared with the AAN criterion. This is probably driven by criteria for location of lesions rather than number of lesions.

After initial screening for alternative diagnoses as performed by the referring neurologist, the AAN criterion would have allowed for 20 (5.3%) incorrect MS diagnoses in a group of 377 patients as opposed to 3 (0.8%) when applying the IP MRI guidelines. This observation is of increasing importance in an era where an early diagnosis of MS is more and more likely to lead to early initiation of disease-modifying treatment, which is both expensive and associated with side effects.
Acknowledgements:

The MS Centre at the VU University is funded by a program grant of the Dutch MS Research Foundation.
References


CHAPTER 2.1A

OVERDIAGNOSIS OF MULTIPLE SCLEROSIS AND MAGNETIC RESONANCE IMAGING CRITERIA
(AUTHORS REPLY)

Jessica M Nielsen
Tijmen Korteweg
Bernard Uitdehaag
Frederik Barkhof
Chris H Polman

Ann Neurol; 2006 Mar;59(3):576
With great interest we read Drs Goodin and Frohman’s response (1) to our article (2).

We agree that determining the true cost-benefit of different diagnostic strategies is complicated. In our judgment, which indeed might be simplistic, we prefer high specificity to high sensitivity because the impact of a potentially life-long false-positive diagnosis might be greater than that of postponing disease modifying therapy (DMT) -for which long-term effects have only incompletely been assessed- until a next attack. It seems likely that the diagnosis of multiple sclerosis (MS) would rather have been delayed than actually prevented, as suggested by Goodin and Frohman, in 25.5% of the cases if these would have relapsing disease and qualify for treatment with disease modifying therapy.

We fully agree with the authors that our sample is not representative of typical MS patients in general. As we stated in our article (2), it concerns cases that were referred for a second opinion, a sample where diagnostically difficult cases are over-represented rather than excluded. It is precisely this group, where the differentiation with other MS-like diseases is so important and difficult and where specific magnetic resonance imaging (MRI) guidelines can be of extra value. We do not know whether these patients were mainly referred because of their MRI or because of their clinical presentation; we can only state that they were referred by certified neurologists because of a diagnosis of MS being seriously considered, ‘a real life’ situation.

As we acknowledged in our article (2), indeed, the design of a study such as the one we performed, should ideally be prospective. Goodin and Frohman do not share our belief that such a study would be difficult to perform. Awaiting the results of this important prospective research, we believe that our data do provide guidance on some features of the proposed diagnostic strategies.
References


CHAPTER 2.2

PERFORMANCE OF THE SWANTON MULTIPLE SCLEROSIS CRITERIA FOR DISSEMINATION IN SPACE

Jessica M Nielsen,
Bernard MJ Uitdehaag,
Tijmen Korteweg,
Frederik Barkhof,
Chris H Polman

Multiple Sclerosis, 2010 Aug;16(8):985-7
Abstract:

New diagnostic criteria for Multiple Sclerosis have been proposed by Swanton and coauthors, but were not yet evaluated in patients suspected of MS, but diagnosed with another disease. The dissemination in space criterion of these Swanton criteria was investigated in such a patient group and compared to the present McDonald criteria. We found that with the Swanton criteria for DIS, simplicity can be combined with some gain in sensitivity, without major loss of specificity.
Introduction:

Current diagnostic guidelines for multiple sclerosis (MS) (McDonald et al. 121-27; Polman et al. 840-46) partly rely on MRI criteria that were proven to be sensitive and specific (Dalton et al. 47-53; Korteweg et al. 221-27; Nielsen et al. 781-83) in their ability to predict a second clinical episode and thus antedate the diagnosis of MS according to the former Poser criteria (Poser et al. 227-31). Unfortunately, these McDonald criteria have high complexity (McDonald et al. 121-27; Polman et al. 840-46), and recently simplified MRI criteria have been proposed by Swanton (Swanton et al. 730-3). Compared to the McDonald criteria, two major changes were incorporated. First, fewer T2 lesions are required; dissemination in space (DIS) can be fulfilled by the presence of T2 lesions in at least two of four locations. Second, a new T2 lesion at any time provides evidence for dissemination in time (DIT), a requirement more sensitive than a gadolinium enhancing lesion as requirement for DIT (Dalton et al. 673-76). Compared to the McDonald criteria, these changes seem to improve the sensitivity, without compromising specificity - which was reported to be 87% in a multicenter study (Swanton et al. 677-86). However, the relevance of this observed specificity can be questioned. The studied patient population comes from several tertiary referral centers and before inclusion other diagnoses have been excluded. Thus, high specificity in this study concerns patients who do not fulfill the criteria nor experience a second episode of MS symptoms during the follow up. This specificity is thus merely related to disease progression rather than a property of the criteria to differentiate MS from other diseases.

To investigate diagnostic performance in clinical practice, we studied the present (revised) McDonald (McDonald et al. 121-27; Polman et al. 840-46) and the newly proposed Swanton MRI criteria (Swanton et al.) for DIS in a patient population (Nielsen et al. 781-83) that was referred for suspected MS by their own neurologist, but in whom another diagnosis was made after a second opinion. This population was previously used to compare diagnostic sensitivity and especially specificity (Nielsen et al. 781-83), comparing the McDonald criteria with the criteria proposed by the AAN (Frohman et al. 602-11).
Patients and methods:

The study population has been described elsewhere in more detail (Nielsen et al. 781-83). Briefly, out of all consecutive 377 patients referred for a second opinion between 1998 and 2001, 28 patients were diagnosed with other neurological diseases (OND): 17 with ischemic cerebrovascular disease, four with angiitis/vasculitis, three with multiple system atrophy and five with single other diagnoses. These and 28 recently diagnosed MS patients randomly selected from the same population were studied. Brain MRI characteristics of these patients were specified as either fulfilling or not fulfilling the criteria for DIS as incorporated in the McDonald guidelines and as proposed by Swanton et. al. Specificity (true negative rates) and sensitivity (true positive rates) and 95% confidence intervals (CIs) were calculated for both the (revised) McDonald criteria and the Swanton criteria using CIA software (version 2.1.2, Trevor Bryant, University of Southhampton). Comparisons of patient characteristics between groups were performed using SPSS software (version 16.0). Reported \( p \) values are based on two-tailed significance tests.

Results:

OND patients were older than MS patients (\( p=0.002 \)) but had comparable gender distribution and disease duration\(^5\). We found no difference in either the OND nor the MS patient groups fulfilling the original McDonald(McDonald et al. 121-27) or the revised McDonald(Polman et al. 840-46) criteria, thus the patient characteristics of these groups are reported as one (Table 1). Four OND patients fulfilled the Swanton criteria for DIS, whereas three patients fulfilled the (revised) McDonald criteria. This results in a specificity of 86% (95% CI, 69 - 94%) for the Swanton and 89% (95% CI, 73 - 96%) for the (revised) McDonald MRI criteria. The patient that did fulfill the Swanton, but not the McDonald criteria had 6 T2 lesions. She was diagnosed with neurological complications of celiac disease . In this sample of MS patients the sensitivity for the McDonald criteria was 64% (95% CI, 46 - 79%), for the Swanton criteria 71% (95% CI, 53 - 85%). This was due to two patients who did not fulfill the McDonald, but did fulfill the Swanton criteria.
Table 1. MRI scans that accomplish the different MRI criteria and their Diagnostic properties.

<table>
<thead>
<tr>
<th>Diagnostic Criteria</th>
<th>OND (n=28)</th>
<th>Specificity (CI)</th>
<th>MS (n=28)</th>
<th>Sensitivity (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swanton DIS</td>
<td>4 (14%)</td>
<td>86 (69 – 94)</td>
<td>20 (71%)</td>
<td>71 (53 – 85)</td>
</tr>
<tr>
<td>2005 McD-DIS</td>
<td>3 (11%)</td>
<td>89 (73 – 96)</td>
<td>18 (64%)</td>
<td>64 (46 – 79)</td>
</tr>
</tbody>
</table>

OND= other neurological disease, DIS=dissemination in space, CI=confidence interval, McD = Mc Donald criteria

Discussion:

This is the first study comparing specificity and sensitivity of the Swanton criteria for DIS with the McDonald criteria in a population in which diagnostically difficult cases are overrepresented rather than excluded. To optimize generalizability, we included all patients referred by neurologists concerning a possible MS diagnosis irrespective of age, symptoms or disease duration, even though this does involve referrals of unusual cases and possibly to some extent cases that were not yet completely evaluated before referral.

The older age of the OND group versus the MS group expresses the average older age of onset of ischemic cerebrovascular disease, the main differential diagnosis. We found the diagnostic performance of the McDonald criteria and the Swanton criteria to be very similar in the population studied in this paper. There was only one OND patient who was diagnosed as MS with the Swanton criteria and not the McDonald criteria (specificity 86% versus 89%) and there were 2 MS patients who were diagnosed with the Swanton criteria and not the McDonald criteria (sensitivity 71% versus 64%). The sensitivity of the Swanton criteria in our study is lower than reported previously (90% and 85.9% [95% CI 76.5-92.5])(Swanton et al.; Swanton et al. 677-86). This might be due to the primary progressive patients in the MS group, as these are known to have fewer cerebral lesions compared with relapsing-remitting patients.

There are several limitations to our study: first we studied only DIS and not DIT. With the simplification of the DIS criteria, it should be remembered that DIT is an important requirement to diagnose MS and thus ensure high specificity. Diagnosing MS without fulfilling the
DIT requirement should be discouraged. Furthermore this study should ideally be carried out prospectively instead of retrospectively as was done in this study. However, this remains a difficult task as the McDonald criteria are standard and there is presently no accepted alternative.

Previously, using exactly the same patient sample, we showed that diagnostic criteria proposed by the AAN behaved sub optimally because simplicity and increased sensitivity came at the price of much lower specificity. Here we show that with the Swanton criteria for DIS, simplicity can be combined with some gain in sensitivity, without major loss of specificity. Ideally our observation should be confirmed in a larger, prospectively collected sample, evaluating not only DIS, but also DIT. In the absence of such sample this study provides some assurance of the diagnostic behavior of the Swanton criteria in a sample which consists of diagnostically difficult cases.
Reference List


CHAPTER 2.3

LONG TERM FOLLOW-UP
OF SUSPECTED THOUGH UNCONFIRMED MS

Jessica M Nielsen,
Bernard MJ Uitdehaag,
Chris H Polman

Abstract

Objective There is no gold standard diagnostic test for MS, and evaluation of present diagnostic guidelines has almost exclusively been done in populations of which the vast majority is prone to develop MS. Patients referred for a potential MS diagnosis in whom ultimately another or no diagnosis is made are seldom reported in a systematic way. We report, after 7 years, on the diagnoses made in a cohort of patients with suspected though unconfirmed MS.

Methods We retrieved information on the current diagnosis of all patients who had visited our centre between 1998 and 2001 for a second opinion concerning a possible MS diagnosis and in whom no diagnosis had been made at that time.

Results Seventy-five patients (86%) could be retrieved and cooperated. In seven patients, a diagnosis of MS, in eight patients another neurological diagnosis had been made. In the remaining 60 patients, still no neurological diagnosis had been made.

Conclusions In potential MS patients seen in a tertiary referral centre, the likelihood that a patient who is not diagnosed with MS will in the future develop a neurological disease is small. This study suggests that, in addition to playing a role in diagnosing MS, MRI can be helpful to exclude MS in clinically doubtful cases.
Introduction

In the past decades, the process of diagnosing MS has fundamentally changed, largely because of the incorporation of (more detailed) MRI criteria in the consecutive versions of diagnostic guidelines (Poser et al. 227-31; McDonald et al. 121-27; Polman et al. 840-46). Nevertheless, a ‘gold standard’ diagnostic test is still lacking and evaluation of the diagnostic guidelines has almost exclusively been done in populations of which the vast majority of patients is likely to develop MS (Brex et al. 158-64). Patients referred for a potential MS diagnosis in whom ultimately another or no diagnosis is made are seldom reported in a systematic way. Previously, we reported on a group of such patients in whom another diagnosis was made short after initial referral for MS (Nielsen et al. 781-83). We now report on the follow up of patients from the same cohort in whom initially no certain diagnosis was made in our MS Centre, a tertiary referral centre. In this group we retrieved additional diagnostic information, 7 years after we had initially seen the patient, to be able to analyse diagnostic errors and potentially identify red flags in order to improve the diagnostic process in future cases.

Patients & methods:

We retrieved medical charts of all cases referred to our MS Centre for a second opinion between January 1998 and January 2001; 377 patients were referred for diagnostic purposes with the referring certified neurologist considering an MS diagnosis. Diagnoses made in these patients have been described before (Nielsen et al. 781-83). In 87 (23 %) patients (mean age 42 yrs; 47 women) no diagnosis could be made at the time of referral. In 2006, these 87 patients were asked to consent to an interview by phone regarding their present medical condition and diagnosis. If a diagnosis had been made in the interval period, additional visits to a neurologist or another relevant specialist were reported or the patient reported to have worsened, the patient’s consent was requested to obtain further information from the general practitioner, neurologist and/or other specialist. The study received approval from the medical ethics committee of the VU Medical Center.
Results:

In 75 out of 87 (86%) cases, the patient or authorized relation consented and was interviewed by phone. Twelve patients (10 women) refused or could not be retrieved. Baseline characteristics of these patients were similar to those of the rest of the group. A flow chart of patients is depicted in figure 1.

![Flow chart of patients referred for suspected MS by a neurologist from 1998 until 2001](image)

**Figure 1** Flow chart of patients referred for suspected MS by a neurologist from 1998 until 2001
In seven (9%) patients (six women) a diagnosis of MS had been made after 7 years on a combination of clinical course and MRI abnormalities.

In eight cases (11%, 6 women) another neurological disease (OND) had been diagnosed;

- In four patients cerebrovascular disease: on follow-up these patients experienced new vascular events and/or had additional investigations, cq (casu quo; as the case may be) in one patient a post mortem was performed. In these patients we had initially rejected the diagnosis MS because of brain MRI and/or clinical presentation being atypical for MS, in the absence of clear evidence for vascular disease.

- Single cases of ALS, hereditary spastic paraplegia and anterior horn cell disease: the first two both presented with a slowly progressive paraparesis but MS was rejected because of normal spinal cord MRI findings.

- A single case of narcolepsy who seven years before had presented with fatigue and intermittent weakness of the left leg, which was found atypical for MS, also because both spinal and brain MRI were normal.

In 60 (80%) patients (47 women) still no diagnosis had been made. Additional medical information was received from 40 of these patients. Twenty-eight patients had again visited a neurologist. Three patients had died because of: a cardiac arrest, an unknown neurological disease and suicide. The median follow-up duration of the remaining 57 patients was seven years. Of 57 patients 23 (40%) had recovered from their presenting symptoms at the time of follow up, in 26 (46%) patients there had been no change in symptoms, 8 (14%) patients reported to have worsened.

**Discussion**

In the vast majority (80%) of patients who were referred because of suspected demyelinating disease, but in whom no definite diagnosis could be made at the time of referral, no neurological diagnosis was made during an average follow-up of seven years. In 20% of these patients (i.e. only 4% (n=15) of the original total cohort of 355 patients)
a diagnosis was eventually made. MS was diagnosed in seven and another neurological disease in eight patients. In most patients in whom ultimately another neurological diagnosis was made, it was found that at initial presentation a diagnosis of MS had been rejected because of MRI findings: brain lesions were atypical for MS or spinal cord MRI was normal where clinical presentation suggested spinal cord involvement. Specific symptoms or signs pointing to the disease that was ultimately diagnosed were not present or not recognized.

Inability to make a final diagnosis in patients referred to a tertiary centre for suspected MS is a well-known problem. To our knowledge, this is one of the first studies to address this issue by performing a systematic long-term follow-up of such patients. Our population is clearly different from that seen in a general neurology clinic and biased towards diagnostic uncertainty. However, we have no indication of any other bias. Given the long interval between referral and this study, the number of patients lost to follow-up is acceptable. Furthermore, we don’t think that with this approach – initially by phone, thereafter requesting information from medical doctors – we missed many important diagnoses, even though we cannot be certain.

The main conclusion is that in potential MS patients seen in a tertiary MS referral centre, the likelihood that a patient who is not diagnosed with MS will in the future develop a neurological disease is small. Whereas current diagnostic criteria emphasize the role of MRI in diagnosing MS, this study points to the role of MRI in excluding MS in clinically doubtful cases.

Acknowledgement

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Reference List


THE ROLE OF SPINAL CORD IMAGING
IN THE DIAGNOSIS OF MULTIPLE SCLEROSIS

Jessica M Nielsen,
Frederik Barkhof,
Bob W van Oosten,
Chris H Polman

May;2(5):283-6
Summary

Background A 29-year-old male presented with fluctuating but progressive sensory disturbances comprising tingling and dysesthesia in his right leg. MRI of the brain showed white matter lesions initially thought to be caused by multiple sclerosis.

Investigations Neurological examination, cerebrospinal fluid examination, laboratory blood testing, brain and spinal MRI scans.

Diagnosis Spinal cord schwannoma.

Treatment and Management Surgical removal of the schwannoma. An algorithm is provided that clarifies the appropriate MRI work-up for cases where the clinical presentation is suggestive of multiple sclerosis.
The case

A 29-year-old man presented to the neurology department of a local hospital with an 18 month history of fluctuating sensory disturbances consisting of tingling and dysesthesia in the right leg. The symptoms had initially been limited to the right foot, but approximately 1 year before his presentation, they had worsened and ascended to the right knee and later to the entire right leg. The patient also complained about a general feeling of stiffness, slight balance problems and falling more easily. He had noticed increased fatigue, especially when walking long distances. He had not noticed any muscle weakness, and his bladder function was normal. His medical history was unremarkable, and revealed no other neurological problems. Neurological examination was normal, apart from brisk muscle tendon reflexes in all four extremities. Laboratory testing for hematology, renal function, glucose, thyroid function and vitamin B12 was normal. Borrelia antibody and treponemal hemagglutination (TPHA) testing was negative in the serum as well as in the cerebrospinal fluid (CSF). CSF testing also showed normal electrophoresis with no oligoclonal bands and a normal IgG index, but a slightly increased total protein level (0.67 g/l). An MRI scan of the brain showed several white matter lesions, some of which were located close to the cerebral ventricles (Figure 1). On the basis of these findings, the patient was diagnosed with multiple sclerosis (MS) and was referred to an MS Center for a second opinion, including a therapy consultation.

Approximately 2 months passed after the diagnosis before the patient was seen at the MS clinic. On presentation, his symptoms had worsened—walking had become more problematic, and he reported an altered sensory function while urinating, although his bladder control was still normal. On neurological examination, no major walking problems were observed. Detailed testing of motor function revealed a slight loss of strength in the left leg. The patient’s abdominal reflexes were absent, and he had very brisk reflexes in the legs and bilateral extensor plantar reflexes. There was a decreased pinprick discrimination descending from thoracic level 10 (T10) and vibration sense was abnormal in both legs. Testing of his coordination revealed a minimal intention tremor of
the right hand. Otherwise, examination of his upper extremities, cranial nerves and cognitive function was normal.

Because the current presentation was one of a slowly evolving spinal cord syndrome, MRI scanning was repeated, this time to also include the spinal cord (Figure 2). This revealed an intraspinal hypointense lesion at the level of T4–5, which enhanced after intravenous administration of a contrast agent. The lesion was surrounded by edema and had a compressing effect on the cord tissue. A diagnosis of an intraspinal tumor was made and the patient was referred for neurosurgical intervention. The tumor was surgically removed and microscopic examination showed it to be a schwannoma. The postoperative course was uneventful and in the following months the patient fully recovered, apart from a focal area of HYPESTHESIA on his trunk that had most probably resulted from the T5 nerve origin of the tumor.

**Discussion of diagnosis**

MS is among the most common causes of disability in young adults in Western countries, with a disease prevalence of approximately 1 per 1000 in Caucasians. However, establishing a diagnosis of MS requires careful consideration. Fluctuating sensory disturbances and discrete motor abnormalities in a young patient are a fairly common presentation of MS. Ever since the disease was first described, doctors have faced difficulties in determining whether an individual with certain neurological signs and symptoms actually has MS, because there is no single definitive diagnostic test available for the disease. Traditionally, the diagnostic process has involved obtaining evidence from the patient’s history, clinical examination and a variety of laboratory tests, all intended to gather data consistent with a diagnosis of MS and to rule out other possible causes of disease (Poser et al. 227-31; Schumacher GA et al. 552-68).

MRI investigations have become important in helping to confirm a diagnosis of MS, but it was not until 2001 that an international panel for the diagnosis of MS presented new diagnostic criteria known as the McDonald criteria, which focused specifically on the use of MRI as an aid
to diagnosis (McDonald et al. 121-27). Although the McDonald criteria stipulate that the core of an MS diagnosis is the demonstration at physical examination of typical disease symptoms and signs disseminated in time and space, they were the first to provide a detailed description of how MRI can be used to demonstrate abnormalities consistent with MS, with respect to dissemination in both time and space. Revisions to the McDonald criteria were recommended in 2005, both to incorporate new research findings and to clarify issues that could easily be misinterpreted.

Figure 1. T2 - weighted transverse image of the brain showing multiple high-signal lesions around the ventricles.
Figure 2. Spinal cord MRI revealing an intradural hypointense (probably calcified) mass on T2-weighted images. (A) with surrounding edema (high signal) in the compressed cord. After contrast administration, the mass enhances and is better delineated on sagittal (B) and axial (C) T1-weighted images.
These revisions relate to the guidelines for the use of MRI to demonstrate dissemination of disease in time, the question of how spinal cord MRI findings should be taken into account in this context, and the criteria required to achieve a diagnosis of primary progressive MS. Even though the MRI criteria have been selected because they have a relatively high specificity both the original publication and the recent revision stress the importance of eliminating alternative conditions that might ‘mimic’ MS.

The MRI criteria to demonstrate brain abnormality and dissemination in space are based on the Tintoré adaptation of the criteria initially provided by Barkhof et al. (Barkhof et al. 2059-69; Tintore et al. 702-06) For these characteristics to be demonstrated, three out of four of the following criteria should be fulfilled on the brain MRI: at least one gadolinium enhancing lesion or nine hyperintense lesions on T2-weighted MRI if there is no gadolinium enhancing lesion; at least one infratentorial or spinal cord lesion; at least one juxtacortical lesion; at least three periventricular lesions. One spinal cord lesion can substitute for one brain lesion.

The presenting symptoms of the patient in this case were mild, abnormal findings at neurological examination. These were not recognized as representing a spinal cord syndrome, and a spinal cord MRI was therefore not performed at the initial stage. Not only was the neuroanatomical interpretation of symptoms and signs at that time inappropriate, but so was the interpretation of the time course of the symptoms. A first episode of MS in a young adult typically presents as a so-called ‘clinically isolated syndrome’ of neurological dysfunction of the type commonly seen in MS (i.e. optic neuritis, incomplete spinal cord syndrome), with a relatively sudden onset (within days), a plateau phase, and at least partial recovery over weeks to months. The patient described here presented with fluctuating but slowly progressive abnormalities, rather than with a discrete relapse (deterioration–plateau–recovery). Certainly, a so-called ‘primary progressive’ disease course does occur in a percentage of MS patients (5-10%), but patients with this disease subtype are typically in their forties or fifties. Moreover, spinal cord MRI is of great diagnostic
relevance—particularly in cases of primary progressive MS—and it is a requirement that this be undertaken in patients presenting with a spinal cord syndrome, irrespective of the suspected underlying disease.

The diagnosis of MS in the present patient was based heavily on the interpretation of the results of his MRI brain scan. On critical review of the scan, there were approximately 10 small lesions distributed throughout the brain white matter, 3 of which were in a periventricular location. In the absence of juxtacortical or infratentorial lesions, only two out of four of the Tintore/Barkhof criteria were fulfilled - insufficient to prove dissemination in space according to the McDonald criteria. In addition, the results of the CSF examination should have provided an alert - not only were signs of intrathecal IgG synthesis lacking (the IgG index was normal and oligoclonal bands were absent), but there was also an elevated total protein concentration, which is atypical of MS.

A spinal cord MRI scan enabled the correct diagnosis to be achieved in the present case. In addition to providing either proof of or evidence to rule out an alternative diagnosis, spinal cord MRI scans often provide positive evidence of MS. Dual-echo spin-echo MRI is most sensitive for the detection of spinal cord abnormalities, which range from focal lesions to signal intensity with greater diffusion, the latter being more frequently observed in (primary) progressive MS (Lycklama et al. 555-62). In a diagnostic setting, spinal cord imaging is valuable for two reasons. First, the presence of asymptomatic spinal lesions can help confirm a diagnosis of MS in cases where there are few brain lesions present,(Bot et al. 226-33) although it should be noted that in patients with very few or only one lesion—as is seen for example in a number of patients with optic neuritis—there is no extra value in performing a spinal cord MRI scan because the presence of an additional typical spinal cord lesion would still not fulfill the McDonald criteria. Second, because asymptomatic spinal cord lesions are rare in disorders other than MS, in a patient with equivocal brain findings such as an elderly patient with ischemic vascular lesions and a prolonged disease duration, a normal spinal cord MRI scan can help rule out MS (Bot et al. 46-56).
**Table 1** Algorithm for an MRI work-up in cases where the clinical presentation is suggestive of multiple sclerosis, either as a first episode or as a slow progression.

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Recommended procedure</th>
<th>Reasons for procedure</th>
<th>Next steps</th>
</tr>
</thead>
</table>
| Spinal cord presentation | Spinal cord MRI | ■ To exclude alternative lesions such as spinal cord compression  
■ To demonstrate multiple-sclerosis-like abnormalities | ■ Brain MRI recommended if multiple sclerosis is suspected, to demonstrate (further) dissemination in space  
■ Consider follow-up brain MRI at 3 months, 12 months, or both to demonstrate dissemination in time |

| Non-spinal-cord presentation (i.e. brain or optic nerve presentation) | Brain MRI | ■ To demonstrate multiple-sclerosis-like dissemination in space  
■ To exclude an alternative diagnosis | ■ Spinal cord MRI recommended if multiple sclerosis is suspected, (only) if brain MRI is inconclusive (e.g. multiple white matter lesions in a hypertensive patient) or if criteria for dissemination in space are not met on brain MRI  
■ Consider follow-up brain MRI at 3 months, 12 months, or both to demonstrate dissemination in time |

Table 1 presents an algorithm for the appropriate MRI diagnostic work-up in cases where the clinical presentation is suggestive of MS: this algorithm is proposed to support, rather than replace, clinical decision making. On the basis of the algorithm, the patient presented in this case should have undergone spinal cord MRI, irrespective of whether the clinical presentation was interpreted as being a spinal cord syndrome.

**Differential diagnosis**

Brain white matter lesions are most frequently seen in normal aging and in cerebrovascular disease, but they are also prevalent in up to 10% of asymptomatic younger adults (Fazekas 164-68). In addition to normal aging and cerebrovascular disease, the differential diagnosis for brain white matter lesions includes systemic inflammatory disease (for example lupus erythematosus or sarcoidosis), brain infection such as neuroborreliosis, and migraine (Fazekas 164-68). In some patients, it
is not possible to identify a specific cause for the lesions, even after extensive diagnostic investigation. In such cases, the lesions are more likely to be of a vascular nature than to be caused by MS. It is advisable, therefore, to apply stringent—rather than lenient—MRI criteria for MS, particularly in an atypical clinical setting.

**Conclusion**

The patient in the present case was initially misdiagnosed with MS, thereby inducing a therapeutic delay of several months that could have been prevented if adequate imaging had been carried out after his initial presentation. This case illustrates that in order to achieve a correct diagnosis in patients presenting with symptoms similar to those seen in the present patient, a careful interpretation of medical history and signs at the time of physical examination is essential. The proposed MRI algorithm ensures that appropriate imaging procedures are undertaken. White matter lesions - even when consistent with a diagnosis of MS - should be interpreted with care, and appropriate application of the McDonald criteria can help to distinguish MS from other conditions.

**Glossary**

DYSESTHESIA An unpleasant abnormal sensation, which can be spontaneous or evoked
HYPESTHESIA A decreased tactile sensitivity
References


CHAPTER 3

EARLY PROGNOSIS
CHAPTER 3.1

CLASSIFICATION OF PATIENTS WITH A CLINICALLY ISOLATED SYNDROME BASED ON SIGNS AND SYMPTOMS IS SUPPORTED BY MRI RESULTS

JM Nielsen, B Moraal, CH Polman, P Poppe, M de Vos, MS Freedman, L Kappos, F Barkhof, L Bauer, C Pohl, R Sandbrink, H-P Hartung, BMJ Uitdehaag

Abstract:

Background: Recently, a clinical classification system was described to determine whether symptoms and signs of patients presenting with a first episode suggestive of multiple sclerosis (MS) indicate the presence of monofocal or multifocal disease.

Objectives: To evaluate the value of this new classification system by comparing the results with those of simultaneously obtained magnetic resonance imaging (MRI) scans.

Methods: The 487 patients randomised in the BENEFIT study were centrally assessed using the new system and classified as monofocal or multifocal based on clinical information by two neurologists, masked for the MRI results. MRI analyses were performed by expert readers masked for the clinical classification.

Results: Patients classified as ‘multifocal’ had more T2 hyperintense (median 21 versus 15.5) and more T1 hypointense lesions (median 2 versus 1) than those classified as ‘monofocal’. Patients classified at the local site as having evidence of a single clinical lesion, but reclassified centrally as having a clinical multifocal central nervous system presentation, had more T2 lesions than monofocal patients. In addition, patients with a multifocal presentation more often fulfilled the MRI criteria for dissemination in space as incorporated in the International Panel (IP) diagnostic criteria for MS.

Conclusion: These data provide justification for the recently proposed clinical classification system to be used in patients who present with a first episode suggestive of MS in that ‘multifocal’ based on symptoms and signs is associated with more lesions on MRI.
Introduction:

A diagnosis of MS requires evidence for dissemination in space and time of lesions in the central nervous system (Schumacher GA et al. 552-68). In providing this, clinical data are essential but additional evidence from paraclinical examinations can also be used. According to the most recent diagnostic criteria for MS, as recommended by the International Panel (IP) for the diagnosis of MS, the amount and type of additional MRI data needed for a diagnosis depend on the clinical presentation, more specifically on whether clinical evidence of one or more suspected anatomical lesions in combination with one or two episodes is already provided (McDonald et al. 121-27; Polman et al. 840-46). This clinical evidence is based upon symptoms and signs resulting from the history and neurological examination of the patient. Whether these can best be explained by one or by more underlying anatomical lesions, and, thus provide, evidence for dissemination in space, is left to the clinical judgment of the physician. Whereas the IP criteria provide detailed rules for dissemination in space based on MRI, no guidance is provided on how to integrate clinical findings. Since this can lead to substantial variability between physicians, a strategy for a uniform approach is imperative. This is especially true with respect to the terminology ‘monosymptomatic’ vs. ‘polysymptomatic’, thought to result from respectively, a single lesion and more lesions in the central nervous system (CNS). It was realized however, that ‘monosymptomatic’ patients can have examination findings indicating silent lesions elsewhere in the CNS and that a single lesion (e.g. brainstem) can result in a ‘polysymptomatic’ clinical presentation.

Recently, a classification system for the interpretation of clinical findings was proposed, which aims to translate signs and symptoms into underlying lesions in a standardized way (Uitdehaag et al. 227-31). This system leads to the classification of patients who present with clinically isolated syndromes (CIS) as monofocal or multifocal disease presentation. It was first applied centrally in the BENEFIT study. The results showed differences in the interpretation of the local investigator and the centrally applied classification system in 81 out of the 496 patients evaluated (16%) with respect to the presumed presence of one or more lesions, based on clinical findings (Uitdehaag et al. 227-31).
Reclassification to multifocal was most common, usually based on extra signs observed at neurological examination. A typical example is a patient who presents with an optic neuritis in whom at physical examination signs of pyramidal tract involvement are found based on the presence of a Babinski’s sign. This kind of patient was often classified by the local investigator as monofocal, but reclassified as multifocal while using the classification system.

Lesions on MRI consistent with demyelination are the best in vivo biological marker of MS. MRI is the most sensitive measurement to show the presence of multiple lesions. Moreover, follow up studies have shown that in CIS patients the number of T2 hyperintense lesions correlate, although moderately, with future disease course (Brex et al. 158-64).

To evaluate the value of the newly proposed clinical classification system, we compared the results with MRI scans performed at the same time. We hypothesised that CIS patients who were clinically classified as multifocal had more MRI abnormalities than monofocal patients and that multifocal CIS patients were more likely to fulfil the MRI criteria for dissemination in space as incorporated in the IP criteria. In addition, we evaluated whether the reclassified cases were justified by the MRI findings.

**Patients and methods:**

All patients in this study were participants in the BENEFIT study, which compares high dose high frequency interferon beta-1b to placebo. (Kappos L. et al. 1242-49) In this study the systematic classification scheme was applied to 496 patients. Eventually 487 patients were randomized in the study and of all these patients quantitative MRI data were available. Main inclusion criteria were: age between 18 and 45; single, first clinical episode suggestive of demyelinating disease within the last 60 days; at least two clinically silent lesions on T2 weighted brain MRI, at least 3 mm in size, one of which should be ovoid, periventricular or infratentorial. As MS according to the IP criteria was one of the primary endpoints for this study, much emphasis was given to systematic classification of clinical presentation in combination with MRI characteristics. All patients were classified by the local investigators
as having mono- or polysymptomatic disease. In the study protocol, polysymptomatic onset was defined as ‘evidence of more than one clinical lesion’. In the central reading centre at the VU Medical Centre all patients were subsequently classified as mono- or multifocal according to a standardized scheme, as previously described (Uitdehaag et al. 227-31). Briefly, on basis of the neurological symptoms the location of the minimum number of lesions that could explain all symptoms is determined. Subsequently, from all information from the neurological examination it is decided whether these abnormalities could in any way be explained by the already identified clinical lesions. If not, this would indicate the presence of an additional clinical lesion. Patients thus classified as having evidence of one clinical lesion were called monofocal, patients thus classified as having evidence of more than one clinical lesion were called multifocal. This classification was done in consensus by two neurologists masked for the MRI results.

At study entry all patients had a brain MRI done both pre and post gadolinium, according to protocol. All MRI studies were sent to the Image Analysis Centre in Amsterdam for centralised analysis of T2 hyperintense, T1 gadolinium enhancing and T1 hypointense lesions, as well as for fulfilment of the criteria for dissemination in space according to the IP criteria. Since for the present study we were only interested in dissemination in space and not in dissemination in time, we only used cross sectional MRI data.

Statistical tests were performed using SPSS software (Version 11.0). For qualitative data chi-square tests were applied. For quantitative data t-tests were applied after checking if data were approximately normally distributed. If that was not the case either log transformation was performed or Mann-Whitney U test was applied. Reported p-values are based on two-tailed significance tests. The threshold for significance was set at 0.05.

Results:

MRI T2 lesion counts as well as clinical data were available for all 487 randomized patients. The number of T1 hypointense lesions was missing in three cases, the number of gadolinium enhancing lesions in four cases.
In four cases, the local investigator changed the classification between screening and baseline (as these patients developed new symptoms after the initial screening examination). Median age was 30 years (range 18-45), 70% of the patients were female. Based on the centrally applied classification scheme, 254 patients were classified as monofocal and 233 as multifocal.

As can be seen in Table 1, age and gender distribution were similar for monofocal and multifocal patients. The median number of T2 lesions in the monofocal cases was 15.5 versus 21 in the multifocal cases ($p=0.016$). The median number of T1 hypointense lesions was 1 in the monofocal and 2 in the multifocal group ($p=0.008$). Patients presenting with multifocal symptoms and signs were more likely to fulfil more criteria for dissemination in space on brain MRI as incorporated in the IP criteria than monofocal patients (chi square test for trend $p=0.005$) (Figure 1).

As overall differences between the classification by the local investigator and the centrally applied classification system were likely to be very small due to the large overlap between the groups, we separately analysed discrepant cases (Table 2). Of the 290 patients (60%) who were classified by the local neurologist as having evidence of one clinical lesion (‘monosymptomatic’), 61 were centrally reclassified as multifocal whereas the other 229 cases were judged to be monofocal. Of

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Age in yrs (range)</td>
</tr>
<tr>
<td>Gender, Female</td>
</tr>
<tr>
<td>Median T2 lesions (IQR)</td>
</tr>
<tr>
<td>Median T1 hypo intense lesions (IQR)</td>
</tr>
<tr>
<td>Median T1 Gado lesions (IQR)</td>
</tr>
</tbody>
</table>

**$p=0.016$ (t-test after log transformation)
#$p=0.008$ (Mann Whitney test)
IQR= Interquartile range
the 197 patients that were classified by the local investigator as having evidence of more than one clinical lesion (‘polysymptomatic’), 25 were centrally reclassified as monofocal, whereas the other 172 patients were classified as multifocal. Comparing these four subgroups, cases that were
centrally reclassified from 'monosymptomatic' to multifocal had more T2 hyperintense lesions than those classified unanimously as monofocal (Table 2). Most of these patients were multifocal on signs (50/61); 38 of these presented with an optic neuritis of which 18 (47%) were multifocal on additional pyramidal and 9 (24%) on additional brainstem signs. In contrast, MRI characteristics of patients who were reclassified from 'polysymptomatic' to monofocal did not differ from patients who were classified unanimously as multifocal.

**Discussion:**

Although a diagnosis of MS according to the International Panel on the diagnosis of MS guidelines depends, to a great extent, on the interpretation of clinical findings, no clear guidance for their interpretation has been presented. In this study, we evaluated the relation between a recently published proposal for clinical classification (Uitdehaag et al. 227-31), which interprets clinical findings in terms of the presumed presence of one (monofocal) or at least two (multifocal) clinical anatomical lesions, and MS related abnormalities on MRI of the brain. Our hypothesis was that patients who were classified as having multifocal disease on the basis of clinical findings had more MRI abnormalities than those classified as being monofocal.

Whereas all patients included in this study have limited clinical disease (first episode of neurological dysfunction, frequently monosymptomatic) they already have significant numbers of brain lesions on their brain MRI. This is a well-known phenomenon (Comi et al. 1576-82) related to the fact that MRI is more sensitive in picking up disease activity, including subclinical activity. In this specific study the number of MRI abnormalities was higher than in an unselected CIS population, since a minimum number of two asymptomatic brain lesions was required as inclusion criterion. Therefore, it remains to be evaluated whether the results of this study can be generalized to an unselected population of CIS patients which also includes patients with less than 2 asymptomatic lesions.

Compared to patients classified as monofocal, indeed, multifocal patients had significantly more T2 hyperintense, and T1 hypointense ('black holes’) lesions, and fulfilled more MRI criteria for dissemination
in space as incorporated in the IP criteria. Apparently the clinical classification is reflected in MRI measures that represent the total burden of disease, the more destructive lesions, as well as the distribution of lesions in more or less MS specific regions of the brain, thereby suggesting that it does have clinical utility. Considering that MRI is a far more sensitive measure of disease activity than clinical episodes are (Isaac et al. 1511-15; Willoughby et al. 43-49), it is not surprising that the relation between the clinical classification and MRI is only weak and that there is a large overlap between the lesion numbers in the mono- versus multifocal cases.

The systematic approach as introduced by the clinical classification scheme induces two types of classification changes. In the first place, some patients who were judged to have one clinical lesion were reclassified as multifocal on the basis of findings at neurological examination. The current study strongly suggests that these often subtle abnormalities do have an anatomical basis: ‘monosymptomatic’ patients who were clinically (re)classified as multifocal had more MRI lesions than those classified as monofocal. In the second place, patients who were ‘polysymptomatic’ could be classified as monofocal if their symptoms were judged to be possibly explained by only one strategically located anatomical lesion. The correlation with MRI does not provide a justification for this, since, among polysymptomatic patients, lesion numbers were not significantly different when comparing mono- versus multifocal.

In conclusion, the current study does provide justification for a recently proposed clinical classification system to be used in patients who present with a first episode suggestive of MS in that ‘clinically multifocal’ is associated with more lesions on MRI. This is especially true for those patients who present with monosymptomatic disease (i.e. isolated optic neuritis or spinal cord syndrome). Further studies should address the question whether the proposed clinical classification also has an impact on future disease course or treatment response.
## Reference List


MRI characteristics are predictive for CDMS in monofocal, but not in multifocal patients with a clinically isolated syndrome.
Abstract

Background: To diagnose multiple sclerosis (MS), evidence for dissemination in space and time is required. There is no clear definition on how symptoms and signs of a patient indicate clinical dissemination in space. To provide a uniform approach on this subject, a clinical classification system was described recently differentiating patients with mono- and multifocal clinical presentation. Here we assess the predictive value of clinically defined dissemination in space at first presentation for time to clinically definite MS (CDMS).

Methods: Four hundred and sixty-eight patients with a first episode suggestive of MS were classified as clinically mono- or multifocal by two neurologists blinded to magnetic resonance imaging (MRI) results. These patients were part of the BENEFIT study in which 292 patients were randomized to interferon beta-1b (IFNB-1b) and 176 to placebo. By using Kaplan-Meier statistics the risk for CDMS was studied in mono- and multifocal patients of the placebo group, both with and without taking into account MRI measures of potential prognostic relevance.

Results: Time to CDMS was similar in monofocal and multifocal patients. In monofocal patients, the risk for CDMS over 2 years was significantly higher when ≥ 9 T2 lesions or at least one Gd-enhancing lesion were present at the first event or 3 or 6 months after the first event. In patients with multifocal presentation, these MRI measures had no significant added value in predicting time to CDMS.

Conclusions: These data indicate that a carefully performed neurological assessment of symptoms and signs, combined with lesions on MRI, is important for defining the risk of conversion to CDMS. The Benefit trial has been registered under NCT00185211 www.clinicaltrials.gov
Background

Multiple sclerosis (MS) has a highly variable disease course (Confavreux, Vukusic, and Adeleine 770-82) and knowledge of factors that predict subsequent disease course in individual patients with a first event suggestive of MS (also called patients with a clinically isolated syndrome: CIS) is limited.

In CIS patients, magnetic resonance imaging (MRI) characteristics have been described as a predictor of conversion to clinically definite MS (CDMS) and of the subsequent disease course. CIS patients with an abnormal cerebral MRI scan at presentation have a substantially higher long-term risk of conversion to CDMS than those with a normal cerebral MRI (Brex et al. 158-64). Diagnostic guidelines for MS include detailed MRI rules for the definition of dissemination in space of MS-specific pathology (McDonald et al. 121-27; Polman et al. 840-46). In untreated (Korteweg et al. 221-27) and treated (Barkhof et al. 718-24) CIS patients fulfillment of these criteria is associated with a high risk of CDMS.

According to the recommendations of the International Panel (IP) on the Diagnosis of Multiple Sclerosis, disease dissemination in CIS patients can also be identified by clinical examination of symptoms and signs at the first clinical event (McDonald et al. 121-27). In contrast to a detailed algorithm on the use of MRI criteria, however, it was left unclear how clinical disease dissemination should be evaluated. Recently it was shown that the clinical assessment of disease dissemination can vary widely between physicians (Uitdehaag et al. 227-31). To standardize these assessments, a clinical classification system was proposed (Uitdehaag et al. 227-31). This system was centrally applied to patients of the BEtaferon®/BEtaseron® in Newly Emerging multiple sclerosis For Initial Treatment (BENEFIT) study, a study evaluating the impact of interferon beta-1b (IFNB-1b) in CIS patients. By analyzing baseline data from this study we have recently shown that patients with clinical dissemination in space (multifocal, indicating more than one clinical lesion) had more lesions on their MRI than monofocal patients (those exhibiting symptoms and signs from only one clinical lesion) (Nielsen et al. 717-21).
In the present study we assessed the prognostic value of this clinical classification system (Uitdehaag et al. 227-31) for conversion to CDMS and the added value of potentially prognostic MRI parameters, by analyzing data obtained during the placebo-controlled treatment period of the BENEFIT study.

Methods

Study design, patients, and procedures
BENEFIT is a multicenter study comparing IFNB-1b to placebo in CIS patients for up to 2 years, followed by a follow-up period with IFNB-1b for up to 5 years after the CIS. For the present analyses we used data from the placebo-controlled first 2 years of the study. The design and main outcomes of the placebo-controlled phase of the BENEFIT trial have been reported elsewhere (Kappos et al. 1242-49). Patients completed the placebo-controlled phase of BENEFIT if they either reached 24 months of follow-up or were diagnosed with CDMS. Briefly, inclusion criteria encompass: age between 18 and 45 years, presentation with a first neurological event suggestive of MS, and the presence of at least two clinically silent lesions on a T2-weighted brain MRI scan with a minimum size of 3 mm, at least one of which was ovoid, periventricular, or infratentorial.

Patients were randomly assigned in a 5:3 ratio to IFNB-1b 250 µg or placebo, by subcutaneous injection every other day. Study treatment was initiated within 60 days of confirmation of the first clinical event. Regular visits were scheduled for collection of clinical, MRI findings, and other data on disability progression as measured by the expanded disability status scale (EDSS) (Kurtzke 1444-52). All MRI scans were performed with 0.1 mmol/kg gadolinium. MRI findings and other parameters at months 3, 6, 9, 12, 18, and 24. Several MRI parameters were analyzed; in particular, number of: gadolinium (Gd)-enhancing lesions, hyperintense T2 lesions, hypointense T1 lesions, and newly active lesions (NALs). A NAL was defined as a new T2 hyperintense or Gd-enhancing lesion, or a newly enlarging T2 lesion. The numbers and volumes of hyperintense lesions on T2-weighted images and Gd-enhancing lesions on T1-weighted images were centrally evaluated at the Image Analysis Center in Amsterdam,
The Netherlands. MRI analyses were performed by expert readers who were blinded to the patients’ clinical classification.

As MS according to the criteria proposed by the IP on the Diagnosis of Multiple Sclerosis (McDonald et al. 121-27) was one of the primary outcome measures, much emphasis was placed on the clinical classification of patients. On the basis of all available information of clinical signs and symptoms, as documented by the local investigator, patients were classified centrally by the consensus of two neurologists (CHP and BMJU) as having an either monofocal or multifocal disease presentation according to the previously described standardized scheme (Uitdehaag et al. 227-31). Briefly, on the basis of the neurological symptoms the minimum number of central nervous system (CNS) areas that could explain all symptoms was determined (=monofocal or multifocal presentation as defined by symptoms). Subsequently, it was decided whether abnormalities as revealed by the neurological examination (=signs) indicated the presence of additional lesions in the CNS (=monofocal or multifocal presentation as defined by signs).

In the case of a multifocal presentation it was then decided whether the patient’s multifocal classification was purely based on multiple presenting symptoms (these patients are denoted as multifocal patients by symptoms) or whether clinical signs indicated additional CNS lesions that did not correspond to any of the presenting symptoms (these patients are denoted as multifocal patients by signs). This sub classification of multifocal patients was carried out under the hypothesis that such additional clinical signs (in the absence of concomitant symptoms) might point to subclinical disease activity preceding the reported onset.

Statistical analysis

The following analyses were performed to evaluate different disease characteristics of 1) monofocal versus multifocal CIS patients; and 2) multifocal CIS patients by signs only versus by symptoms only. In order to avoid any influence of IFNB-1b treatment on the results, analyses on time to CDMS were only performed in placebo patients whilst analyses on baseline parameters were performed in the total patient cohort. Analyses were performed using SAS.
Comparison of key baseline characteristics between mono- and multifocal patients at the first event and between the multifocal subgroups by signs and by symptoms (all patients)
The following parameters were analyzed: Age, sex, steroid use at first event, EDSS at screening, positive CSF findings, number of T2-hyperintense lesions, number of / proportion of subjects with at least one Gd-enhancing lesion(s), proportion of subjects with at least one T1 hypointense lesion.

Comparison of time to CDMS and MRI disease activity between the monofocal and multifocal patients and between the multifocal subgroups by signs and by symptoms (placebo patients)
Time to CDMS was analyzed as a measure for clinical activity and the annualized cumulative number of NALs over the study was analyzed as a measure of subclinical activity.

Comparison of the impact of MRI findings at screening, month 3, and month 6 on time to CDMS within the monofocal and multifocal group separately (placebo patients)
These analyses were only performed on data from the mono- and multifocal subgroups, as patient numbers were too small to further stratify the multifocal subgroups by symptoms and by signs. The following MRI parameters were evaluated: presence of Gd-enhancement, or pronounced disease dissemination (≥ 9 T2 lesions) on the screening MRI; new Gd-enhancement at months 3 or 6.

Dichotomous variables were compared using Fisher’s exact test. Continuous variables were compared using the Mann-Whitney U-test (comparison of the cumulative number of NALs was done by a Wilcoxon test). Kaplan-Meier survival analysis was used to analyze time to CDMS. Group comparisons for this outcome measure were performed using the log-rank test. Interaction of clinical mono-/multifocality and MRI parameters was analyzed by Cox proportional hazards regression. Reported p-values are based on two-tailed significance tests, with the threshold for significance set at 0.05. Analyses were performed post hoc.
on data from the placebo-controlled period of the BENEFIT study for all patients who were randomized and received study medication at least once.

Results

Four hundred and eighty-seven patients were randomized and 468 started treatment in the BENEFIT study. Four hundred and thirty-seven of these (93.6%) completed the placebo-controlled study. Two hundred and ninety-two patients received IFNB-1b and 176 received placebo. The main outcome data have previously been published (Kappos et al. 1242-49).

Table 1. Disease characteristics of monofocal vs. multifocal CIS patients

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Monofocal</th>
<th>Multifocal</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>468 (100%)</td>
<td>246 (53%)</td>
<td>222 (47%)</td>
<td></td>
</tr>
<tr>
<td>Sex – % of females</td>
<td>71%</td>
<td>66%</td>
<td>76%</td>
<td><strong>0.0325†</strong></td>
</tr>
<tr>
<td>Age, median (quartiles)</td>
<td>30 (24–37)</td>
<td>29 (24–37)</td>
<td>31 (25–37)</td>
<td>0.0820‡</td>
</tr>
<tr>
<td>Steroid treatment – %</td>
<td>71%</td>
<td>72%</td>
<td>70%</td>
<td>0.6835†</td>
</tr>
<tr>
<td>EDSS (screening), median (quartiles)</td>
<td>2 (1–2.5)</td>
<td>1.5 (1–2)</td>
<td>2 (1.5–2.5)</td>
<td>&lt;0.0001‡</td>
</tr>
<tr>
<td>CSF positive of samples taken – %</td>
<td>267/314</td>
<td>149/176</td>
<td>118/138</td>
<td>0.8745†</td>
</tr>
<tr>
<td>Number of T2 lesions, median (quartiles)</td>
<td>17 (7–38)</td>
<td>16 (6–36)</td>
<td>21 (8–41)</td>
<td>0.0182‡</td>
</tr>
<tr>
<td>At least one Gd-enhancing lesion – %</td>
<td>42%</td>
<td>42%</td>
<td>43%</td>
<td>0.9254†</td>
</tr>
<tr>
<td>At least one T1 hypointense lesion – %</td>
<td>68%</td>
<td>63%</td>
<td>73%</td>
<td><strong>0.0300†</strong></td>
</tr>
</tbody>
</table>

*Compares monofocal vs. multifocal patients. P-value in bold when p ≤ 0.05
†Fisher’s exact test, ‡Mann-Whitney U-test

EDSS: expanded disability status scale, CSF: cerebrospinal fluid, Gd: gadolinium
Comparison of key baseline characteristics of mono- and multifocal CIS patients (all patients)

Two hundred and forty-six (53%) patients were classified as monofocal and 222 (47%) as multifocal. Baseline characteristics of mono- and multifocal patients are outlined in Table 1 and have been reported previously (Nielsen et al. 717-21). In summary: Multifocal patients had a higher number of T2-hyperintense lesions ($p = 0.018$) and more frequent T1-hypointense lesions ($p = 0.030$).

Comparison of time to CDMS and MRI disease activity between the monofocal and multifocal patients (placebo patients)

Neither time to CDMS (Hazard ratio / ± 95% CI: 1.09 / 0.70-1.71; $p = 0.71$) nor the annualized cumulative number of NALs ($p=0.47$ by Wilcoxon test and $p = 0.51$ by baseline adjusted non-parametric ANCOVA, see Table 2) differed significantly between mono- and multifocal placebo patients.

Comparison of the impact of MRI findings at screening, month 3, and month 6 on time to CDMS within the monofocal and multifocal group separately (placebo patients)

The risk of CDMS was significantly higher in monofocal placebo patients with $\geq 9$ T2-hyperintense lesions at screening (Hazard ratio / ± 95% CI: 2.13 / 1.05-4.34; $p = 0.032$), with at least one Gd-enhancing lesion at screening (Hazard ratio / ± 95% CI: 2.28 / 1.24-4.18; $p = 0.006$), with at least one Gd-enhancing lesion at month 3 (Hazard ratio / ± 95% CI: 3.03 / 1.51-6.07; $p < 0.002$), and with at least one Gd-enhancing lesion at month 6 (Hazard ratio / ± 95% CI: 3.98 / 1.84-8.65; $p < 0.001$) than in monofocal placebo patients without these criteria (Figure 1, 2).

The risk of CDMS was not significantly higher in multifocal placebo patients with $\geq 9$ T2-hyperintense lesions at screening (Hazard ratio / ± 95% CI: 0.74 / 0.36-1.54; $p = 0.42$), with at least one Gd-enhancing lesion at screening (Hazard ratio / ± 95% CI: 0.96 / 0.48-1.93; $p = 0.92$), with at least one Gd-enhancing lesion at month 3 (Hazard ratio / ± 95% CI: 1.03 / 0.48-2.23; $p = 0.94$), and with at least one Gd-enhancing lesion at month 6 (Hazard ratio / ± 95% CI: 2.04 / 0.86-4.86; $p = 0.11$), than in multifocal placebo patients without these criteria (Figure 1, 2).
Table 2. Disease course of monofocal vs. multifocal placebo patients after the CIS

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Monofocal</th>
<th>Multifocal</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>176</td>
<td>93</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>CDMS %* over 2 years</td>
<td>45%</td>
<td>47%</td>
<td>44%</td>
<td>0.7052†</td>
</tr>
<tr>
<td>Median annualized cumulative number of NALs over the study (quartiles)</td>
<td>3.2 (0.96–10.4)</td>
<td>3.0 (0.5–9.4)</td>
<td>3.6 (1.0–12.5)</td>
<td>0.4698‡</td>
</tr>
</tbody>
</table>

*Compares monofocal vs. multifocal patients
NAL: newly active lesion
CDMS: clinically definite MS
*Kaplan-Meier estimate at day 720, Log rank test
‡Wilcoxon test

Table 3. Disease characteristics of multifocal patients by symptoms and by signs at the CIS

<table>
<thead>
<tr>
<th></th>
<th>Multifocal</th>
<th>Multifocal by symptoms</th>
<th>Multifocal by signs</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>222</td>
<td>122</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Sex – % of females</td>
<td>76%</td>
<td>77%</td>
<td>74%</td>
<td>0.6389†</td>
</tr>
<tr>
<td>Age, median (quartiles)</td>
<td>31 (25-37)</td>
<td>30.5 (25-36)</td>
<td>31 (25-38)</td>
<td>0.7919‡</td>
</tr>
<tr>
<td>Steroid treatment – %</td>
<td>70%</td>
<td>72%</td>
<td>67%</td>
<td>0.4632‡</td>
</tr>
<tr>
<td>EDSS (screening), median (quartiles)</td>
<td>2 1.5-2.5</td>
<td>2 1.5-2.5</td>
<td>2 1.5-2.5</td>
<td>0.9598‡</td>
</tr>
<tr>
<td>CSF positive of samples taken – %</td>
<td>118/138 86% (53%)</td>
<td>62/70 89% (51%)</td>
<td>56/68 82% (56%)</td>
<td>0.3405†</td>
</tr>
<tr>
<td>Number of T2 lesions, median (quartiles)</td>
<td>21 (8-41)</td>
<td>19.5 (8-47)</td>
<td>22.5 (9-40)</td>
<td>0.9130‡</td>
</tr>
<tr>
<td>At least one Gd-enhancing lesion – %</td>
<td>42%</td>
<td>45%</td>
<td>39%</td>
<td>0.3376†</td>
</tr>
<tr>
<td>At least one T1 hypo intense lesion – %</td>
<td>73%</td>
<td>71%</td>
<td>74%</td>
<td>0.7627†</td>
</tr>
</tbody>
</table>

†Fisher’s exact test, ‡Mann-Whitney U-test , EDSS: expanded disability status scale, CSF: cerebrospinal fluid, Gd: gadolinium
This differential effect of MRI parameters on the risk of conversion to CDMS in these two patient groups (monofocal and multifocal) was confirmed by Cox proportional hazards regression. This analysis revealed a significant interaction between mono-/multifocality and either ≥ 9 T2-hyperintense lesions at screening (Hazard ratio / ± 95% CI: 0.35 / 0.13-0.96; p = 0.042) or at least one Gd-enhancing lesion at month 3 (Hazard ratio / ± 95% CI: 0.34 / 0.12-0.96; p = 0.042), but not between mono/multifocality and at least one Gd-enhancing lesion at screening (Hazard ratio / ± 95% CI: 0.42 / 0.17-1.05; p=0.064) or at least one Gd-enhancing lesion at month 6 (Hazard ratio / ± 95% CI: 0.50 / 0.16-1.6; p = 0.246).

Comparison of key baseline characteristics of multifocal patients by symptoms and multifocal patients by signs at the first event (all patients)
One hundred and twenty-two (55%) of the 222 multifocal patients presented by symptoms, while 100 (45%) presented by signs (the classification of these latter patients was based on the presence of signs indicating an additional clinical lesion, according to the central classification). Baseline characteristics did not differ significantly between multifocal patients by symptoms and by signs (Table 3).

Table 4. Disease course of multifocal placebo patients by symptoms and by signs after the CIS

<table>
<thead>
<tr>
<th></th>
<th>All multifocal</th>
<th>Multifocal by symptoms</th>
<th>Multifocal by signs</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>83</td>
<td>50 (60%)</td>
<td>33 (40%)</td>
<td>0.3554†</td>
</tr>
<tr>
<td>CDMS % over 2 years</td>
<td>44%</td>
<td>49%</td>
<td>37%</td>
<td>0.0424‡</td>
</tr>
<tr>
<td>Median annualized cumulative number of NALs over the study (quartiles)</td>
<td>3.6 (1.0–12.5)</td>
<td>5.3 (1.6–13.4)</td>
<td>2.6 (0–7.0)</td>
<td>0.0424‡</td>
</tr>
</tbody>
</table>

*Compares multifocal patients by symptoms vs. multifocal patients by signs
†Kaplan-Meier estimate at day 720, Log rank test
‡Wilcoxon test
CDMS: clinically definite MS, NAL: newly active lesion, Gd: gadolinium
Comparison of time to CDMS and MRI disease activity between multifocal patients by symptoms and by signs (placebo patients)

There was no statistically significant difference between the survival curves of “Time to CDMS” comparing multifocal placebo patients by symptoms and by signs (Hazard ratio / ± 95% CI: 0.72 / 0.36-1.45; p = 0.36). Multifocal placebo patients by symptoms developed a higher annualized number of NALs over the study period (p = 0.042 by Wilcoxon test; Table 4, supplemental data file).

Discussion

In a cross-sectional analysis of baseline data from CIS patients in the BENEFIT study we have recently demonstrated that clinical dissemination of the disease corresponds to more widespread subclinical CNS pathology as detected by cerebral MRI (Nielsen et al. 717-21). In the present study we addressed whether clinical disease dissemination in these patients also indicates an increased risk for subsequent disease activity, and whether the presence versus absence of clinical dissemination has an impact on the prognostic value of MRI parameters.

Patients with monofocal versus multifocal clinical presentation did not differ in terms of their risk for CDMS or with respect to the annualized number of NALs over the 2-year placebo-controlled period, as has been reported previously (Polman et al. 480- 87). However, we did find that MRI findings of subclinical disease dissemination or activity have a different prognostic value for development of CDMS in mono- versus multifocal CIS patients. The presence of at least nine T2 lesions or at least one Gd-enhancing lesion during screening was predictive for time to CDMS in monofocal patients though not in multifocal patients. Similar observations were made for the prognostic value of a new Gd-enhancing lesion on an MRI scan performed at month 3 or month 6. Thus, in monofocal, but not in multifocal patients the risk for CDMS depends on MRI findings. This differential impact of MRI findings in CIS patients with clinical monofocal versus clinical multifocal presentation was supported by a significant interaction between the impact of clinical mono-/multifocality and ≥ 9 T2 lesions at baseline and at least one Gd-enhancing lesion at month 3 on time to CDMS.
These findings strongly suggest that only in CIS patients with monofocal clinical presentation do MRI findings have prognostic value. We hypothesize that, whilst in monofocal CIS patients more pronounced subclinical disease dissemination might primarily reflect more active disease, similar findings in multifocal patients may be more indicative of prolonged subclinical disease evolution, and as such MRI adds less information in these patients.

Figure 1 Time to CDMS in mono- vs. multifocal placebo patients stratified by MRI findings at screening.

Note the predictive value of baseline MRI findings in monofocal patients (left panels) and the absence of predictive value of MRI in multifocal patients (right panels). There was a significant interaction between mono-/multifocality and the presence of either ≥ 9 T2 hyper intense lesions ($p = 0.042$). CDMS: clinically definite MS.
Figure 2  Time to CDMS in mono- vs. multifocal placebo patients stratified by MRI findings at month 3 and month 6.

Note the significant predictive value of months 3 and 6 MRI findings in monofocal patients (left panels) and the absence of predictive value in multifocal patients (right panels). There was a significant interaction between mono-/multifocality and the presence of at least one Gd-enhancing lesion at month 3 (both \( p = 0.042 \)). CDMS: clinically definite MS.

To further elaborate on this hypothesis we expanded these comparisons to subgroups of multifocal patients: those by symptoms and those by signs, under the assumption that especially those patients multifocal by signs may have had an earlier event that was asymptomatic or forgotten, and therefore may have a longer and more benign form of the disease. We found similar baseline characteristics and only a nonsignificant difference in time to CDMS in these subgroups. The
observation that multifocal placebo patients by symptoms tended to have more active MRI lesions during the study than multifocal placebo patients by signs further supports our hypothesis that the former may be considered more acute and at higher risk for future disease activity than a multifocal patient by signs in whom a longer subclinical disease history might be assumed. Differences with respect to patients showing at least one Gd-enhancing lesion (more in patients multifocal by symptoms) and patients showing at least one T1-hypointense lesion (more in patients multifocal by signs) as shown in Table 3, although not significant, are also supportive of our hypothesis.

We compared our results to those obtained in the Early Treatment of MS (ETOMS) (Comi et al. 1576-82) and Controlled High-Risk Avonex® Multiple Sclerosis Prevention Study (CHAMPS) (Jacobs et al. 898-904) studies, other interventional trials in CIS patients where comparable analyses were performed. In the ETOMS study, the presence of three or more MRI criteria as incorporated in the International Panel on the Diagnosis of Multiple Sclerosis guidelines (McDonald et al. 121-27) was also predictive for CDMS only in patients who were classified as clinically unifocal (Barkhof et al. 718-24). Unlike our observation, multifocal patients in ETOMS had a higher risk for CDMS. This difference in the predictive value of “multifocality” in the BENEFIT and the ETOMS cohort may result from the different methods used to classify patients in the two studies. Evaluation of clinical dissemination in ETOMS was based on the local investigator’s assessment, whilst multifocality in BENEFIT was based on a central assessment procedure according to a proposed classification system of all presenting clinical symptoms and signs. Thus, multifocality in BENEFIT was also assumed in patients who, in addition to a monosymptomatic presentation (e.g. optic neuritis), presented with additional clinical signs (e.g. pyramidal dysfunction as indicated by extensor plantar response) indicating an additional clinical lesion. Also, in a post hoc analysis of the CHAMPS study (Kinkel RP, O’Connor, and Kremenchutzky M Abstract P04.070.) all patients were reclassified, taking into account the results of neurological examinations at baseline. In a multivariate analysis, classification by focality was not predictive of conversion to CDMS, which is in line with our results.
All patients in BENEFIT, ETOMS, and CHAMPS had a minimum number of asymptomatic T2 lesions; therefore it is unclear whether these results also can be applied to CIS patients with fewer or no lesions. Further limitations of our analyses should be considered. All subgroup analyses were performed post hoc and our results need confirmation, particularly the novel findings in the subgroups of multifocal CIS patients. However, we would like to emphasize the similarities between our findings and the ETOMS study (Barkhof et al. 718-24) in terms of the lack of impact of MRI findings in multifocal patients on the risk of CDMS.

**Conclusion:**
To summarize, MRI lesions may generally be interpreted as indicators of past and future disease activity in patients with monofocal presentation, though not in multifocal patients, in whom their presence does not add to the risk as defined by the clinical evaluation only. Our findings show that a carefully performed neurological assessment of symptoms and signs in CIS patients is important to define the risk of conversion to CDMS and the potential added value of MRI investigations.

**Author’s contribution section:**
JN drafted the manuscript, performed the statistical analysis and participated in the design of the study, CP participated in the design and coordination of the study, drafted the manuscript and performed the statistical analysis, CHP participated in the design and coordination of the study, and drafted the manuscript, FB commented on the manuscript and participated in the design and coordination of the study, MF commented on the manuscript and participated in the design and coordination of the study, GE commented on the manuscript and participated in the design and coordination of the study, DM commented on the manuscript and participated in the design and coordination of the study, LB commented on the manuscript and participated in the design and coordination of the study, RS commented on the manuscript and participated in the design and coordination of the study, LK commented on the manuscript and participated in the design and coordination of the study, BU drafted the
manuscript, performed the statistical analysis and participated in the design of the study. All authors read and approved the final manuscript.

Acknowledgment

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References


CHAPTER 4:

GENERAL DISCUSSION
AND FUTURE PERSPECTIVES
In this thesis we evaluated different properties of diagnostic guidelines for MS. Our results first suggest that the 2005 McDonald criteria, along with the proposed criteria by Swanton et al. for MS, are indeed specific in discriminating MS from other diagnostically difficult cases, in contrast to criteria as proposed by the American Academy of Neurology (AAN). Secondly, our results suggest that when using the present MS guidelines in the clinical practice of a specialized MS center, only few patients initially not diagnosed with MS, after long term follow up, will turn out to have MS or develop another neurological disease. Thirdly, our results suggest that in multifocal patients, who fulfill criteria for dissemination in space (DIS) on clinical grounds, more MRI parameters are present which are known to represent the pathophysiological burden of the disease, than in monofocal patients. Finally, we demonstrated that in monofocal patients, the presence of $\geq 9$ T2 lesions or enhancement of lesions on MRI, is predictive for the development of CDMS, whereas this is not the case for multifocal patients. In this section the main outcomes will be discussed as well as future perspectives.

**Differentiating MS from other neurological diseases**

We confirmed the specificity of the MRI criteria for DIS (McDonald et al. 121-27;Polman et al. 840-46;Swanton et al.) as incorporated in the diagnostic criteria for MS. As differentiating MS from other diseases is a key issue in clinical practice, it is of great importance to study the performance of the MRI criteria and MS guidelines in patients suspected of MS, yet who are ultimately not diagnosed with MS. Clearly the criteria should not be met in these patients. We investigated (2.1) the ability of the DIS MRI criteria to differentiate MS from other diagnoses in this population and found high specificity for the 2001 McDonald and
2005 Revised McDonald criteria, as well as for criteria as proposed by Swanton et al. Several other papers have reported on specificity of the different diagnostic MRI criteria and found high specificity (Dalton et al. 47-53; Korteweg et al. 221-27; Swanton et al.; Swanton et al. 677-86). Even though, in these papers specificity was calculated in patient groups in whom other diagnoses had been excluded before. Reported specificity in these papers can therefore be perceived as a parameter for disease progression, rather than as an instrument to differentiate between MS and other neurological diseases. Whereas an MS diagnosis requires DIS as well as DIT, we only studied dissemination in space (DIS) criteria. Both have been proven specific for a definite MS diagnosis, but especially the latter component (Swanton et al.) (Dalton et al. 673-76; Swanton et al. 677-86). Therefore, the specificity in our study of the different criteria is likely to be systematically underrated, although is unclear to what extent as there are no other studies investigating DIS and/or DIT in patients suspected of MS, but ultimately diagnosed with another disease. However, it is unlikely that this underestimation would be much larger for the AAN than for the McDonald or Swanton criteria, therefore the difference in specificity will most likely remain (in some measure).

Striving for utmost specificity of (MRI) criteria is one way of avoiding an incorrect MS diagnosis. Consecutive versions of published diagnostic guidelines for MS (McDonald et al. 121-27; Polman et al. 840-46; Polman et al. 292-302; Poser et al. 227-31; Schumacher GA et al. 552-68) demand that: ‘there must be no better explanation for the clinical presentation’. Another similar way to avoid an incorrect MS diagnosis, is to find ‘a better explanation for the clinical picture’ by defining alternative diagnoses of MS, and specific features that positively indicate another diagnosis. We’ve described the alternative diagnoses we found in the retrospective consecutive patient group (chapter 2.1 and 2.4) and in the case report (chapter 2.3). We found that the major differentially diagnostic group comprises of cerebrovascular disease and we found several rarer diagnoses. In the past years two papers (Charil et al. 841-52; Miller et al. 1157-74) have reported on features (‘red flags’) positively indicating other diagnoses. These papers report a consensus view of MS (MRI) specialists, as a first step, on differential diagnoses and an extensive list
DISCUSSION AND FUTURE PERSPECTIVES

of MRI and clinical characteristics that are atypical for MS (‘red flags’) and characteristic of other diagnoses. A more recent paper by Albertyn et al. (Albertyn et al. 678-84) found that in a general neurology practice those patients who did not meet the diagnostic MS criteria after more than a median of 4 years of follow up, clearly had such red flags, but the presence of these red flags did not lead to other diagnoses. Therefore further defining differentiating characteristics of these alternative diagnoses should be a future goal. Diagnostic practical algorithms further focusing on and prioritizing these most prevalent and important differentially diagnostic diseases, such as cerebrovascular disease, and highlighting the differences of clinical and paraclinical investigations between such other diagnoses and MS, may be helpful. Such an algorithm should be prospectively tested in the appropriate populations. Even though it is unlikely that this process - which is different for each patient - will ever be fully covered by such an algorithm and replace clinical experience.

Although with different versions of the McDonald criteria (McDonald et al. 121-27) (Polman et al. 840-46) accuracy has improved and an MS diagnosis can be made earlier, the criteria have been shown complex in clinical use (Hawkes and Giovannoni; Korteweg et al. 67-71; McHugh, Galvin, and Murphy 81-85). This is probably due to the complexity of the MRI guidelines (Korteweg et al. 67-71), the complexity of the clinical scheme to be followed, and ambiguous clinical definitions (Hawkes and Giovannoni). In patients suspected of MS in a general neurology practice,

Table 1 criteria for DIS as incorporated in the McDonald criteria 2010 based on Swanton et al. 677-86

<table>
<thead>
<tr>
<th>DIS Can Be Demonstrated by ≥1 T2 Lesiona in at Least 2 of 4 Areas of the CNS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periventricular</td>
</tr>
<tr>
<td>Juxtacortical</td>
</tr>
<tr>
<td>Infratentorial</td>
</tr>
<tr>
<td>Spinal cordb</td>
</tr>
</tbody>
</table>

**a** Gadolinium enhancement of lesions is not required for DIS

**b** If a subject has a brainstem or spinal cord syndrome these lesions are excluded from the Criteria and do not contribute to the lesion count
Table 2. The 2010 McDonald criteria for diagnosis of MS (Polman et al. 292-302)

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Additional Data Needed for MS Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 2 attacks(^a); objective clinical evidence of ≥ 2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack(^b)</td>
<td>None(^c)</td>
</tr>
<tr>
<td>≥ 2 attacks(^a); objective clinical evidence of 1 lesion</td>
<td>Dissemination in space, demonstrated by: ≥ 1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)(^d); or Await a further clinical attack(^e) implicating a different CNS site</td>
</tr>
<tr>
<td>1 attack(^a); objective clinical evidence of ≥ 2 lesions</td>
<td>Dissemination in time, demonstrated by: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack(^e)</td>
</tr>
<tr>
<td>1 attack(^a); objective clinical evidence of 1 lesion (clinically isolated syndrome)</td>
<td>Dissemination in space and time, demonstrated by: For DIS: ≥ 1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)(^d); or Await a second clinical attack(^e) implicating a different CNS site; and For DIT: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack(^e)</td>
</tr>
<tr>
<td>Insidious neurological progression suggestive of MS (PPMS)</td>
<td>1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria(^d):</td>
</tr>
</tbody>
</table>
DISCUSSION AND FUTURE PERSPECTIVES

1. Evidence for DIS in the brain based on \( \geq 1 \) T2 lesions in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions
2. Evidence for DIS in the spinal cord based on \( \geq 2 \) T2 lesions in the cord
3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

If the Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is "MS"; if suspicious, but the Criteria are not completely met, the diagnosis is "possible MS"; if another diagnosis arises during the evaluation that better explains the clinical presentation, then the diagnosis is "not MS."

An attack (relapse; exacerbation) is defined as patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection. It should be documented by contemporaneous neurological examination, but some historical events with symptoms and evolution characteristic for MS, but for which no objective neurological findings are documented, can provide reasonable evidence of a prior demyelinating event. Reports of paroxysmal symptoms (historical or current) should, however, consist of multiple episodes occurring over not less than 24 hours. Before a definite diagnosis of MS can be made, at least 1 attack must be corroborated by findings on neurological examination, visual evoked potential response in patients reporting prior visual disturbance, or MRI consistent with demyelination in the area of the CNS implicated in the historical report of neurological symptoms.

Clinical diagnosis based on objective clinical findings for 2 attacks is most secure. Reasonable historical evidence for 1 past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristics for a prior inflammatory demyelinating event; at least 1 attack, however, must be supported by objective findings.

No additional tests are required. However, it is desirable that any diagnosis of MS be made with access to imaging based on these Criteria. If imaging or other tests (for instance, CSF) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS, and alternative diagnoses must be considered. There must be no better explanation for the clinical presentation, and objective evidence must be present to support a diagnosis of MS.

Gadolinium-enhancing lesions are not required; symptomatic lesions are excluded from consideration in subjects with brainstem or spinal cord syndromes.

MS = multiple sclerosis; CNS = central nervous system; MRI = magnetic resonance imaging; DIS = dissemination in space; DIT = dissemination in time; PPMS = primary progressive multiple sclerosis; CSF = cerebrospinal fluid; IgG = immunoglobulin G.
an MS diagnosis was frequently made even though DIT was not present and an MRI was frequently not repeated (McHugh, Galvin, and Murphy 81-85). To improve accuracy and to simplify the diagnostic process, diagnostic criteria were proposed by Swanton et al. It was proposed to diminish the number of lesions, while retaining their specific locations as evidence for DIS (table 1). In these criteria at least 1 T2 lesion is required in at least 2 out of 4 for MS typical locations (periventricular, juxtacortical, infratentorial and spinal cord). In chapter 2.3 we compared the specificity of the (revised) McDonald MRI criteria to these Swanton criteria (Swanton et al.) and found comparable specificity. In a large multicenter study of CIS patients (Swanton et al. 677-86) these criteria were found to be simpler than the former criteria without compromising specificity while slightly increasing sensitivity. The criteria as proposed by Swanton et al. were then incorporated in the revised 2010 McDonald criteria (Polman et al. 292-302) (Table 2).

Several other revisions have been made in this latest version of the diagnostic criteria: In the 2005 McDonald criteria DIT was defined as a new T2 lesion appearing on MRI at least 30 days after a reference scan. Tur et al. (Tur et al. 631-35) found unchanged specificity when defining DIT as a new T2 lesion appearing at any time, as compared to appearing within 30 days after the reference. Additionally, it was demonstrated (Rovira et al. 587-92) that a single brain MRI could be sufficient to prove DIT: the presence of both enhancing and non-enhancing lesions at the same time was shown to be highly specific for CDMS. Furthermore the MRI criteria for primary progressive MS (PP-MS) have been adapted: DIS can now be accomplished by the presence of ≥ 1 T2 lesion in a for MS characteristic region (periventricular, infratentorial or juxtacortical), therefore the criteria have become more similar to those for relapsing MS. This modification results from a study that found a high fulfillment in PP MS patients of the DIS criteria as used for RR MS patients, thereby suggesting that similar criteria for these two groups of patients are feasible (Montalban et al. 1459-65).

Further modifications concern different subgroups: Neuromyelitis optica (NMO) is now recognized as a separate entity because of its different clinical course, prognosis, pathophysiology and response to
therapy compared to MS. There is consensus in the 2010 revisions that the criteria probably also serve well for pediatric patients that present as CIS, but this should still be confirmed in a prospective fashion. Recently, the McDonald 2001 MRI criteria were compared to modified criteria that require fewer total, fewer periventricular lesions and that omit juxtacortical lesions in pediatric patients. These modified criteria were found to be somewhat more sensitive than the 2001 McDonald criteria while also being highly specific (Callen et al. 961-67).

**Clinical definition of dissemination in space, relation to MRI and prognostic evidence**

In spite of an increasing role for MRI in diagnosing MS, clinical data remain essential. In contrast to the interpretation of MRI, no clinical classification existed up until now. Therefore a classification system to define dissemination in space in more detail was proposed to provide further guidance on this subject. In chapter 3.1 we justified this classification system by showing that multifocal patients have significantly more T2 hyperintense and T1 hypointense (‘black holes’) lesions than monofocal patients. Accordingly ‘clinically multifocal’ is associated with more lesions on MRI. In chapter 3.2 we investigated the prognostic value of the classification system. We found that the initial presence of at least nine T2 lesions or at least one Gadolinium-enhancing lesion, was predictive for time to CDMS in monofocal but not in multifocal patients. Therefore in CIS patients with monofocal, but not with multifocal clinical presentation, these MRI findings seem to have prognostic value. Possibly more pronounced subclinical disease dissemination in monofocal CIS patients reflects more active disease, whereas similar findings in multifocal patients may be more indicative of prolonged subclinical disease evolution. MRI might contribute less information in these latter patients. In addition, we hypothesized that signs not accompanied by symptoms from the same location (for example an extensor plantar reflex not accompanied by leg motor symptoms) might be due to a past episode of inflammation that has not fully recovered. In these patients one might assume a longer subclinical disease history. Aside from prognostic information, a different treatment response in mono and
multifocal patients might help in deciding which patients to treat. In the same trial, a treatment effect was found for interferon in both groups. This effect was more pronounced yet not significant in the monofocal group. This treatment effect was especially present in monofocal patients with ≥ 9 T2 lesions, compared to monofocal patients with less lesions in whom the treatment effect was lower and not significant (Polman et al. 480-87). However, all these findings are the result of post hoc analysis and still need confirmation. The clinical relevance, with regard to both prognosis and treatment effect of the clinical classification system, need to be investigated prospective with a longer follow up.

Future diagnostic criteria may benefit from new MRI techniques and different cerebral lesion features. Cortical lesions are not usually seen on conventional MR images, even though they contain a large amount of lesions. With double inversion recovery (DIR), an MRI technique where the signal from white matter as well as from cerebrospinal fluid is suppressed, cortical lesions can be more accurately depicted (Filippi and Rocca 659-81). These lesions were present in 30% of a group of typical CIS patients. It was shown in this same study that the presence of an intracortical lesion is an independent predictor of CDMS, increasing specificity in comparison to the present criteria (Filippi et al. 1988-94). Another future MRI characteristic that seems to be associated with conversion to MS and that might have additional value to the Swanton criteria, is a lesion in the corpus callosum. This was shown recently (Jafari et al. 1837-41) in a group of 158 CIS patients that was followed for 39 months. These findings should be further investigated in larger multicenter groups of CIS patients, but suggest that the incorporation of cortical and corpus callosum lesions in the diagnostic criteria could be useful. Another promising MRI technique is scanning with high-field strength. Present criteria have been investigated with 1.0 or 1.5 Tesla field strength, however scanning with as much as 7.0 Tesla is now possible, even though this is not commonly available. Higher field strength has been shown to improve infratentorial lesion detection (Wattjes et al. 1159-63). Although 3 Tesla scanning resulted in little improvement in meeting criteria for dissemination in space in CIS patients in one
study (Wattjes et al. 54-59), higher field strength scanning should be prospectively evaluated in modified criteria in cohorts of CIS patients.

Alternatively, the development of specific biomarkers should have additional value in future diagnostic criteria. Such biomarkers should clearly have (additional) diagnostic value, yet should ideally also have clinicopathological correlations. An exemplary biomarker is NMO- IgG, an antibody that selectively targets the aquaporine-4 water channel. This antibody is not only able to distinguish neuromyelitis optica (NMO) from MS (Lennon et al. 473-77), but is also implicated in the pathophysiology of NMO (Jarius et al. 3072-80;Roemer et al. 1194-205;Takahashi et al. 1235-43).

Issues remain for patients who present in a less typical manner (Rudick 234-36). Some patients are being investigated for other reasons than suspected MS, when MRI shows lesions that are highly suspicious of the disease. One cannot diagnose MS in these patients due to the absence of MS like symptoms. However, a substantial number of these develop disease defining symptoms at follow up, and some seem to be at high risk for disease progression (Okuda et al. 800-05;Okuda et al. 686-92). Other patients presenting with a CIS have had previous symptoms regarded as atypical. The predictive value for MS diagnosis and disease progression in these subjects should be studied further and incorporated in future diagnostic criteria.
Reference List


ABBREVIATIONS
AAN | American Academy of Neurology  
ALS | Amyotrophic Lateral Sclerosis  
CIS | clinically isolated syndrome  
CDMS | Clinically Definite Multiple Sclerosis  
CNS | central nervous system  
CSF | cerebrospinal fluid  
DIS | dissemination in space  
DIT | dissemination in time  
DMT | disease modifying therapy  
IgG | immunoglobulin G  
ICVD | ischemic cerebrovascular disease  
IP | international panel  
MS | Multiple Sclerosis  
MRI | magnetic resonance imaging  
NMO | Neuromyelitis Optica  
OND | other neurological disease  
PML | Progressive Multifocal Encephalopathy  
PPMS | Primary Progressive Multiple Sclerosis  
PRMS | Progressive Relapsing Multiple Sclerosis  
RRMS | Relapsing Remitting Multiple Sclerosis  
SPMS | Secondary Progressive Multiple Sclerosis  
TPHA | treponemal hemagglutination
Diagnose en vroege prognose van Multiple Sclerose
Multiple Sclerose (MS) is bij jong volwassenen de meest voorkomende invaliderende ziekte van het centraal zenuwstelsel. De meeste patiënten presenteren zich aan het begin van de ziekte met een acute of sub-acute episode van klachten, ook wel een ‘clinically isolated syndrome’ (CIS) genoemd. Patiënten hebben meestal klachten van de oogzenuw, het ruggenmerg en/of de hersenstam. Van de patiënten die zich met een eenmalige episode presenteren krijgt 30-70% uiteindelijk MS en daarmee de zogenaamde relapsing remitting vorm van MS (RR-MS). Een klein deel van de patiënten presenteert zich met langzaam progressieve klachten en heeft primair progressieve MS (PP-MS).

Er is geen eenvoudige diagnostische test om de diagnose te stellen. Wel zijn er diagnostische criteria. Om de diagnose MS te kunnen stellen is bewijs nodig voor ‘spreiding in ruimte en tijd’ van lesies in het centraal zenuwstelsel. Dat betekent dat de klachten en bevindingen bij het onderzoek te herleiden moeten zijn tot minimaal 2 plekken in het centrale zenuwstelsel (bijvoorbeeld de oogzenuw en het ruggenmerg) op minimaal 2 verschillende tijdstippen ontstaan. Werd aanvankelijke de diagnose vooral met klinische gegevens , evt. een liquorpunctie en/of VEP gesteld, de laatste decade is de rol van MRI enorm toegenomen. MRI is het meest gevoelige onderzoek voor MS. Bij ca. 95% van de patiënten met MS laat de MRI typische afwijkingen zien. Daarnaast is MRI waardevol voor het uitsluiten van andere ziektebeelden. De opeenvolgende versies van de diagnostische criteria bevatten gedetailleerde en steeds verbeterde MRI criteria. Bij aanwezigheid van een minimum aantal (nieuwe) lesies op voor MS specifieke plaatsen (oorspronkelijk de zgn. Barkhof-Tintore criteria) levert de MRI voldoende bewijs voor ‘spreiding in ruimte’ en/of ‘spreiding in tijd’ en kan zo een deel van het klinische bewijs vervangen worden door MRI bevindingen. Zo hoeft vaak niet meer gewacht te
worden of en wanneer er een tweede episode van klachten optreedt en kan de diagnose sneller gesteld worden. Deze MRI criteria zijn getest in groepen patiënten die zich presenteerden met één episode typische MS klachten en vervolgd zijn in de tijd. Van deze patiënten is daardoor bekend is of ze nog een episode MS klachten hebben gekregen. Deze studies vinden plaats in gespecialiseerde MS centra en patiënten waarbij er in tweede instantie toch verdenking is op een andere ziekte dan MS zijn niet geïncludeerd. In dergelijke patiënten groepen bleken de MRI criteria een goede sensitiviteit en specificiteit te hebben voor het ontstaan van een tweede episode klachten. Echter, het is onbekend hoe goed deze criteria andere ziektebeelden, die zich op een vergelijkbare manier als MS kunnen presenteren, uitsluiten. Deze patiënten zijn immers niet in deze groepen geïncludeerd. Voor de neuroloog in de dagelijkse praktijk is het uitsluiten van andere diagnoses erg belangrijk. Hier gaat het tweede hoofdstuk grotendeels over: hoe goed kunnen de diagnostische (MRI) criteria de diagnose MS uitsluiten en hoe vaak wordt bij een patiënt waarbij bij een second opinie geen diagnose gesteld kon worden alsnog een diagnose gesteld. In 2003 heeft de American Academy of Neurology (AAN) een stuk gepubliceerd waarin wordt gesteld dat de diagnose MS net zo goed te stellen is door 3 T2 lesies op een MRI van de hersenen aan te tonen als door het toepassen van de hierboven beschreven MRI criteria. Om dit te onderzoeken worden in 2.1 van dit proefschrift de MRI criteria zoals in de diagnostische criteria staan vergeleken met de criteria uit het AAN artikel. Dit wordt gedaan in een groep patiënten die in een periode van 3 jaar naar een gespecialiseerd MS centrum werden verwezen vanwege een mogelijke MS diagnose. De verschillende MRI criteria worden toegepast op patiënten uit deze groep die een andere diagnose kregen (om te kijken hoe vaak inderdaad niet aan de criteria werd voldaan) en patiënten die wel de diagnose MS kregen (om te kijken of inderdaad ook aan de criteria werd voldaan). De MRI criteria zoals in de diagnostische richtlijn staan blijken specifiek terwijl de criteria zoals voorgesteld door de AAN dit niet zijn. Desalniettemin blijken de diagnostische criteria ingewikkeld voor de dagelijkse praktijk voor zowel neurologen als radiologen. In 2005 wordt de richtlijn aangepast om hem
te versimpelen, ruggenmerglesies beter te incorporeren en de diagnose sneller, maar net zo betrouwbaar te kunnen stellen. In 2006 worden opnieuw aangepaste MRI criteria voorgesteld, de criteria volgens Swanton et al., ook dit keer om de diagnose verder te versimpelen. In 2.2 worden deze MRI criteria volgens Swanton et al. vergeleken met de MRI criteria zoals in de 2001 en 2005 McDonald criteria zijn geïncorporeerd. De Swanton criteria blijken in deze groep even specifiek. In 2.3 worden patiënten die geen zekere diagnose kregen bij een second opinion wegens een mogelijke MS vervolgd om te kijken bij hoeveel patiënten in het beloop alsnog een diagnose is gesteld. Dit blijkt bij 15 patiënten (dit is 4% van de hele patiëntengroep en 20% van de patiënten die initieel geen diagnose kregen) het geval te zijn. Zeven patiënten kregen alsnog de diagnose MS en 8 patiënten een andere diagnose waarvan bij 4 patiënten de andere diagnose cerebrovasculaire ziekte was. Hieruit wordt geconcludeerd dat de kans op een andere diagnose na een verwijzing naar een tertiair MS centrum klein is. In 2.4 wordt de waarde van de MRI gedemonstreerd voor het stellen van een andere diagnose bij een verdenking op MS. Er wordt een casus beschreven van een patiënt met fluctuerende, progressieve sensibiliteitsstoornissen aan het been bij wie de diagnose MS is gesteld vanwege witte stof lesies op de MRI cerebrum, die echter niet aan de MRI criteria voldoen. Vanwege de klinisch mogelijke localisatie in het ruggenmerg wordt een MRI van het ruggenmerg gemaakt waarop een schwannoom de oorzaak van de klachten blijkt te zijn. Er wordt een flow chart gesuggereerd voor het gebruik van de MRI bij de verdenking op MS.

In hoofdstuk 3 staat een mogelijke klinische definitie van spreiding in ruimte centraal. Hoewel voor de MRI regels zijn opgesteld waaraan deze moet voldoen om te mogen spreken van spreiding in ruimte, een van de voorwaarden om de diagnose MS te mogen stellen, staat er in de diagnostische criteria niet wanneer de bevindingen uit de anamnese en het lichamelijk onderzoek voldoende zijn om te spreken van spreiding in ruimte. Uit eerder onderzoek bleek dat er veel verschillen zijn tussen artsen wanneer er sprake is van spreiding in ruimte. In 2005 werd een klinisch classificatiesysteem voorgesteld om deze spreiding in ruimte uniform te definieren. In dit systeem worden de klachten van patiënten
en de bevindingen bij lichamelijk onderzoek vertaald naar onderliggende lelies en zo bepaald of er sprake zal zijn van één lesie (monofocaal) of meer dan één lesie (multifocaal). In 3.1 wordt dit systeem geëvalueerd door het te vergeleken met MRI lelies. Patiënten waarvan de presentatie gedefinieerd wordt als monofocaal zouden minder lelies moeten hebben dan patiënten waarvan de presentatie gedefinieerd wordt als multifocaal en zouden minder vaak moeten voldoen aan de criteria voor spreiding in ruimte volgens MRI. Hiervoor werden gegevens van alle patiënten bij aanvang en van de placebo patiënten over de tijd uit de BENEFIT studie gebruikt. In deze studie wordt interferon beta-1b met placebo vergeleken. De geïncludeerde patiënten werden geclasseerd als mono- of multifocaal. De multifocaal patiënten bleken inderdaad meer T2 lelies en meer T1 hypointense lelies te hebben en vaker aan de MRI criteria voor spreiding in ruimte te voldoen. Er was geen verschil in het aantal aankleurende lelies. Hiermee lijkt deze classificatie inderdaad klinische betekenis te hebben. In 3.2 wordt gekeken naar de prognostische waarde van het classificatiestyom. Er wordt gekeken of er een verschil is in tijd tot een tweede episode van klachten tussen mono- en multifocaal patiënten. Hierbij worden opnieuw data van (placebo) patiënten uit de BENEFIT studie gebruikt. Er blijkt geen verschil te zijn tussen mono- en multifocaal patiënten in tijd tot een tweede episode (ofwel tijd tot CDMS). Wel blijkt het risico op CDMS bij monofocaal patiënten in 2 jaar groter te zijn als er ≥ 9 T2 of minimaal één met gadolinium aankleurende lesie aanwezig is. Bij multifocaal patiënten hebben deze MRI parameters geen voorspellende waarde. Het lijkt er dus op dat de MRI bij monofocaal patiënten een voorspellende waarde heeft, maar niet bij multifocaal patiënten. Deze bevindingen wijzen erop dat bij patiënten met een CIS een nauwkeurige anamnese en lichamelijk onderzoek van belang zijn voor het risico op een tweede episode van klachten.
PUBLICATIES


Nielsen, J. M., C Pohl, CH Polman, F Barkhof, MS Freedman, G Edan, DH Miller, L Bauer, R Sandbrink, L Kappos, and BMJ Uitdehaag “MRI characteristics are predictive for
CDMS in monofocal, but not in multifocal patients with a clinically isolated syndrome.”  


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