MAGNETIC RESONANCE IMAGING IN THE STUDY
OF CLINICALLY ISOLATED SYNDROMES SUGGESTIVE
OF MULTIPLE SCLEROSIS

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Abstract

In this thesis I used magnetic resonance imaging (MRI) to study patients with clinically isolated syndromes (CIS) suggestive of multiple sclerosis (MS). Asymptomatic T2 lesions were present in the brain in 71% and in the spinal cord in 36% of CIS patients at presentation and their presence increased the risk of early clinical MS. Contrast-enhancing lesions, present in 31% of patients, were the most predictive finding for early clinical MS from a single MRI. More robust overall prognostic data was provided by a combination of T2 lesions at baseline and new T2 lesions after 3 months. Quantitative MRI studies found evidence for mild CNS atrophy, but MR spectroscopy and magnetisation transfer imaging detected tissue damage in lesions and not the widespread damage that has been described in established MS.

The relationship between MRI and disability was assessed in 71 CIS patients who had been followed-up for a mean of 14 years. Clinically definite MS had developed in 88% who had cerebral T2 lesions at presentation, compared to only 19% with a normal MRI. Disability, measured on the expanded disability status score (EDSS), in the MS patients was generally mild (median EDSS 3.25), although 15 (32%) had an EDSS > 6, 3 of whom had died as a result of the disease. The EDSS at 14 years correlated moderately with T2 lesion volume at presentation (r = 0.48), but more strongly with T2 lesion volume at 5-years (r = 0.60) and with increase in T2 lesion volume over the first 5 years (r = 0.61).
Serial MRI findings in CIS patients identified those at greatest risk of developing MS and disability. A 3-month follow-up MRI was the best predictor of early clinical MS and lesion volume increase in the first 5 years correlated strongly with long-term disability. Early MRI findings are important for prognosis and for selection into therapeutic trials. They also suggest a potential for therapies that suppress MRI lesion formation to have long-term benefits if given early in the course of MS.
Description of Thesis

The thesis is divided into four parts.

Part 1 gives an introduction to multiple sclerosis (MS) and describes the relationship between it and clinically isolated syndromes (CIS), such as optic neuritis, brainstem and spinal cord syndromes. The principles of magnetic resonance imaging are described with an overview of recent developments and their application to MS.

Part 2 comprises of a series of studies on a cohort of unselected CIS patients at presentation and over the subsequent year. High field imaging of the brain and spinal cord was performed at presentation, after 3 and 12 months using sequences that included fast spin-echo (FSE), fast fluid-attenuated inversion recovery (fFLAIR) and T1-weighted spin-echo following the administration of contrast. The focus of these studies was to determine the frequency and extent of asymptomatic disease in CIS patients at presentation and the predictive value of the findings for the subsequent development of radiological and clinical MS. Quantitative MR techniques, such as MR spectroscopy, magnetisation transfer imaging and the measurement of atrophy, were also used to explore the pathological changes that are found at what in many cases is the earliest clinical stage of MS.

In Part 3, the long-term value of MRI in CIS patients was assessed. The relationship between early MRI findings and the risk of MS and disability after a mean follow-up
period of over 14 years was determined and the relationship between clinical and MRI evolution over time was evaluated.

The final part consists of a summary of the principle findings and the conclusions of the thesis.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>$^1$H-MR</td>
<td>Proton Magnetic Resonance</td>
</tr>
<tr>
<td>CD</td>
<td>Clinically Definite (MS)</td>
</tr>
<tr>
<td>Cho</td>
<td>Choline-containing compounds</td>
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<tr>
<td>CIS</td>
<td>Clinically Isolated Syndrome</td>
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<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>CoV</td>
<td>Coefficient of variation</td>
</tr>
<tr>
<td>CP</td>
<td>Clinically Probable (MS)</td>
</tr>
<tr>
<td>Cre</td>
<td>Creatine / phosphocreatine</td>
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<tr>
<td>(C)SE</td>
<td>(Conventional) Spin-echo</td>
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<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
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<tr>
<td>CT</td>
<td>Computerised tomography</td>
</tr>
<tr>
<td>DTPA</td>
<td>Diethyl-enetriaminepentacetic acid</td>
</tr>
<tr>
<td>EDSS</td>
<td>Expanded Disability Status Scale</td>
</tr>
<tr>
<td>ETL</td>
<td>Echo train length</td>
</tr>
<tr>
<td>(f)FLAIR</td>
<td>(fast) Fluid-attenuated inversion recovery</td>
</tr>
<tr>
<td>FOV</td>
<td>Field of view</td>
</tr>
<tr>
<td>FSE</td>
<td>Fast spin-echo</td>
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<tr>
<td>FSPGR</td>
<td>Fast spoiled gradient echo</td>
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<tr>
<td>Ins</td>
<td><em>myo</em>-inositol</td>
</tr>
<tr>
<td>IR</td>
<td>Inversion Recovery</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
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<tr>
<td>MS</td>
<td>Multiple Sclerosis</td>
</tr>
<tr>
<td>MTI / R</td>
<td>Magnetisation Transfer Imaging / Ratio</td>
</tr>
<tr>
<td>NAA / tNAA</td>
<td>N-acetyl aspartate / total N-acetyl derived groups</td>
</tr>
<tr>
<td>NAWM / NABT</td>
<td>Normal appearing white matter / brain tissue</td>
</tr>
<tr>
<td>NEX</td>
<td>Number of excitations</td>
</tr>
<tr>
<td>PD</td>
<td>Proton density</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
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<tr>
<td>PPV</td>
<td>Positive predictive value</td>
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<tr>
<td>PRESS</td>
<td>Point-resolved Spectroscopy</td>
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<tr>
<td>PROBE</td>
<td>Proton Brain Examination</td>
</tr>
<tr>
<td>r</td>
<td>Spearman Rank Correlation Coefficient</td>
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<tr>
<td>RARE</td>
<td>Rapid acquisition and relaxation enhancement</td>
</tr>
<tr>
<td>RF</td>
<td>Radio-frequency</td>
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<tr>
<td>ROI</td>
<td>Region of interest</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SNR</td>
<td>Signal to Noise Ratio</td>
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<tr>
<td>T</td>
<td>Tesla</td>
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<tr>
<td>TE</td>
<td>Echo time</td>
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<tr>
<td>TI</td>
<td>Inversion time</td>
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<tr>
<td>TR</td>
<td>Repetition time</td>
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<tr>
<td>VEP</td>
<td>Visual Evoked Potentials</td>
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Measurement of spinal cord area in clinically isolated syndromes suggestive of MS.

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INTRODUCTION & BACKGROUND
CHAPTER 1
Multiple Sclerosis and the Clinically Isolated Syndromes

1.1 Multiple Sclerosis

1.1.1 Introduction

Multiple sclerosis (MS) is an acquired primary demyelinating disease that is specific to the central nervous system (CNS). It is a common cause of neurological disability in the young adult in the UK, where it has an incidence is approximately 7 / 100 000 [McDonnell & Hawkins 1998, MacDonald et al. 2000] and a prevalence of 130 / 100 000 [Compston 1998a]. Women are more likely to be affected than men, with a ratio of approximately 2:1. This ratio differs with age of onset - there is a more marked female preponderance in children and young adults (3:1) and a more equal sex distribution in later life [Compston 1998b]. The mean age of onset in both sexes is around 31 – 33 years, with the mean age slightly lower in females. The initial diagnosis is only rarely made in patients whose ages are outside the ranges of 10 – 59 years.

The prevalence of MS varies widely throughout the world. Zones of high-, medium- and low-risk for MS have been defined [Kurtzke 1977a]. High-risk zones include northern Europe, northern USA, southern Canada, southern Australia and New Zealand, where in excess of 30 / 100 000 people are affected (rising to as many as 300 / 100 000 people in the Orkney and Shetland Islands). Medium risk zones include southern USA and northern Australia where the prevalence is 5 – 30 / 100 000. Low risk zones include Asia, Latin America, Africa and the Middle East where less than 5 / 100 0000 people are thought to suffer with MS.
1.1.2 Aetiology

The aetiology of MS is unknown. Racial differences in its prevalence, e.g. more common in descendants of Northern Europeans than in native black Africans, imply that genetic factors are involved [Compston 1998b]. The presence of the HLA-DR2 allele has been found to increase the risk of MS and populations with a high frequency of this allele have the highest risk of the disease [Jersild et al. 1973]. Family studies have provided further evidence for the influence of genetic factors; the lifetime risk of MS for a first-degree relative of an affected individual has been found to be around 3% and for a second-degree relative around 1% in populations with a general risk of 0.2% [Sadovnick et al. 1988, Robertson et al. 1996]. However, the finding that the concordance rate (the frequency when both twins were affected) in monozygotic twins, who share identical genotypes, is only 25% [Ebers et al. 1986, Sadovnick 1993a, Mumford et al. 1994] means that other, non-genetic factors must also be involved.

A contributing environmental cause has been indicated by a number of findings. (1) Latitude-dependant gradients in MS prevalence have been reported in several countries where the populations are racially homogeneous [Hammond et al. 1988, Ebers et al. 1993], although this is not the case in all countries and the prevalence of MS can vary greatly in areas that are geographically in close proximity, e.g. Malta (4 / 100 000) and Sicily (53 / 100 000) [Sadovnick 1993b]. (2) Migration studies have demonstrated a reduced risk of MS in patients moving from a high- to a low-risk country [Dean 1967, Hammond et al. 1988]. (3) Clustering of MS has been reported in which several cases have arisen at the same time in the same location, e.g. in the
Faroe Islands [Kurtzke et al. 1979]. The nature of any environmental causes remains unknown, although candidates have included dietary factors and infections.

1.1.3 Pathology

MS is generally believed to be an immune-mediated disorder that results primarily in the destruction of myelin and oligodendrocytes. The precise mechanisms are not known, but the following section summarises current opinion.

1.1.3.1 Immunology

Potentially auto-aggressive T-lymphocytes normally occur in the circulation. Mechanisms, which include peripheral clonal inactivation (anergy) and suppression, are usually in place to control these. Non-activated T-lymphocytes cannot penetrate the blood-brain barrier. In susceptible individuals who are exposed to an unknown environmental trigger, these T-lymphocytes become activated outside the CNS. Upon activation T-lymphocytes increase their expression of adhesion molecules, which allow them to attach to endothelial cells bearing the appropriate counter receptors. Once the activated T-lymphocytes reach the CNS, they search until they find their target antigen being presented by an antigen-presenting cell (probably microglia). If their target is not present the activated cells pass out without incident.

When a sufficient number of T-lymphocytes are present in an area of the CNS, inflammation begins. Cytokines (mainly interferon-gamma and tumour necrosis factor-alpha) are released that attract further lymphocytes and activate macrophages. The macrophages phagocytose myelin, release effector molecules and cytokines and present antigen to other T-lymphocytes. This inflammatory reaction causes damage to
myelin and oligodendrocytes and causes a local breakdown of the blood-brain barrier allowing a secondary influx of immune cells. Plasma cells are found in high numbers in the cerebrospinal fluid (CSF) of MS patients [Thompson et al. 1979]. Oligoclonal bands of IgG, indicating clones of antibodies directed against specific but unidentified antigens, have been demonstrated in 95% of CD MS cases using techniques such as isoelectric focusing [McLean et al. 1990].

The mechanism by which this inflammatory process is subsequently down regulated is not clear. Apoptosis of T-lymphocytes may be a contributing factor, as may the release of certain anti-inflammatory cytokines, e.g. interleukin-10, transforming growth factor-beta.

1.1.3.2 Histopathology

At post-mortem, the brain and spinal cord of MS patients usually appear atrophic with numerous, sharply demarcated plaques found throughout the CNS, but most pronounced in white matter. These vary in appearance, age and size (less than one millimetre to several centimetres) and tend to occur around venules. The pattern of plaque distribution is variable, but is usually widespread and typical sites include the optic nerves, corpus callosum, medulla, pons, spinal cord (cervical region more commonly than thoracic) and around the lateral ventricles. They are usually round or oval in shape although may have finger-like extensions in the periphery that follow the path of vessels. Old lesions appear grey, firm and translucent, whereas newer lesions appear soft and pink.
The hallmark of classical MS plaques is demyelination (caused both from damage to myelin and to oligodendrocytes) and gliosis (sclerosis), with relative preservation of axons. Inflammatory cells are abundant, being found throughout normal-appearing white matter (NAWM) as well as in lesions. It is not certain whether the inflammation is a cause or a consequence of demyelination and indeed either may be possible in some instances. The plaques may be described as being active (acute), chronic active or chronic inactive.

(1) In active (acute) plaques, inflammatory cells, particularly macrophages and to a lesser extent T-lymphocytes, are found predominantly at the edges. Plasma cells are also seen later in the course of the disease. Myelin and lipid degradation products from the breakdown of the myelin sheaths are abundant. The degree of oligodendrocytes destruction is variable with the number of oligodendrocytes remaining almost normal early in the disease enabling extensive remyelination to occur [Prineas et al. 1993]. This may be due to the existence of oligodendrocyte progenitor cells, which can replace those that are destroyed. Later in the disease, oligodendrocytes are increasingly lost (possibly because the oligodendrocyte progenitor cells have become depleted) and remyelination becomes less common [Ozawa et al. 1994].

(2) Chronic inactive plaques are hypocellular with evidence of demyelination (but not myelin breakdown products), oligodendrocytes loss, gliosis and have naked axons running across them.
(3) *Chronic active* plaques are long-standing acute plaques that remain active at the edges, a potential mechanism by which lesions enlarge, whilst the centre of the plaque becomes inactive.

Although axons are *relatively* spared in MS, their loss can in fact be extensive [Lovas *et al.* 2000] and may already occur during the acute inflammatory phase of lesion development [Ferguson *et al.* 1997, Trapp *et al.* 1998]. The cause(s) of axonal damage are unclear. It is unlikely to be as a result of direct immune attack, but more probably be due to the loss of the protection that myelin would normally provide from inflammatory molecules, such as proteolytic enzymes, cytokines, oxidative products and free radicals. Alternatively it may occur by mechanisms that are, at least in part, independent from demyelination [Bitsch *et al.* 2000].

The macroscopically NAWM also contains abnormalities. These may result from remyelinated plaques (shadow plaques), microscopic plaques, oedema, astrocytic proliferation, perivascular inflammation or Wallerian degeneration [Allen & McKeown 1979]. In addition, in older patients with long-standing disease, other brain diseases may co-exist, such as vascular or neurodegenerative disorders.

Most histopathological information has been obtained at post-mortem from patients with chronic MS or from biopsy specimens taken for diagnostic reasons from patients with atypical features. Relatively, little information is therefore available about pathological changes early in the disease. There do appear to be important differences in plaque formation at different stages in the disease, particularly with regard to the potential for remyelination (greatest early on) and loss of oligodendrocytes (greater
with increased disease duration). With suggestions that there may be more than one pathological mechanism causing MS [Lucchinetti et al. 2000], the identification of pathological / pathogenetic differences between patients, using in vivo techniques, such as magnetic resonance imaging (MRI) (see Chapter 2), is becoming increasingly important as these may reveal differing prognoses for which different therapeutic strategies may eventually be needed.

1.1.4 Pathophysiology

The relationship between the pathology and symptoms in MS, which results in interference with conduction in relevant nerve pathways, is complex. Plaques do not always cause symptoms. This may be because (i) they lie in areas that are clinically silent, (ii) effective impulses can be transmitted through the lesion or (iii) the plasticity of the CNS enables function to be preserved.

Symptoms in MS may be negative, e.g. visual loss or paralysis, or positive, e.g. paraesthesia. Negative symptoms are primarily due to the loss of nerve conduction. This may result from conduction block, which is largely due to demyelination [McDonald & Sears 1969] and inflammation (resulting in increased levels of nitric oxide [Redford et al. 1997]). This often recovers as the axons are remyelinated and inflammation subsides or as a reorganisation of sodium channels takes place along the demyelinated axon but the conduction in axons following recovery is neither as fast as normal nor as secure. This marked slowing of conduction can be detected by visual [Halliday, et al. 1972], somatosensory [Small et al, 1978] and brainstem auditory [Robinson & Rudge 1977] evoked potentials. Function, however, is often restored, although in some patients an increase in body temperature, such as from exercise or a
hot bath, appears to promote conduction block leading to a deterioration in function (Uhthoff’s phenomenon).

Positive symptoms appear to be due to hyperexcitability of previously demyelinated axons. These are more usually sensory than motor symptoms, although facial myokymia and myoclonus can occur. They result from spontaneously generated trains of spurious impulses that arise from the site of demyelination and spread in both directions [Smith & McDonald 1980]. Other causes of positive symptoms are thought to include “ephaptic” transmission of conduction by adjacent axons or by mechanical mechanisms (Lhermitte’s phenomena) [Smith & McDonald 1999].

The accumulation of axonal loss over time in MS may help to explain the progressive neurological disability that often occurs. Early in the disease it is likely that the CNS is able to compensate for the loss of axons and most symptoms are due to inflammation and demyelination. However, once a threshold of axonal loss has been reached, the functional reserve of the brain becomes exhausted.

1.1.5 Diagnosis

The symptoms seen in MS can vary greatly between individuals. Any area of the CNS may be affected, but there are certain areas of predilection, which result in characteristic symptoms and signs. These include the optic nerves causing visual symptoms, particularly optic neuritis; the spinal cord causing sensory symptoms, motor weakness and sphincter disturbances; the cerebellum causing nystagmus, dysarthria and ataxia; and the brainstem causing diplopia, facial weakness and sensory disturbance. Other common symptoms include fatigue, mood disturbances and
cognitive impairment. Abrupt attacks of neurological deficit, lasting a few seconds or 
minutes, and sometimes recurring many times daily, are less frequent but well 
recognised. Prominent cortical or extrapyramidal signs rarely dominate the clinical 
picture.

In order to make a clinical diagnosis of MS, current criteria require there to be 
evidence of dissemination of disease in both time and space (Table 1.1) [Schumacher 
et al. 1965]. Certain historical information can be substituted for clinical evidence if it 
is reliable, has no other explanation and is adequate to localise a lesion typical of MS, 
e.g. Lhermitte’s sign, optic neuritis, trigeminal neuralgia, and transient paraparesis.

Table 1.1  Schumacher criteria for the diagnosis of definite MS

- Neurological examination reveals objective abnormalities of CNS function
- History indicates involvement of two or more parts of the CNS
- CNS disease predominantly reflects white matter involvement
- Involvement of the CNS follows one or two patterns:
  (a) Two or more episodes, each lasting at least 24 hours, and more than 1 
  month apart
  (b) Slow progression of signs and symptoms over at least 6 months
- Patient 10 – 50 years old at onset
- Signs and symptoms cannot be better explained by other disease process
The most recent revision of these criteria, by the Poser committee [Poser et al. 1983] (Table 1.2), allows paraclinical evidence of disease, i.e. demonstration of dissemination of disease using laboratory investigations, to be used to establish the diagnosis. These include the demonstration of oligoclonal bands in the CSF, without matched bands in the serum, and evidence of disseminated disease on evoked potentials, urological studies, computerised tomography (CT) or MRI scans. The diagnosis of clinically definite MS made using Poser criteria was found to be correct in 94% of 518 patients in one post-mortem study [Engell 1988].

<table>
<thead>
<tr>
<th>Table 1.2</th>
<th>The Poser criteria for MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category</td>
<td>Attacks</td>
</tr>
<tr>
<td></td>
<td>Evidence</td>
</tr>
<tr>
<td><strong>A Clinically Definite (CD)</strong></td>
<td></td>
</tr>
<tr>
<td>CD MS A1</td>
<td>2</td>
</tr>
<tr>
<td>CD MS A2</td>
<td>2</td>
</tr>
<tr>
<td><strong>B Laboratory-supported Definite (LSD)</strong></td>
<td></td>
</tr>
<tr>
<td>LSD MS B1</td>
<td>2</td>
</tr>
<tr>
<td>LSD MS B2</td>
<td>1</td>
</tr>
<tr>
<td>LSD MS B3</td>
<td>1</td>
</tr>
<tr>
<td><strong>C Clinically Probable (CP)</strong></td>
<td></td>
</tr>
<tr>
<td>CP MS C1</td>
<td>2</td>
</tr>
<tr>
<td>CP MS C2</td>
<td>1</td>
</tr>
<tr>
<td>CP MS C3</td>
<td>1</td>
</tr>
<tr>
<td><strong>D Laboratory-supported probable (LSP)</strong></td>
<td></td>
</tr>
<tr>
<td>LPMS D1</td>
<td>2</td>
</tr>
</tbody>
</table>

OCB = oligoclonal bands
It is 17 years since the Poser criteria were published. The wealth of new data on MRI in patients with clinically isolated syndromes (CIS) and MS suggest that they should be reviewed. An International Panel met in London, UK in July 2000 to develop new criteria. A report from this meeting is in preparation.

1.1.6 Disease course

The most common disease course in MS is one of relapses and remissions (relapsing-remitting MS), although a small proportion of patients (10%) suffer from a progressive neurological deterioration from the outset (primary progressive MS). A relapse is defined by a period of at least 24 hours in which new symptoms develop, or existing ones deteriorate, with objective evidence from examination for a change, and against a background of stability for at least one month [Schumacher et al. 1965]. There should be no other cause that could explain the new symptoms; particularly fever should be excluded. The time course of a relapse is characteristic though not invariable; symptoms usually develop over a few days, remain constant for a few weeks and resolve slowly over a few months. Relapses may remit completely or partially leaving permanent disability, but the relapsing-remitting phase is characterised by a stable disease course between relapses. As the disease advances, approximately two-thirds of patients will develop progressive disability regardless of whether or not they suffer further relapses (secondary progressive MS). The remainder of patients do not develop progressive disability and remain relatively unimpaired for many years; patients who are “fully functional” after more than 15 years are often termed as having benign MS [Lublin & Reingold 1996]. Some patients appear to have MS at post-mortem, yet remain asymptomatic throughout their lives. In a study of 2500 consecutive autopsy cases over the age of 16 years in Western
Ontario, five patients were found to have typical MS plaques despite having had no known symptoms in life [Gilbert & Sadler 1983].

1.1.7 Natural history

The study of the natural history of MS is made particularly difficult by its long duration and markedly varied clinical course. Several differing approaches have been used.

1.1.7.1 Relapse rate: Relapses occur more commonly in young patients and decrease in frequency with disease duration regardless of the disease course [Lhermitte et al. 1973]. On average a patient with relapsing-remitting MS suffers approximately one relapse per year [IFNB MSSG 1993, Johnson et al. 1995, Jacobs et al. 1996, PRISMS 1998], although some patients may suffer many more and many far less.

1.1.7.2 Disability: Disability results from either incomplete resolution of relapses in the relapsing-remitting stage or due to progressive deterioration in primary or secondary progressive MS patients. Most studies have found that only 50% of MS patients are independent and able to walk after 15 years [Confavreux et al. 1980, Weinshenker et al. 1989, Runmarker & Andersen 1993]. For research purposes, disability in MS is measured using disability scales, such as the expanded disability status scale (EDSS) described by Kurtzke (Table 1.3) [Kurtzke 1983]. The EDSS is based on ambulation and scores from different functional systems, i.e. pyramidal, cerebellar, brainstem, vegetative, visual, sensory, cerebral and other. It is heavily weighted towards walking ability in the higher scores and is not a linear measurement,
<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal neurological examination (all FS normal, mild cerebral signs acceptable)</td>
</tr>
<tr>
<td>1.0</td>
<td>No disability, minimal signs in one FS</td>
</tr>
<tr>
<td>1.5</td>
<td>No disability, minimal signs in more than one FS</td>
</tr>
<tr>
<td>2.0</td>
<td>Minimal disability in one FS</td>
</tr>
<tr>
<td>2.5</td>
<td>Minimal disability in two FS</td>
</tr>
<tr>
<td>3.0</td>
<td>Moderate disability in one or mild disability in up to four FS though fully ambulatory</td>
</tr>
<tr>
<td>3.5</td>
<td>Fully ambulatory but with a moderate disability in one FS and mild disability in one or two others; or moderate disability in two FS; or mild disability in five FS</td>
</tr>
<tr>
<td>4.0</td>
<td>Fully ambulatory without aid; self-sufficient; up and about some 12 hours a day despite relatively severe disability in one FS or combinations of exceeding the limits of the previous step. Able to walk without aid or rest for 500m.</td>
</tr>
<tr>
<td>4.5</td>
<td>Fully ambulatory without aid; up and about much of the day; may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m</td>
</tr>
<tr>
<td>5.0</td>
<td>Ambulatory without aid or rest for 200m; disability severe enough to impair full daily activities.</td>
</tr>
<tr>
<td>5.5</td>
<td>Ambulatory without aid or rest for 100m; disability severe enough to preclude full daily activities.</td>
</tr>
<tr>
<td>6.0</td>
<td>Intermittent or unilateral constant assistance required to walk 100m</td>
</tr>
<tr>
<td>6.5</td>
<td>Constant bilateral assistance to walk 20m without rest</td>
</tr>
<tr>
<td>7.0</td>
<td>Unable to walk 5m even with aid. Essentially restricted to a wheelchair. Transfers alone.</td>
</tr>
<tr>
<td>7.5</td>
<td>Unable to walk more than a few steps. May need aid with transfers</td>
</tr>
<tr>
<td>8.0</td>
<td>Restricted to bed or chair or perambulated in wheelchair. Generally has effective use of arms. Out of bed for much of day</td>
</tr>
<tr>
<td>8.5</td>
<td>Essentially restricted to bed for much of the day. Retains some self-care functions</td>
</tr>
<tr>
<td>9.0</td>
<td>Helpless bed patient; can communicate and eat</td>
</tr>
<tr>
<td>9.5</td>
<td>Totally helpless, unable to communicate effectively or eat /swallow</td>
</tr>
<tr>
<td>10.0</td>
<td>Death due to MS</td>
</tr>
</tbody>
</table>
but it enables comparison of disabilities between groups of patients with some degree of consistency. Several longitudinal studies of disability in MS have now been performed [Confavreux et al. 1980, Weinshenker et al. 1989, Phadke 1990, Runmarker & Andersen 1993]. Factors that have been found to indicate a better or worse prognosis are summarised in Table 1.4.

**Table 1.4** Early predictors of disability in MS

<table>
<thead>
<tr>
<th>Better</th>
<th>Worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>Male sex</td>
</tr>
<tr>
<td>Onset: remitting, sensory / optic neuritis</td>
<td>Onset: progressive, motor</td>
</tr>
<tr>
<td>Complete recovery from relapse</td>
<td>Incomplete recovery from relapse</td>
</tr>
<tr>
<td>Long inter-attack interval</td>
<td>Short inter-attack interval</td>
</tr>
<tr>
<td>Low relapse frequency</td>
<td>High relapse frequency</td>
</tr>
<tr>
<td>Long time to EDSS 3</td>
<td>Short time to EDSS 3</td>
</tr>
<tr>
<td>Younger age</td>
<td>Older age</td>
</tr>
<tr>
<td>Monosymptomatic presentation</td>
<td>Polysymptomatic presentation</td>
</tr>
</tbody>
</table>

Several studies have found the disability status at five years to be strongly predictive of future course [Kurtzke et al. 1977b, Weinshenker et al. 1989, Miller et al. 1992a]. The early clinical course also appears, at least in some studies, to be important in determining future disability. A high frequency of relapses in the first two years after the onset of MS has been associated with increased disability after prolonged follow-up [Weinshenker et al. 1991]. This finding was, however, contrary to those of
Runmarker & Andersen [1993], who described no such association. This difference may be accounted for by the inclusion of patients with progressive disease in the latter study, in whom a rapid increase in disability in the absence of relapses is the usual course.

Most studies of disability in MS have focused on physical problems, but it has become increasingly recognised that cognitive problems also frequently (40 – 60%) occur in MS patients and may be marked [Minden et al. 1987]. The pattern of cognitive decline is variable. Often the effect on attention, memory and information processing is greatest, although a lesser effect on language function may mask the severity of the deficit [Rao et al. 1991]. These cognitive deficits may remain static for many years but do appear to be worse in patients with secondary progressive disease [Ron et al. 1991]. Psychiatric problems, particularly depression, may also occur in MS contributing to overall disability and quality of life and contribute to the increased risk of suicide seen in MS patients [Sadovnick et al. 1991, Stenager et al. 1992]. Euphoria, an organic personality change with a chronically elevated mood, has previously been over reported in MS and probably only occurs in 10% of patients [Diaz-Olavarrieta et al. 1999].

1.1.7.3 Temporal course: The time to conversion from relapsing-remitting to secondary progressive MS is an important prognostic landmark in the development of MS. This usually occurs when the patient has an EDSS of about 4.0 [Runmarker & Andersen 1993]. Once a progressive course has become established the development of an EDSS of 6.0 usually occurs within 3 – 7 years [Runmarker & Andersen 1993]. Conversion with the first five years is a poor prognostic sign. However, a limitation
with this method of studying natural history of MS is that the diagnosis of secondary progression can only be made retrospectively, after at least six months of continued deterioration.

1.1.7.4 **Survival studies:** Studies performed since the introduction of antibiotics have found a 75 - 85% survival rate in MS patients 25 years after the onset of the disease. MS has little influence on the cause of death until at least 15 years into the illness. Survival studies are an insensitive measure in MS because half of deaths are not disease related; being caused by conditions that affect the population as a whole, such as vascular disease or malignancy. Death nevertheless may occur due to complications of severe MS, such as pneumonia or urinary tract infection and overall life expectancy is reduced by about five years [Phadke 1987, Sadovnick *et al.* 1992]. The risk of suicide is increased in MS populations, being several times than of an age-adjusted general population [Sadovnick *et al.* 1991, Stenager *et al.* 1992].

1.1.8 **Treatment**

1.1.8.1 **Supportive measures:** Following a diagnosis of MS, information should be made readily available for the patient about the condition. As well as discussing the diagnosis with a neurologist, many patients benefit from access to specialist nurses and the introduction to groups or societies unconnected with the hospital, such as the MS Society, which can offer support throughout the course of the disease. In addition to follow-up by a neurologist and a general practitioner, access should be available, when necessary, to physiotherapy, occupational therapy, neuro-rehabilitation and respite care.
1.1.8.2 Symptomatic treatment: There are a wide variety of symptoms in MS and these often require individual treatment e.g. spasticity, ataxia, bladder dysfunction, sexual dysfunction, pain, fatigue, depression.

1.1.8.3 Treatment of a relapse: Corticotrophin has been demonstrated to accelerate recovery from a relapse [Miller et al. 1961, Rose et al. 1968]. Intravenous methylprednisolone has now largely replaced corticotrophin because of the more practical and rapid administration (3 day versus 14 day course) and fewer side effects. Three-day or five day courses may be given and have been shown to speed up the recovery from a relapse [Milligan et al. 1987]. Oral steroids are also used and have been shown to be as effective as intravenous methyprednisolone when given in a three-week tapering course [Barnes et al. 1997].

1.1.8.4 Disease Modifying Treatment: Two forms of recombinant interferon beta, -1a (Avonex, Rebif) and -1b (Betaferon), are licensed in Europe for the treatment of patients with relapsing-remitting MS. Interferon beta has been shown to reduce the frequency of relapses by approximately one third and to reduced the severity of relapse [IFNB-1b MSSG 1993, IFNB-1b MSSG 1995, Jacobs et al. 1996, PRISMS 1998]. Interferon beta-1b has also been licensed for the treatment for secondary progressive MS, on the basis of a single trial, which demonstrated a significant but small benefit on progressive disability [European Study Group 1998]. Two subsequent interferon beta trials in secondary progressive MS have been negative. Glatiramer acetate (Copaxone) has very recently been licensed for the treatment of relapsing-remitting MS on the basis of a reduction in relapse frequency comparable with interferon beta in MS [Johnson et al. 1995, 1998].
1.2 Clinically Isolated Syndromes

1.2.1 Introduction

When a patient presents with a single inflammatory demyelinating episode, the diagnosis of MS cannot be made because there has not been evidence of dissemination of disease in time and space. The initial symptoms are usually monosymptomatic, most commonly affecting the optic nerve, brainstem or spinal cord, although less commonly a combination of these areas may be involved simultaneously. When one region is involved, such an episode is termed a clinically isolated syndrome (CIS) suggestive of MS. Many CIS patients will have a further clinical episode, confirming the diagnosis of MS. However, not all such patients do, even after prolonged follow-up [Rizzo & Lessell 1988, Sandberg-Wollheim et al. 1990, O'Riordan et al. 1998a, Frith et al. 2000], suggesting that CIS may also occur as monophasic syndromes distinct from MS.

The relative frequency of the different syndromes has not been well documented. Most studies of CIS have been performed retrospectively in patients who have subsequently developed MS. These have been prone to errors caused by patients frequently forgetting earlier mild symptoms and result in a bias towards including the more severely symptomatic patients.

In a review of previously published reports on the initial symptoms of MS, McAlpine et al. [1972] found weakness of one or more limb to be most common symptom (40%), followed by optic neuritis (22%), paraesthesia (21%), diplopia (12%), vertigo (5%), disturbances of micturition (5%) and others (<5%). Cerebellar ataxia has also been recognised as a presenting symptom but was not clearly described in many of
these early reports. Psychiatric symptoms are very rarely the initial manifestation of MS and when they do occur usually consist of depression as a result of misdiagnosis of physical symptoms [Skegg 1993].

There do appear to be geographical differences in the relative frequency of the syndromes, for example optic neuritis is much a more common presenting symptom of MS in oriental countries than in the UK [Shibasaki et al. 1981].

Few prospective studies of CIS have been performed. Of those that have been [O’Riordan et al. 1998a, Jacobs et al. 2000], optic neuritis has been the most common presenting complaint; although whether this is because of its frequency or the ease with which it can be recognised is not clear.

1.2.2 The Relationship between Clinically Isolated Syndromes and MS

The relationship between CIS and MS has been explored in numerous studies. Most have focussed on optic neuritis, the most distinctive and homogenous of the syndromes, because its classical presentation is more specific for demyelination than symptoms due to a brainstem or spinal cord syndrome. The development of MS following an isolated episode of optic neuritis was noted in the early part of the twentieth century by observers such as Fleischer (1908), Langenbeck (1914), Lenoir (1917), Marburg (1920) [cited in Perkin & Rose 1979]; optic neuritis having first been described by Edward Nettleship in 1884. Subsequently, a number of studies have tried to quantify the risk (Tables 1.5 and 1.6).
<table>
<thead>
<tr>
<th>Year</th>
<th>First Author</th>
<th>Number of Patients</th>
<th>Follow-up, years</th>
<th>MS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1964</td>
<td>McAlpine (after Lynn 1959)</td>
<td>67</td>
<td>18 (5 – 34)</td>
<td>85</td>
</tr>
<tr>
<td>1968</td>
<td>Bradley</td>
<td>66</td>
<td>10 (0.5 – 20)</td>
<td>52</td>
</tr>
<tr>
<td>1976</td>
<td>Hutchinson</td>
<td>127</td>
<td>8 (0 – 15)</td>
<td>53</td>
</tr>
<tr>
<td>1987</td>
<td>Francis (after Compston 1978)</td>
<td>146</td>
<td>12</td>
<td>57</td>
</tr>
</tbody>
</table>

**UK & Ireland**

**Scandinavia**

<table>
<thead>
<tr>
<th>Year</th>
<th>First Author</th>
<th>Number of Patients</th>
<th>Follow-up, years</th>
<th>MS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1961</td>
<td>Hyllested</td>
<td>38</td>
<td>(2 – 15)</td>
<td>40</td>
</tr>
<tr>
<td>1966</td>
<td>Hyllested</td>
<td>84</td>
<td>(26 – 51)</td>
<td>57</td>
</tr>
<tr>
<td>1974</td>
<td>Nikoskelainen</td>
<td>91</td>
<td>10 (3 – 22)</td>
<td>56</td>
</tr>
<tr>
<td>1978</td>
<td>Stendahl-Brodin</td>
<td>100</td>
<td>(0 – 14)</td>
<td>32</td>
</tr>
<tr>
<td>Year</td>
<td>First Author</td>
<td>Number of Patients</td>
<td>Follow-up, years</td>
<td>MS (%)</td>
</tr>
<tr>
<td>------</td>
<td>--------------------</td>
<td>--------------------</td>
<td>------------------</td>
<td>-------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>mean (range)</td>
<td></td>
</tr>
<tr>
<td>1983</td>
<td>Kinnunen</td>
<td>296</td>
<td>5.1 (1–10)</td>
<td>19</td>
</tr>
<tr>
<td>1989</td>
<td>Anmarkrud</td>
<td>30</td>
<td>(2–11)</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other European</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1962</td>
<td>Otradovec (Czech.)</td>
<td>82</td>
<td>(5–15)</td>
<td>40</td>
</tr>
<tr>
<td>1980</td>
<td>Haller (Germany)</td>
<td>30</td>
<td>(0.5–2.5)</td>
<td>80</td>
</tr>
<tr>
<td>1993</td>
<td>Congia (Italy)</td>
<td>69</td>
<td>(4–13)</td>
<td>54</td>
</tr>
<tr>
<td>1998</td>
<td>Deya (Spain)</td>
<td>26</td>
<td>4.5</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Israel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1976</td>
<td>Kahana</td>
<td>105</td>
<td>9.5 (3–16)</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1952</td>
<td>Bagley</td>
<td>47</td>
<td>(0–7)</td>
<td>0</td>
</tr>
<tr>
<td>1954</td>
<td>Taub</td>
<td>87</td>
<td>(10–15)</td>
<td>32</td>
</tr>
</tbody>
</table>
Table 1.5 (cont.)

<table>
<thead>
<tr>
<th>Year</th>
<th>First Author</th>
<th>Number of Patients</th>
<th>Follow-up, years mean (range)</th>
<th>MS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA (cont.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1965</td>
<td>Collis</td>
<td>75</td>
<td>(7 – 20)</td>
<td>32</td>
</tr>
<tr>
<td>1966</td>
<td>Kurland</td>
<td>183</td>
<td>(12 – 18)</td>
<td>14</td>
</tr>
<tr>
<td>1972</td>
<td>Percy</td>
<td>24</td>
<td>18 (2 – 23)</td>
<td>17</td>
</tr>
<tr>
<td>1973</td>
<td>Alter</td>
<td>41</td>
<td>(1 – 10)</td>
<td>29</td>
</tr>
<tr>
<td>1974</td>
<td>Appen</td>
<td>56</td>
<td>10 (3 – 18)</td>
<td>27</td>
</tr>
<tr>
<td>1995</td>
<td>Rodriguez</td>
<td>95</td>
<td>10</td>
<td>39</td>
</tr>
</tbody>
</table>

Latin America

<table>
<thead>
<tr>
<th>Year</th>
<th>First Author (Country)</th>
<th>Number of Patients</th>
<th>Follow-up, years mean (range)</th>
<th>MS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989</td>
<td>Alvarez (Chile)</td>
<td>23</td>
<td>(2 – 18)</td>
<td>4.2</td>
</tr>
<tr>
<td>1997</td>
<td>Corona-Vazquez (Mexico)</td>
<td>110</td>
<td>2</td>
<td>12</td>
</tr>
</tbody>
</table>

Australia

<table>
<thead>
<tr>
<th>Year</th>
<th>First Author</th>
<th>Number of Patients</th>
<th>Follow-up, years mean (range)</th>
<th>MS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1968</td>
<td>Rischbieth</td>
<td>103</td>
<td>(0 – 52)</td>
<td>83</td>
</tr>
<tr>
<td>Year</td>
<td>First Author (after)</td>
<td>City / State / Country</td>
<td>Follow-up, years mean (range)</td>
<td>MS / ON (%)</td>
</tr>
<tr>
<td>------</td>
<td>----------------------</td>
<td>------------------------</td>
<td>-----------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>1979</td>
<td>Perkin &amp; Rose (after Rose 1970)</td>
<td>London</td>
<td>3 (0.5 – 5)</td>
<td>45 / 78 (58)</td>
</tr>
<tr>
<td>1981</td>
<td>Nikoskelainen</td>
<td>Turku, Finland</td>
<td>(7 – 10)</td>
<td>27 / 48 (56)</td>
</tr>
<tr>
<td>1978 / 83</td>
<td>Stendahl-Brodin</td>
<td>Stockholm, Sweden</td>
<td>11 (6 – 20)</td>
<td>10 / 30 (33)</td>
</tr>
<tr>
<td>1990</td>
<td>Sandberg-Wollheim</td>
<td>Lund, Sweden</td>
<td>13</td>
<td>33 / 86 (38)</td>
</tr>
<tr>
<td>1994 / 95 / 98</td>
<td>Soderstrom</td>
<td>Stockholm, Sweden</td>
<td>(0 – 6)</td>
<td>53 / 147 (36)</td>
</tr>
<tr>
<td>1996</td>
<td>Frederiksen</td>
<td>Copenhagen, Denmark</td>
<td>1</td>
<td>8 / 48 (17)</td>
</tr>
<tr>
<td>1985 / 91</td>
<td>Mapelli</td>
<td>Ferrara, Italy</td>
<td>&gt; 10</td>
<td>10 / 40 (25)</td>
</tr>
<tr>
<td>1994</td>
<td>Filippini</td>
<td>Milan, Italy</td>
<td>3</td>
<td>1 / 21 (5)</td>
</tr>
<tr>
<td>1996 / 99</td>
<td>Ghezzi (after Martinelli 1991)</td>
<td>Gallerate, Italy</td>
<td>6.3</td>
<td>37 / 102 (36)</td>
</tr>
<tr>
<td>1997</td>
<td>Rio</td>
<td>Barcelona, Spain</td>
<td>2.4</td>
<td>5 / 35 (14)</td>
</tr>
<tr>
<td>1999</td>
<td>Druschky</td>
<td>Erlangen, Germany</td>
<td>8 (6 – 9)</td>
<td>14 / 26 (54)</td>
</tr>
<tr>
<td>Year</td>
<td>First Author</td>
<td>City / State / Country</td>
<td>Follow-up, years mean (range)</td>
<td>MS / ON (%)</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------</td>
<td>------------------------------</td>
<td>--------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>USA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1988</td>
<td>Rizzo (after Cohen 1979)</td>
<td>Boston, MA</td>
<td>15 (5 – 21)</td>
<td>35 / 60 (58)</td>
</tr>
<tr>
<td>1991</td>
<td>Scholl</td>
<td>Boston, MA</td>
<td>3.5</td>
<td>35 / 81 (43)</td>
</tr>
<tr>
<td>1991 / 97</td>
<td>Jacobs</td>
<td>Buffalo, NY</td>
<td>5.6 (0 – 20)</td>
<td>21 / 74 (28)</td>
</tr>
<tr>
<td>1997</td>
<td>*ONSG</td>
<td>Multi-centre</td>
<td>5</td>
<td>141 / 388 (36)</td>
</tr>
<tr>
<td>Latin America</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1991</td>
<td>Lana-Piexoto</td>
<td>Bello Horizonte, Brazil</td>
<td>4.6 (0 – 9)</td>
<td>9 / 88 (11)</td>
</tr>
<tr>
<td>Japan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1982</td>
<td>Isayama</td>
<td>Kobe, Japan</td>
<td>5 (1 – 12)</td>
<td>7 / 84 (8)</td>
</tr>
<tr>
<td>Australia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Frith (after Hely 1986)</td>
<td>Sydney, Australia</td>
<td>13.2</td>
<td>33 / 71 (46)</td>
</tr>
</tbody>
</table>

* Optic Neuritis Study Group (isolated optic neuritis patients only)
These have varied widely in their reported results. There are a number of methodological factors that may explain these differences.

(1) **Study designs** vary, with many studies retrospective, based on discovering the subsequent course of patients who have been recorded as attending hospital with optic neuritis, whilst more recent studies tend to be prospective, following patients from onset of symptoms. Retrospective studies in this population are likely to be biased towards including patients who have had subsequent symptoms and are therefore easier to trace. Prospective studies are more likely to include patients regardless of further disease activity, but do suffer from the confounding effects of patients becoming lost to follow up.

(2) The **criteria for the diagnosis** of both optic neuritis and MS were not standardised between studies. Some included patients presenting with bilateral simultaneous optic neuritis (which has a lower risk of progression to MS [Parkin et al. 1984]) or with a history suggestive of disseminated disease at the time of presentation. The diagnosis of MS may have been possible, rather than definite, or may have rested only on recurrent episodes of optic neuritis.

(3) **Geographical variation** in conversion rates also occurs following optic neuritis. For example, they are low in Japan [Isayama et al. 1982] and Brazil [Lana-Piexoto et al. 1991], and particularly high in the UK [Francis et al. 1987]

(4) **Criteria of patient selection**. Some studies have included patients attending hospital whilst others have been population surveys. Hospital-based studies and
studies in which patients are seen from onset may represent a more severely affected group of patients who are likely to have a worse prognosis. Gender and racial differences in the studied population may also affect the outcome.

(5) The length of follow-up has varied between studies. Although most MS-defining episodes happen within a few years after the initial symptoms (see later), in some patients many years may elapse before further symptoms occur. Short follow-up periods will therefore under-report the risk of MS. To compensate for limitations in the length of follow-up, some studies have tried to assess the risk by the use of life-table analysis [Percy et al. 1972, Kahana et al. 1976, Kinnunen et al. 1983, Hely et al. 1986, Francis et al. 1987, Rizzo & Lessell 1988, Rodriguez et al. 1995, ONSG 1997].

Other CIS have been less well studied than optic neuritis because of their heterogeneity and wider differential diagnosis. These conditions are likely to be due to the same pathological process with the differences between the clinical presentations being determined merely by the location of the symptomatic new lesion. Prospective follow-up studies that have included brainstem and spinal cord syndromes in addition to optic neuritis, have reported comparable rates of conversion to MS in the different syndromes [Lee et al. 1991, Barkhof et al. 1997, O’Riordan et al. 1998a, Tintore et al. 2000]. An exception, however, may be patients with a complete transverse myelitis, a condition that is unusual in MS, in whom a much lower rate of developing MS has been reported [Lipton et al. 1973]. The results of follow up studies in CIS groups are summarised in Table 1.7.
<table>
<thead>
<tr>
<th>Year</th>
<th>First Author</th>
<th>City / Country</th>
<th>Syndrome</th>
<th>Follow-up, years mean (range)</th>
<th>MS / CIS ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1973</td>
<td>Lipton</td>
<td>Baltimore, USA</td>
<td>SC (complete)</td>
<td>(5 – 42)</td>
<td>1 / 29 (3)</td>
</tr>
<tr>
<td>1991</td>
<td>Shareif</td>
<td>London, UK</td>
<td>BS/SC</td>
<td>1.5</td>
<td>13 / 45 (29)</td>
</tr>
<tr>
<td>1992</td>
<td>Ford</td>
<td>Montreal, Canada</td>
<td>SC</td>
<td>3.2</td>
<td>12 / 15 (80)</td>
</tr>
<tr>
<td>1994</td>
<td>Filippini</td>
<td>Milan, Italy</td>
<td>SC/BS/Cerebrum</td>
<td>2.9</td>
<td>11 / 34 (32)</td>
</tr>
<tr>
<td>1995</td>
<td>Martinelli</td>
<td>Milan, Italy</td>
<td>SC</td>
<td>2</td>
<td>6 / 27 (22)</td>
</tr>
<tr>
<td>1996</td>
<td>Paolino</td>
<td>Ferrara, Italy</td>
<td>BS/SC</td>
<td>2.2</td>
<td>30 / 66 (68)</td>
</tr>
<tr>
<td>1997</td>
<td>Barkhof</td>
<td>Multi-centre Europe</td>
<td>ON/BS/SC</td>
<td>(0.5 – 8)</td>
<td>33 / 74 (45)</td>
</tr>
<tr>
<td>1998</td>
<td>O’Riordan</td>
<td>London, UK</td>
<td>ON/BS/SC</td>
<td>9.7</td>
<td>48 / 81 (59)</td>
</tr>
<tr>
<td></td>
<td>(after Morrissey 1993 Miller 1988 / 89)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Tintore</td>
<td>Barcelona, Spain</td>
<td>ON/BS/SC</td>
<td>2.4</td>
<td>22 / 70 (31)</td>
</tr>
</tbody>
</table>

SC = spinal cord syndrome, BS = brainstem syndrome, ON = optic neuritis
There is little consensus about the demographic and clinical findings that influence the subsequent risk of MS. Some of those that have been suggested in optic neuritis are provided in Table 1.8.

### Table 1.8 Reported clinical prognostic factors in patients with optic neuritis

<table>
<thead>
<tr>
<th>Increased risk of MS</th>
<th>Decreased risk of MS</th>
<th>No effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young adults</td>
<td>Onset in childhood</td>
<td>Advanced age</td>
</tr>
<tr>
<td>Women</td>
<td>Bilateral (simultaneous)</td>
<td>Laterality</td>
</tr>
<tr>
<td>Uhthoff’s phenomena</td>
<td>Presence / absence of pain</td>
<td></td>
</tr>
<tr>
<td>Retinal venous sheathing</td>
<td>Degree of visual loss</td>
<td></td>
</tr>
<tr>
<td>Early recurrence</td>
<td>Disc oedema</td>
<td></td>
</tr>
</tbody>
</table>

#### 1.2.3 Investigations

Most investigations performed in CIS are aimed at excluding alternative pathologies. They may also, however, have a role in assessing the likelihood of further relapses leading to MS. This is usually by the identification of symptomless abnormalities that provide evidence of disseminated disease. Undoubtedly, the most useful investigation is magnetic resonance imaging (MRI) of the brain and this is discussed more fully in Chapter 2.

Abnormal intrathecal IgG synthesis, reflected as two or more oligoclonal bands of IgG seen in the CSF while not present in the corresponding serum, has been found in 60 – 70% of optic neuritis patients [Frederiksen et al. 1991, Soderstrom et al. 1998]. The presence of these abnormalities has been found to increase the subsequent risk of MS [Stendahl-Brodin et al. 1983, Sandberg-Wollheim et al. 1990, Soderstrom et al. 1998].
1998], although whether the presence of oligoclonal bands provides information independent of MRI abnormalities with which they often co-exist has been questioned [Rolak et al. 1996]. Oligoclonal IgM bands in the CSF may also have a predictive role in CIS patients [Sharief et al. 1991].


1.2.4 Natural History Studies

The natural history of patients from presenting with CIS is less well characterised than that of patients with established MS. Isolated optic neuritis has been most studied. Optic neuritis recurs either in the same or the contra-lateral eye in around 35% [Francis et al. 1987, Rizzo & Lessell 1988]. A recurrence of optic neuritis does not indicate sufficiently wide dissemination of disease for MS to be diagnosed [Kurtze 1985]. Most MS-defining relapses occur within 2 – 5 years [Cohen et al. 1979, Landy et al. 1983, Filippi et al. 1994], although symptom free periods of several decades have been reported in the literature [Ebers 1985].

The accumulation of disability following optic neuritis has been found to be generally slow, with 70 – 80% of patients remaining unrestricted after up to 15 years [Bradley & Whitty 1968, Hutchinson 1976, Rizzo & Lessell 1988, Ghezzi et al. 1999]. This
may reflect that the course of MS is more benign when the initial symptom is optic neuritis or alternatively that the disease is being identified at a much earlier stage.

Cognitive impairment is subtle in CIS patients and subjective symptoms are usually absent. However, psychometric studies of CIS patients at presentation have detected impairment of cognitive function [Callanan et al. 1989, Pelosi et al. 1997]. In a 4-year follow-up study of CIS patients, cognitive deterioration was only found to occur in those developing MS [Feinstein et al. 1992].

1.2.5 Treatment

1.2.5.1 Counselling: The decision whether or not to discuss MS with patients who present with CIS has been controversial. There was an argument in the past for not worrying a patient about a condition that might never occur and for which there has been no treatment. Surveys of patients with optic neuritis, however, have revealed that the majority of patients feel that they should be informed despite this [Slamovits et al 1991]. With the increased access of the public to information, e.g. through the Internet, and with treatments being introduced which can modify the course of the disease, discussing the risks of MS and disability with CIS patients has become increasingly important, particularly in those patients who are identified from MRI findings as being at high risk for development of CD MS.

1.2.5.2 Symptomatic treatment: CIS can be treated with steroids in much the same way as an MS relapse. As in established MS, treatment may reduce the time to recovery from optic neuritis but has not been shown to have any impact on final outcome [Beck et al. 1993].
1.2.5.3 *Disease-modifying treatments*

A three-day course of intravenous methyl-prednisolone followed by 11 days of oral prednisolone was found in one study to delay the conversion from optic neuritis to MS within two years [Beck *et al.* 1993]. However, this beneficial effect diminished after more than two years and was no longer apparent after three years [Beck 1995]. Conversely, a study from Israel has reported increased MS conversion rates in patients treated with intravenous methyl-prednisolone [Herishanu *et al.* 1989]. Oral steroids do not appear to affect the risk of MS [Sellebjerg *et al.* 1999] although in one study were found to *increase* the risk of recurrent optic neuritis [Beck *et al.* 1993].

Trials of interferon beta-1a (Avonex and Rebif) given to patients with CIS or clinically probable early MS have been performed and shown to delay the time to conversion to clinically definite MS [Jacobs *et al.* 2000, Comi *et al.* 2000]. As substantial numbers of CIS patients will not develop further symptoms there is a need to develop techniques that can identify patients at greatest risk so that these can be offered treatment or entered into future treatment trials. This issue will be addressed in later chapters of this thesis.
2.1 The principles of magnetic resonance imaging

MRI utilises the properties of hydrogen atoms, which are found in abundance in the human body. Hydrogen nuclei consist of single, positive protons and so the terms hydrogen nucleus and proton are often used interchangeably.

Under normal circumstances, each proton acts as though it were spinning around its axis producing a magnetic field. As they are randomly orientated the human body has no overall magnetic field. When protons are placed in an external magnetic field, they align themselves either parallel or anti-parallel to it. As less energy is required to become parallel, marginally more protons align in this way, resulting in an overall magnetic moment that is almost, but not quite, zero. Once aligned the protons continue to spin on their axis, but due to the influence of the external magnetic field, a secondary motion occurs called precession.

The frequency of precession depends on the strength of the magnetic field in which the protons are placed, e.g. in a magnetic field strength of 1 Tesla (T) protons in the human body precess at 42 MHz, whereas at 1.5 T the precession frequency is 63 MHz. The precession frequency can be calculated using the Larmor equation.
The Larmor equation

\[ f_0 = \left( \gamma / 2\pi \right) B_0 = \gamma B_0 \]

Where:

- \( f_0 \) precession frequency \((\text{Hz})\)
- \( B_0 \) strength of the external magnetic field \((\text{T})\)
- \( \gamma \) gyro-magnetic ratio \((\text{Hz} / \text{T})\) – dependant on material

The precession of protons causes them to be misaligned with the external magnetic field resulting in longitudinal and transverse magnetic properties. The combined longitudinal component of the protons produces a small magnetic field (longitudinal magnetisation), which cannot be directly measured. The transverse magnetic fields of the protons cancel each other out because the protons precess out of phase with each other.

In order to measure the magnetic properties of the protons, a radio frequency pulse (RF) pulse with the same frequency as the precessing protons, is used to transfer energy to them (resonance). The power and duration of the RF pulse can be manipulated to produce specific effects on protons. A 90° RF pulse will rotate the net magnetisation into the transverse plane, so that it produces a measurable magnetic effect (transverse magnetisation). The magnetisation vector precesses at the same frequency as the protons and induces a voltage in a receiver coil placed in the transverse plane, which constitutes the MR signal.
Switching off the RF pulse has two important effects:

1. Longitudinal magnetisation increases as the protons revert to aligning themselves parallel to the external magnetic field. This is known as T1-relaxation and is caused by the exchange of energy from the nuclei to their surrounding environment or lattice. The T1 of a tissue is the time constant that describes how fast the longitudinal magnetisation returns to normal after the RF pulse is switched off; defined by the time it takes for a 63% recovery (Figure 2.1). Further 90° RF pulses can be sent in to recreate transverse magnetisation; the time period between two 90° RF pulses is known as the repetition time (TR).

2. Transverse magnetisation starts to disappear causing the signal induced in the receiver coil to decrease (free induction decay) as protons come out of synchrony. The dephasing relaxation process is known as T2-relaxation and occurs as a result of the intrinsic magnetic fields of the nuclei interacting with one another. The T2 of a tissue is a time constant that describes how fast the transverse magnetisation disappears due to the properties of a tissue; defined by the time it takes for 63% to be lost (Figure 2.2). Inhomogeneities in the external magnetic field will result in some protons experiencing different magnetic field strengths to others and precessing at different rates causing the protons to dephase more quickly than would occur due to the tissues properties alone (measured by the time constant T2*). T2* often provides little useful information and therefore must be eliminated. This can be achieved by applying a 180° RF pulse at a time TE/2, which rephases the protons, so that by the echo time (TE), when the signal is collected, only true T2 effects contribute to the signal. The combination of 90° and 180° RF pulses is known as a spin-echo (SE) pulse sequence.
Figure 2.1  T1 curves for grey matter (gm), white matter (wm) and CSF
(Reproduced with the permission of GJ Barker.)
Figure 2.2  T2 curves for grey matter (gm), white matter (wm) and CSF. (Reproduced with the permission of GJ Barker.)
By altering the length of the TR and TE, different tissues can be differentiated depending on their T1 and T2 properties. Using a short TR prevents tissue with a longer T1 from recovering to the extent of those in which the T1 is short, so that there will be a greater transverse magnetisation following a second RF pulse in a tissue with the faster recovery time. Similarly, by altering the TE, tissues with properties with different T2 properties can be distinguished. However, if the TE is too long the signal becomes too small and the signal-to-noise ratio (SNR) becomes too small.

The combination of a short TR and a short TE provides images that mainly differentiate between tissues based on their T1 properties and are therefore termed T1-weighted. Conversely, by combining a medium to long TR with a long TE, contrast mainly results from differences in T2 properties resulting in a T2-weighted image. When a medium to long TR and short TE are used, the signal is mainly due to the proton densities of the tissues, providing a proton-density (PD)-weighted image. In a clinical setting, the TR and TE selected for the PD-weighted image produces contrast between grey and white matter due to differences in their proton densities, but the CSF remains T1-weighted (hypointense to brain tissue) as this enables better visualisation of the periventricular pathology (Figure 2.3).

In a homogenous magnetic field, all protons precess at the same frequency and it is impossible to identify the source of each signal. In order to produce an image, the location of different protons within the tissues needs to be determined. By superimposing a magnetic field gradient (gradient field) on the external field using gradient coils, protons at different sites are exposed to slightly different magnetic field strengths and precess at different frequencies.
Figure 2.3  (a) T1- (TR 600 ms, TE 14 ms), (b) PD- (TR 2000 ms and TE 34 ms) and (c) T2-weighted (TR 2000 ms, TE 90 ms) SE axial images of the author’s brain.
A *slice-selecting gradient* is turned on during the RF pulses. This causes protons at different locations to precess at different frequencies. Only the protons in the desired region will be precessing at the same frequency as the RF pulse and so have energy transferred to them. Slice thickness can be adjusted by either altering the range of frequencies in the RF pulses (bandwidth) or by altering the gradient of the magnetic field.

Once the slice-selecting gradient is switched off, the magnetic field strength experienced by all the protons within the slice will be the same. In order to gain two-dimensional information from the protons in this slice a further gradient is switched on (*phase-encoding gradient*) along one axis causing protons in different locations to precess at different frequencies. When this is switched off the protons all precess at the same frequency again, but because some have been travelling faster than others they are out of phase with each other enabling them to be spatially located. The phase-encoding has to be repeated several times (once per TR), depending on the matrix size, in order to enable the spatial localisation of all the protons in a slice.

A third gradient (*frequency-encoding gradient*) corresponding to the remaining dimension is then switched on during the echo, when the data is acquired. The frequency change caused by the gradient is used to locate each signal in the final dimension.

The information obtained from the encoding process now has to be translated onto the image. The system maps each signal by placing it onto a two-dimensional grid or matrix. Following each TR, a single line of data is acquired and stored in "k-space".
The position of each data point is determined by the gradients used to create it; data with high phase-encoding gradients are placed in different lines to those with low phase-encoding gradients. Similarly, data collected early during the readout are placed in different columns to those collected later. Each point in the $k$-space contributes to the entire image. The central lines of $k$-space are responsible for the majority of signal in the image, whilst the outer lines are responsible for the spatial resolution. The system, using a mathematical process known as Fourier transform, can then process the signals obtained from the slices, columns and lines and an image is constructed.

The acquisition time of an image is determined by the TR, the number of phase encodings that need to be performed (determined by the size of the matrix) and by the number of times the echo is phase-encoded with the same phase-encoding gradient (number of excitations, NEX). As the TR is the most time consuming parameter in MRI, the dead time between excitation and acquisition of the long echo necessary to produce T2-weighted images can be filled by also collecting signal at shorter echo times. The PD-weighted image is usually collected at the same time as the T2-weighted image (dual-echo sequence). Multiple slices may also be collected during a single TR; since using different slice-selecting gradients means that the RF pulse for one slice doesn’t affect any other. In some sequences a NEX of 0.5 or 0.75 (fractional NEX) is used. This is achieved by acquiring data and storing it in k-space for half or three-quarters of the time and filling the rest of the $k$-space with zeroes. The resulting image will have lower SNR but enables the acquisition time to be reduced.
2.2 Conventional MRI techniques in MS and CIS

2.2.1 Role of MRI in the diagnosis of MS

The first application of MRI in patients with MS utilised T1-weighted SE images, identifying MS plaques as areas of hypointensity compared to normal white matter [Young et al. 1981]. Shortly after this, PD- and T2-weighted SE images were acquired [Bailes et al. 1982] on which plaques appeared as areas of high signal (T2 lesions) making them easier to identify. Post-mortem studies have confirmed that these T2 lesions do correlate with the position of MS plaques [Stewart et al. 1984, Stewart et al. 1986, Ormerod et al. 1987]. Lesions can now be identified using MRI in more than 90% of patients with clinically definite MS.

MRI should only assist in diagnosing MS in a patient with an appropriate history or clinical signs. MS lesions are detectable because they have a higher density and mobility of water protons than normal white matter. This makes them relatively non-specific. Different pathological processes occurring in MS, e.g. inflammation, demyelination, remyelination, gliosis, and in other diseases, e.g. infarcts, granulomas, as well small vessel changes associated with normal ageing, can give a similar appearance. The presence of T2 lesions is, therefore, not sufficient to make the diagnosis of MS although a typical distribution of lesions (see Chapter 1) can lend considerable further support to it (Figure 2.4).

To improve the likelihood that brain abnormalities seen on T2-weighted images are due to MS, criteria have been devised by which to assess the images based on the number and distribution of the lesions [Paty et al. 1988, Fazekas et al. 1988, Barkhof et al. 1997].
Figure 2.4  (a) T1- (TR 600 ms, TE 14 ms). (2) PD- (TR 2000 ms, TE 34 ms) and (c) T2-weighted (TR 2000 ms, TE 90 ms) SE axial brain images showing typical MS lesions (taken from a 23 year old lady (TW) with secondary progressive MS)
Table 2.1  Paty, Fazekas and Barkhof criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paty</td>
<td>Four T2 lesions of greater or equal to 3mm OR three lesions, one of which is periventricular</td>
</tr>
<tr>
<td>Fazekas</td>
<td>Three or more T2 lesions AND at least two of the following characteristics: (a) &gt;5mm, (b) periventricular, (c) infratentorial</td>
</tr>
<tr>
<td>Barkhof</td>
<td>Cumulative chance model for conversion to MS (80% with all four features fulfilled) (a) At least one contrast-enhancing lesion (see below), (b) at least one juxtacortical T2 lesion, (c) at least one infratentorial T2 lesion, (d) at least three periventricular T2 lesions.</td>
</tr>
</tbody>
</table>

2.2.2 Monitoring the course of MS: T2 lesions

The high sensitivity of T2-weighted MRI to lesions has enabled the natural history of MS to be studied in more detail than was previously possible. It has also become pivotal as a monitor of disease activity in treatment trials for MS, which previously had been hampered by the high degree of variability of clinical signs and symptoms over time and between individuals with MS. New T2 lesions have been shown to occur 5 – 10 times more frequently than clinical disease in patients with relapsing-remitting MS [Isaac et al. 1988, Willoughby et al. 1989]. The increase in volume of T2 lesions from yearly follow up of patients can be quantified using computer techniques. Several methods have been used to do this. Manually tracing around lesions was initially used, but this was time-consuming and suffered from poor
reproducibility [Paty et al. 1993]. Semi-automated thresholding techniques (lesion by lesion) are equally time-consuming, but are more accurate [Grimaud et al. 1996] and are widely used. Global thresholding techniques are also available, but the standardisation of a single threshold across serial images is not yet possible, limiting the role of this technique in longitudinal studies [Molyneux et al. 1998].

In established MS, there is only a modest correlation between T2 lesion load and disability, as measured by the EDSS [Filippi et al. 1995a], probably reflecting the relative pathological non-specificity of T2 lesions. Measurement of T2 lesion load should therefore only be used as a secondary outcome marker in phase III treatment trials, with clinical outcome remaining as the primary endpoint.

2.2.3 Assessing the risk of MS in patients with CIS

Shortly after the discovery that MRI was able to detect lesions in MS patients, it was used in the investigation of patients presenting with a CIS [Ormerod et al. 1986a, Ormerod et al. 1986b, Jacobs et al. 1986, Miller et al. 1987]. Between 50 and 75% were found to have clinically silent lesions in the brain, identical in appearance to those seen in established MS. MRI has since become established as the most sensitive paraclinical test for detecting dissemination of disease in these patients, being more sensitive than either the presence of oligoclonal bands or evoked potential abnormalities [Frederiksen et al. 1991, Lee et al. 1991, Martinelli et al. 1991].

Prospective MRI studies have found that the presence of cerebral T2 lesions in patients presenting with CIS significantly increases the risk of MS developing with follow-up (Table 2.2). However, it should be noted that not all patients with
asymptomatic T2 lesions have developed MS while a small proportion of patients with a normal brain MRI at presentation have. The number of T2 lesions at baseline predicts time to developing MS and future disability; with the number of T2 lesions at presentation correlating with EDSS after five and ten years [O'Riordan et al. 1998a, Sailer et al. 1999].

2.3 Newer MRI techniques and their applications in MS

MRI has rapidly evolved in recent years. Advances have occurred in hardware, with stronger magnets and improved receiver coils. Newer sequences have been developed for the study of MS to enable improved detection of T2 lesions in both the brain and the spinal cord. More pathologically specific MR measures, e.g. hypointense T1 lesions and contrast-enhancing lesions, have become available and quantitative techniques, e.g. magnetisation transfer imaging (MTI), 1H-MR spectroscopy and the measurement of atrophy, have been developed which enable both the study of lesions and also NAWM, which has become increasingly recognised as a site for more subtle pathology in MS.

2.3.1 High field imaging

As higher field scanners become more widely used, imaging at higher resolutions has become possible enabling the detection of more T2 lesions. Imagers operating at 1.5 T have reported a 30% increase in T2 lesion load compared with older models operating at 0.5 and 1.0 T [Filippi et al. 1997].
### Table 2.2 Prospective MRI studies of clinically isolated syndromes

<table>
<thead>
<tr>
<th>Year</th>
<th>First Author</th>
<th>Location</th>
<th>CIS</th>
<th>Mean follow-up (years)</th>
<th>Relationship between baseline MRI and MS at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Abnormal</td>
</tr>
<tr>
<td><strong>UK</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1991</td>
<td>Sharief</td>
<td>London</td>
<td>BS/SC</td>
<td>1</td>
<td>11/24 (46%)</td>
</tr>
<tr>
<td><strong>Scandinavia</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1996</td>
<td>Frederiksen</td>
<td>Denmark</td>
<td>ON</td>
<td>1</td>
<td>6/25 (24%)</td>
</tr>
<tr>
<td>1994/98</td>
<td>Soderstrom *patients only followed until CDMS</td>
<td>Sweden</td>
<td>ON</td>
<td>2*</td>
<td>40/64 (63%)</td>
</tr>
<tr>
<td><strong>Other European</strong></td>
<td></td>
<td></td>
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<tr>
<td>1994</td>
<td>Filippini *suspected MS</td>
<td>Italy</td>
<td>CIS*</td>
<td>2.9</td>
<td>27/57 (47%)</td>
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<td>1996</td>
<td>Paolino *patients who did not develop MS followed for a further 7 years</td>
<td>Italy</td>
<td>SC/BS</td>
<td>2.2*</td>
<td>18/22 (82%)</td>
</tr>
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<td>1997</td>
<td>Barkhof</td>
<td>Multi-centre</td>
<td>CIS</td>
<td>3</td>
<td>32/61 (52%)</td>
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Table 2.2 (cont.)

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<th>Year</th>
<th>First Author</th>
<th>Location</th>
<th>CIS</th>
<th>Mean follow-up (years)</th>
<th>Relationship between baseline MRI and MS at follow-up</th>
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<tr>
<td>1998</td>
<td>Deya</td>
<td>Spain</td>
<td>ON</td>
<td>4.5</td>
<td>2 / 10 (20%)</td>
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<tr>
<td>1996/99</td>
<td>Ghezzi</td>
<td>Italy</td>
<td>ON</td>
<td>6.3</td>
<td>37 / 71 (52%)</td>
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<td>1999</td>
<td>Druschky</td>
<td>Germany</td>
<td>ON</td>
<td>8</td>
<td>13 / 19 (68%)</td>
</tr>
<tr>
<td>1999</td>
<td>Tintore (after Rio 1997)</td>
<td>Spain</td>
<td>CIS</td>
<td>2</td>
<td>19 / 41 (46%)*</td>
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**USA & Canada**

<table>
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<tr>
<th>Year</th>
<th>First Author</th>
<th>Location</th>
<th>CIS</th>
<th>Mean follow-up (years)</th>
<th>Relationship between baseline MRI and MS at follow-up</th>
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<td>1991</td>
<td>Lee (after Paty 1988)</td>
<td>Canada</td>
<td>all*</td>
<td>2.1</td>
<td>52 / 118 (44%)</td>
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<td>* suspected MS</td>
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<tr>
<td>1992</td>
<td>Ford</td>
<td>Canada</td>
<td>SC</td>
<td>3.2</td>
<td>11 / 12 (92%)</td>
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<tr>
<td>1997</td>
<td>ONSG</td>
<td>USA</td>
<td>ON</td>
<td>5</td>
<td>39 / 104 (38%)</td>
</tr>
<tr>
<td>1991/97</td>
<td>Jacobs</td>
<td>USA</td>
<td>ON</td>
<td>5.6</td>
<td>16 / 42 (38%)</td>
</tr>
</tbody>
</table>

BS = brainstem, SC = spinal cord syndrome, ON = optic neuritis
2.3.2 Newer sequences

2.3.2.1 Fast spin-echo (FSE): This sequence is based on the rapid acquisition with relaxation enhancement (RARE) sequence [Hennig et al. 1986]. The primary advantage is speed without a reduction in the SNR. In FSE, several echoes are collected per TR. Each echo is preceded by a different value of the phase-encoding gradient, so that between 2 and 16 lines of k-space may be filled per TR. The number of echoes collected per TR is known as the echo train length (ETL) and the time between each as the echo spacing. This enables imaging time to be increased by a factor proportional to the ETL, e.g. the 8 – 12 minutes required for a T2-weighted conventional SE (CSE) of the brain can be acquired in between 60 and 90 seconds if eight echoes are collected. All the echoes contribute to the signal instead of a single one, as with CSE, and so the echo with the lowest phase encoding gradient determines the effective TE. FSE has reduced the time necessary to perform imaging, enabling thinner slices to be acquired in an acceptable time frame whilst maintaining an adequate SNR. The only limitation on the total number of echoes is the speed and strength of the gradients and signal remaining following T2 decay at long TE. At similar slice thickness, FSE detects similar lesion loads as CSE [Thorpe et al. 1994]. The thinner slices made possible by FSE, however, enables more lesions to be detected [Filippi et al. 1995b]. As with CSE, more lesions are detected on the PD- than the T2-weighted images [Thorpe et al. 1994].

2.3.2.2 Fluid-attenuated inversion recovery (FLAIR): The FLAIR sequence uses an inversion recovery (IR) sequence to enable CSF to be nulled, while maintaining contrast between lesions and the brain. In an IR sequence, a 180° RF pulse precedes the 90° RF pulse normally used in CSE, to turn the longitudinal magnetisation in the
opposite direction, followed by 90° and 180° pulses, to provide transverse magnetisation as in CSE (Figure 2.5). The time between the 180° pulse and the initial 90° pulses is the inversion time (TI). Using a FLAIR sequence, a heavily T2-weighted image can be obtained but with improved visualisation of periventricular lesions due to nulling the signal from CSF. This is achieved by selecting a TI that produces no signal from the CSF. This TI however, produces low tissue contrast and a long TE is necessary to provide sufficient contrast, resulting in a relatively poor SNR. FLAIR can also be combined with a FSE sequence to produce fast FLAIR (fFLAIR). fFLAIR has been shown to improve the detection of periventricular and subcortical lesions in MS patients but it is inferior to CSE at detecting lesions in the posterior fossa [Filippi et al. 1996, Bastianello et al. 1997, Gawne-Cain et al. 1997]. For these reasons it tends to be used in addition, rather than instead of, CSE or FSE sequences (Figure 2.6).

2.3.2.3 Gradient-echo sequences: In some sequences it may be necessary to have a very short TR and this may not allow time for a 180° RF pulse to be delivered. In this case, a gradient-echo can be used in its place to rephase the protons. This involves the brief application of a magnetic field gradient following the 90° RF pulse, which results in larger magnetic field inhomogeneities in the examined slice than would otherwise occur, causing the transverse magnetisation signal to disappear faster (shorter T2*). The magnetic field gradient is then switched back on with the same strength but in the opposite direction, rephasing the protons and increasing the signal. With a short TR, it is often necessary to use smaller flip angles (usually between 10 – 35°) of the RF pulse (rather than the 90° pulse for SE), because otherwise the longitudinal relaxation has too little time to recover to produce adequate signal.
Figure 2.5  Inversion time (TI) plotted against signal intensity for white matter (wm), grey matter (gm) and CSF
(Reproduced with the permission of GJ Barker)
Figure 2.6  Comparison of PD-weighted (a) FSE and (b) FLAIR images of MS lesions (taken from a 57 year old lady with relapsing-remitting MS)
The Ernst angle is the optimum angle required to obtain the maximum SNR. Spoiling is used to destroy residual transverse magnetisation prior to the next excitation at the desired flip angle.

2.3.3 Spinal cord imaging

There are several problems that have made imaging of the spinal cord more difficult than brain imaging. Firstly, the cord is very long but with a small cross-sectional area. Secondly, it lies at a depth of several centimetres from the surface and this depth increases in the cervical and lumbar regions when a natural lordosis occurs. Thirdly, the cord is surrounded by CSF, which moves in a pulsatile manner producing flow artefacts. Spinal cord imaging has improved since the introduction of FSE, since it is less prone to CSF motion artefacts than CSE and allows a faster acquisition time. The use of phased-array coils, which contain several coils that receive the MR signal from different positions simultaneously, has enabled the whole length of the cord to be covered with high SNR on a single sagittal image.

Spinal cord imaging is now possible with sufficient resolution to detect lesions (Figure 2.7). Detection of spinal cord lesions in MS is important, as they are more likely than brain lesions to cause disability. They have been found in the majority of MS patients, more commonly in the cervical than thoracic regions [Kidd et al. 1993]. Lesions have been found in the spinal cord in some patients with negative brain imaging and so imaging of the spinal cord can assist in the diagnosis of MS [Thorpe et al. 1996].
Figure 2.7  Spinal cord T2 lesions (arrows) in MS. (a) PD- and (b) T2-weighted sagittal FSE images (taken from 38-year-old gentleman (MW) with relapsing-remitting MS)
2.3.4 Contrast-enhanced images

Paramagnetic substances, such as the rare earth element gadolinium, have small local magnetic fields that cause a shortening of the relaxation times of surrounding protons (proton relaxation enhancement). Gadolinium is toxic in its free state and so is used chelated to diethyl-enetraminepentacetic acid (DTPA). Following intravenous administration of gadolinium-DTPA, focal defects in the blood brain barrier can be seen. The contrast medium changes the signal intensity by shortening T1 and T2 in its surroundings. On T1-weighted MRI, the reduction of T1 in the tissue containing the contrast medium increases the signal at short TR, providing an increase in the contrast with other tissues. On T2-weighted MRI, less signal comes from the tissue containing the contrast medium (although, in some instances, because of some residual T1-weighting, high signal lesions may actually increase in signal on PD- or T2-weighted images). As loss of signal is more difficult to appreciate than signal enhancement, T1-weighted MRI is the preferred imaging technique following contrast administration (Figure 2.8).

Contrast-enhancement may be the earliest visibly detectable change in the development of a new lesion in MS [Kermode et al. 1990, Lai et al. 1996] and lasts on average 4 – 6 weeks [Miller et al. 1988b]. The counting of new contrast-enhancing lesions on monthly T1-weighted MRI has become recognised as a useful method of monitoring disease activity [Miller et al. 1993] and is the primary outcome measure for most phase II treatment trials. Almost all new T2 lesions begin with disruption of the blood-brain barrier and few contrast-enhancing lesions appear without accompanying T2 lesions. As with new T2 lesions, new contrast-enhancing lesions
Figure 2.8  Contrast-enhancing lesions in MS. (a) PD-weighted FSE image and (b) post-contrast T1-weighted axial brain images of a 23 year old lady with SP MS (TW). A large number of lesions can be seen, only some of which demonstrate contrast-enhancement, whilst the others are iso- or hypointense compared to surrounding white matter on the T1-weighted images.
often occur in clinically stable patients. In relapsing-remitting MS, the number of
enhancing lesions may vary widely between different patients and fluctuates from
month to month in individual patients, but overall each individual patient tends to
remain in a particular range of lesion activity [McFarland et al. 1992].

2.3.5 Hypointense T1 lesions

A proportion of T2 lesions appear as areas of low signal on T1-weighted images
[Uhlenbrock et al. 1989]. Some of these lesions enhance following contrast
administration demonstrating that they represent acute inflammatory lesions, but
many will remain hypointense (Figure 2.9). Both histopathological [Bruck et al. 1997,
van Walderveen et al. 1998, van Waesberghe et al. 1999] and MR [Loevner et al.
1995, van Walderveen et al. 1999, Brex et al. 2000] studies of these hypointense T1
lesions have suggested that they represent areas of more severe tissue damage. As
such, they may have a greater impact on disability than the total T2 lesion load.
Indeed, some [van Walderveen et al. 1995, Truyen et al. 1996], but not all [O’Riordan
et al. 1998b] studies have shown the T1 lesions load to correlate more strongly with
EDSS than does the T2 lesion load. Treatment trials have started to also measure the
T1 as well as T2 lesion loads to monitor disease progression [Gasperini et al. 1999,
Barkhof et al. 2000, Simon et al. 2000].

2.3.6 Atrophy

Atrophy has been well documented in post-mortem studies of patients with chronic
MS. MRI offers the opportunity to study atrophy of the brain (Figure 2.10) and spinal
cord (Figure 2.11) in vivo and many techniques have been developed to quantify it.
Figure 2.9  Hypointense T1 lesions in MS
Comparison of (a) T2-weighted FSE images with T1-weighted SE images (b) pre- and (c) post administration of gadolinium-DTPA. A proportion of the T2 lesions appear as hypointense T1 lesions. These can be seen on the unenhanced images (b). Some of these demonstrate contrast-enhancement (c) indicating that they represent oedematous new lesions, whilst those that remain hypointense post-contrast are more likely to represent lesions in which severe tissue damage has occurred.

Atrophy of some CNS regions has been found to correlate to disability [Davie et al. 1995, Losseff et al. 1996a, Edwards et al. 1999] and cognitive impairment [Comi et al. 1993], suggesting that it may be of functional importance. Whereas demyelination itself may result in tissue loss, it is probable that axonal loss is the most significant component of atrophy. The positive correlation between cerebral atrophy and white matter N-acetyl aspartate (NAA) (see below) that has been reported in one study of patients with secondary progressive MS would suggest that this is the case [Coles et al. 1999]. Recent technological improvements, such as the development of three-dimensional MRI techniques [Losseff et al. 1996a, Liu et al. 1999, Fox et al. 2000] and the ability to register serial images [Fox et al. 2000] should enable more accurate quantification of atrophy in the different stages of MS and help determine the relationship between lesion formation, changes in NAWM and atrophy.

2.3.7 Magnetisation Transfer Imaging

Magnetic transfer imaging (MTI) examines the non-water components of tissue via their observable effect on water protons. Protons in tissue can be described as existing in two pools. Conventional MRI is dominated by the contribution of freely mobile
Figure 2.10  Brain atrophy in MS
Coronal brain images, acquired using a volume-acquired inversion-prepared fast spoiled gradient echo (FSPGR) sequence, comparing a 57 year old healthy control subject (a), with a 42 year old patient with secondary progressive MS (b).
Figure 2.11  Spinal cord atrophy in MS
Volume-acquired inversion-prepared fast spoiled gradient echo (FSPGR) images of the spinal cord, reformatted to show cross-sectional area of the spinal cord at the level of C2 in (a) a 30 year old healthy control, and (b) a 39 year old gentleman (SL) with secondary progressive MS.
water protons. This pool has a narrow spectral line and a relatively long T2. The second pool consists of protons bound to macromolecules, such as myelin. This pool does not directly contribute to conventional imaging, i.e. it is “MRI-invisible”, because of its short T2 relaxation time. These two pools have approximately the same central Larmor frequency, but the latter has a much broader range of resonant frequencies. Magnetisation is continually transferred from one pool to the other by dipole-dipole interaction between spins or by transfer of nuclei by direct chemical means. At equilibrium, the rates of losses and gains made by each pool are equal. Because of its properties, it is possible to hold the bound pool in a state of saturation, i.e. a state in which there is very little net longitudinal or transverse magnetisation. This is achieved using an off-resonance RF pulse that has a negligible effect on the free proton pool. As the magnetisation in the bound pool is reduced, transfer from the free to the bound pool dominates the exchange of magnetisation between the pools. This reduces the MR-visible magnetisation and also reduces the longitudinal relaxation time of the free pool (MT effect). To quantify the effect of MT contrast, two data sets are required – one with saturation and one without. The difference between signal intensities in the two images may be quantified as the MT ratio (MTR).

\[ \text{MTR} = \frac{M_0 - M_S}{M_0} \]

Where: \( M_0 = \) magnetisation before saturation RF pulse
\( M_S = \) magnetisation after saturation RF pulse
The MTR varies markedly according to tissue type, e.g. the MTR is low in the CSF, in which there few bound protons, and high in white matter where they are plentiful.

A major decrease in white matter MTR is thought to predominantly result from demyelination, although it may also be related to other causes of tissue damage, such as axonal loss [Kimura et al. 1996, Davie et al. 1999]. Evidence for this comes from several sources:

(i) Only modest reductions in MTR were found in brain lesions in guinea pigs after induction of experimental allergic encephalomyelitis (in which inflammation and oedema occur in the absence of demyelination) [Dousset et al. 1992];

(ii) The MTR has been found to be markedly reduced in patients with central pontine myelinosis, in which demyelination occurs in the absence of inflammation or axonal loss [Silver et al. 1996, Davie et al. 1999];

(iii) The MTR in the optic nerves in patients with optic neuritis has been shown to correlate with the prolongation of the VEP latency, a characteristic finding in demyelinated optic nerves [Thorpe et al. 1995].

Serial studies of MS lesions have shown the MTR falls initially, when the lesion can be seen to enhance, and then partial or complete recovery usually occurs over the next 1 – 6 months [Goodkin et al. 1998, Silver et al. 1998, van Waesberghe et al. 1998, Dousset et al. 1998]. This may reflect demyelination followed by remyelination. Oedema and its resolution may also play a role but, for reasons given above, this is unlikely to be the major cause of these changes in MTR. The effect of gliosis on MTR is unknown. Tracking of individual new lesions has shown that in some, the MTR
may decrease over the first few months, perhaps representing lesions in which severe damage has occurred [van Waesberghe et al. 1998, Dousset et al. 1998, Filippi et al. 1999a].

The MTR of established MS lesions visible on T2-weighted images has been found to be lower than in NAWM [Dousset et al. 1992, Filippi et al. 1995c, Loevner et al. 1995]. A wide range of MTR values has been recorded for lesions, consistent with the pathological heterogeneity of lesions that is known to exist. Hypointense T1 lesions have been reported to have the lowest MTR values, a finding in-keeping with the theory that these are the lesions in which the most severe tissue damage has occurred [Hiehle et al. 1995, van Waesberghe et al. 1998]. The MTR has been correlated with the degree of T1 hypointensity [Hiehle et al. 1995, van Waesberghe et al. 1997].

A mild reduction in the MTR has been found in the NAWM of MS patients both near to and distant from lesions visible on T2 weighted imaging using regional studies [Dousset et al. 1992, Filippi et al. 1995c, Loevner et al. 1995, Leary et al. 1999a]. These changes may precede new lesion formation [Filippi et al. 1998b, Goodkin et al. 1998] in some cases. They appear to represent abnormalities that are invisible on conventional MRI. These milder MTR abnormalities are pathologically non-specific, and in MS may be due to oedema, patchy inflammation or demyelination, gliosis or Wallerian degeneration.

2.3.8 Proton magnetic resonance spectroscopy

Proton magnetic resonance ($^1$H-MR) spectroscopy is another technique that relies on nuclear magnetic resonance, but rather than providing spatial information in the form
of images, it provides chemical information on proton-containing metabolites (other than water). A SE-based sequence is typically used to acquire the data; the length of the TE determines which metabolites can be quantified. Spectra acquired using a short TE identify significantly more peaks (with a shorter T2) than do spectra acquired with long echo times. The volume of brain to be studied is selected using a pulse sequence such as Point-RESolved Spectroscopy (PRESS). No frequency-encoding gradient is used in $^1$H-MR spectroscopy so that the frequencies of the protons are unaltered from their natural state. The signal is collected and processed using the Fourier transform, which extracts frequency information from the signal. A spectrum is produced with peaks representing the different proton containing compounds. In the brain the vast majority of protons exist in water molecules and in the scalp in fat molecules. The concentrations of the metabolites of interest are minute by comparison and in order to quantify them, tiny differences in their magnetic field properties due to their bonding and chemical environment (chemical shift) need to be distinguished. This requires strong magnetic fields to separate the peaks, along with effective suppression of the water peak and the signals from scalp lipids. Automated procedures, such as the single voxel PROton Brain Exam (PROBE/SV; GE Medical Systems) enable rapid acquisition of reliable and reproducible spectra from a region of the brain and incorporate water suppression techniques.

The spectrum from such a complex sample as brain tissue is a composite of all the contributing spectra, with the peaks representing several related compounds (Figure 2.12). The four principal peaks in a normal spectrum are attributed to (i) N-acetyl aspartate (NAA) (or more correctly, to N-acetyl derived groups (tNAA), which also include a small concentration of N-acetyl aspartylglutamate (NAAG)), (2) choline-
containing compounds (Cho), (3) creatine / phosphocreatine (Cre) and (4) myo-inositol (Ins). The position of the peaks in the spectrum is standardised by expressing them as parts per million (ppm) which refers to the frequency of a signal divided by the precession frequency of protons in the scanner used. The areas of peaks in a spectrum are proportional to how many nuclei of a given chemical environment contribute to their signals. They are also dependent on the T1 and T2 relaxation times of the nuclei. It is therefore possible to calculate the concentrations of the different metabolites from the spectrum.

\(^1\)H-MR spectroscopy has become useful in MS as it can provide more specific information about the composition of lesions and NAWM than conventional MRI. In particular, it enables measurement of the concentration of NAA, which forms the largest peak in a normal human brain spectrum. NAA is thought to be almost exclusively restricted to neurons in adults [Simmons et al. 1991, Urenjak et al. 1993] and therefore its concentration is thought to reflect axonal density. This has been supported by the finding that NAA is reduced in patients in which neurodegeneration is known to occur [Miller et al. 1993, Jenkins et al. 1993, Davie et al. 1995]. In animal or in vitro studies, a small amount of NAA is also contained in oligodendrocytes [Bhakoo & Pearce 2000] or their precursors [Urenjak 1993].

reduced in MS lesions suggesting that axonal loss / damage has occurred. This damage appears to be more severe in the lesions that appear hypointense on T1-weighted images [van Walderveen et al. 1999, Brex et al. 2000]. MRS has also been able to detect more subtle abnormalities in NAWM [Arnold et al. 1992, Husted et al. 1994, Davie et al. 1994, Rooney et al. 1997]. The NAA appears to be lower in the NAWM of patients with secondary progressive compared with relapsing-remitting MS [Fu et al. 1998].

$^1$H-MR spectroscopy has provided further evidence that axonal loss / damage in MS may be the cause of the progressive disability that is seen in this condition. NAA concentration has been found to correlate with disability [Davie et al. 1995, De Stefano et al. 1995, Davie et al. 1997, Fu et al. 1998, Sarchielli et al. 1999]. The concentration of NAA has also been shown to fall as disease progresses [Arnold et al. 1994, De Stefano et al. 1998]. The reduction of NAA seen in acute lesions may be partially reversible over several months, however, indicating that axonal loss is not the only cause of a reduced NAA [Davie et al. 1994, De Stefano et al. 1995]. This reversible axonal damage or dysfunction is correlated with reversible functional impairments [De Stefano et al. 1998]. Only a small proportion of the observed recovery can be due to resolution of oedema. The initial reduction of NAA may also be due to shrinkage of axons following injury, followed by expansion with recovery, or due to metabolic dysfunction.
Figure 2.12  Spectrum from healthy NAWM.
An axial image of the author’s brain showing the site of a voxel placed over NAWM (voxel size = 1.90 ml). The spectrum from the lesion, showing both raw data and a fitted line, generated by the LCModel. Values of the concentrations of the main metabolites were tNAA = 9.3 mM, Cre = 4.5 mM, Cho = 1.4 mM, myo-inositol (Ins) = 3.4 mM.
The axial image of a 33-year old lady (AB) with secondary progressive MS demonstrating the position of the voxel (size = 1.59 ml) over a lesion. The spectrum, generated using the LCModel, shows both the raw data and a fitted line. The main metabolite concentrations were tNAA = 7.1 mM, Cre = 5.2 mM, Cho = 1.6 mM, myo-inositol (Ins) = 8.7 mM;
PART 2

EARLY MRI FINDINGS IN PATIENTS WITH

CLINICALLY ISOLATED SYNDROMES
PART 2

Early MRI findings in Patients with Clinically Isolated Syndromes

Introduction

The following four chapters present the findings from a single cohort of patients who were prospectively followed for one year following their presentation with a CIS. The first two chapters describe the early MRI findings and examine its predictive role for the development of new T2 lesions or clinical symptoms with a view to improving methods of identifying patients at greatest risk of MS and disability. The second two chapters employ quantitative techniques to assess CNS tissue damage. Through the use of these techniques in CIS patients it was hoped for better characterisation of the pathology, at what in many of the patients, is the earliest stage of MS.

Methods

Patients

Dr JI O’Riordan (31 patients) and I (50 patients) recruited patients from the wards and clinics of The National Hospital for Neurology and Neurosurgery and from the Physicians’ Clinic at Moorfields Eye Hospital between 1995 and 1999. Men and women aged between 16 and 50 years were considered for inclusion. The upper limit was set in order to minimise the effect of non-specific age-related MRI changes [Fazekas et al. 1988] and the lower limit because of the more favourable prognosis seen in children following an attack of optic neuritis [Kriss et al. 1988]. CIS were defined by the occurrence of a presumed inflammatory demyelinating event of acute onset (reaching a peak within 14 days) in any part of the central nervous system in an individual with no previous history of symptoms suggestive of demyelination.
Patients with optic neuritis were assessed by a neuro-ophthalmologist (Dr GT Plant) and diagnosed using previously agreed clinical criteria [Compston et al. 1978]. Patients with bilateral simultaneous optic neuritis, defined as the involvement of both optic nerves within a period of 3 months, were also included. In patients with brainstem or spinal cord syndromes, an inflammatory aetiology was suggested by the time-course of the onset and recovery, and clinical localisation of the lesion. In all patients appropriate investigations were carried out as necessary to exclude alternative diagnoses. The Joint Medical Ethics Committees of the Institute of Neurology and the National Hospital for Neurology and Neurosurgery and the Medical Ethics Committee of Moorfields Eye Hospital, London approved the study. Informed consent was obtained from all patients prior to entry into the study. At each visit, I assessed the patients to record their level of disability, as measured by on the EDSS [Kurtzke et al. 1983], and to determine whether or not clinically definite (CD) or clinically probable (CP) MS had developed using Poser’s criteria [Poser et al. 1983]. A period of three months was required between relapses to diminish the likelihood of slowly evolving acute disseminated encephalomyelitis (ADEM) cases being included.

**MRI Protocol**

All imaging was performed on a 1.5 T Signa (General Electric, Milwaukee, WI) imager provided by the Multiple Sclerosis Society of Great Britain and Northern Ireland. For brain imaging a standard head coil was used; FOV 24cm, matrix 256², and NEX 1. For spinal cord imaging a phased-array coil was used; FOV 48cm, matrix 512² and NEX 2. In each examination, prior to dual-echo FSE and T1-weighted imaging a bolus of 0.1 mmol / kg gadolinium-DTPA was administered intravenously.
Baseline MRI examination

**Brain**  
*Dual-echo FSE* (TR 3200 ms, effective TE 15/95 ms, ETL 8, 46 x 3 mm axial slices; acquisition time 8 minutes)

*fFLAIR* (TR 11000, TE 143 ms TI 2600 ms, ETL 8, 46 x 3 mm axial slices; acquisition time 7 minutes)

*T1-weighted SE* (TR 600 ms, TE 14 ms, 46 x 3 mm axial slices, 15 minutes post-contrast administration; acquisition time 6 minutes)

**Cord**  
*T1-weighted SE* (TR 500 ms, TE 19 ms, 13 x 3 mm sagittal slices, 30 minutes post-contrast administration; acquisition time 4 minutes)

*Dual-echo FSE* (TR 2500 ms, effective TE 56/98 ms, 9 x 3 mm sagittal slices, acquisition time 6 minutes)

*Volume-acquired inversion-prepared fast spoiled gradient-echo (FSPGR)* (see Chapter 6.2 for details)

Three-months after baseline

**Brain**  
*1H-MR spectroscopy* (see Chapter 5.1 for details)

*MTI* (see Chapter 5.2 for details)

*Dual-echo FSE* (as baseline)

*T1-weighted SE* (as baseline)

One year after baseline

**Brain**  
*Dual-echo FSE* (as baseline)

*T1-weighted SE* (as baseline)

**Cord**  
*T1-weighted SE* (as baseline)

*Dual-echo FSE* (as baseline)

*FSPGR* (as baseline)

* Not performed in all 81 patients
CHAPTER 3

Early multi-parameter MRI findings in patients with CIS

3.1 Aims

In this study, I measured the frequency and extent of MRI abnormalities in the brain and spinal cord of CIS patients at presentation and over the subsequent year. I also compared the newer techniques commonly used to acquire T2-weighted images (FSE and fFLAIR), to determine which provided the best detection of T2 brain lesions and I quantified contrast-enhancing and hypointense T1 lesions. The predictive value of the baseline findings for further lesion activity was investigated.

3.2 Methods

CIS patients had both clinical and MRI examinations as outlined. Together with an experienced neuroradiologist (Dr K Miszkiel), I recorded the number and site of any abnormalities detected on the baseline and one-year follow-up brain and spinal cord FSE images. The neuroradiologist, who was blinded to the clinical state of the patients, ultimately made the decision about the number, size and distribution of lesions. We reported images as normal if they were completely normal, or if only the symptomatic lesion was seen. They were reported as abnormal if there were one or more asymptomatic lesions compatible with demyelination. In patients who had both FSE and fFLAIR sequences acquired, the images were reported alongside one another. On the FSE sequences the lesion had to be seen on both the PD- and T2-weighted images to be counted. The presence of lesions in four pre-specified regions of the brain was recorded at baseline for both these sequences. These were: (i) posterior cranial fossa, (ii) discrete - cerebral white matter or basal ganglia discrete
from, i.e. not in contact with, the cortex or ventricles, (iii) subcortical / cortical -
lesions in the cortex or the adjacent subcortical white matter (iv) periventricular, i.e.
in contact with the ventricles. The presence of lesions in the corpus callosum was also
recorded. Contrast-enhancing and hypointense T1 lesions were counted on the T1-
weighted images. All hypointense T1 lesions were confirmed as T2 lesions on the
FSE images. Intrinsic spinal cord lesions were located and counted on the appropriate
sagittal images.

Following the identification of the lesions on hardcopy, I quantified the total cerebral
T2 lesion volume and hypointense T1 lesion volume for each patient using a semi-
automated local thresholding technique [Plummer 1992]. In the minority of cases
when I could not fully contour the lesions semi-automatically using this programme, I
would either partially or fully manually outline them. The T2 lesion volume was
calculated automatically by multiplying the lesion area by slice thickness. Using this
approach intra-rater variability of T2 lesion volume quantification has been reported
as being only 2 – 4% [Grimaud et al. 1996].

Statistical analysis

Comparisons between baseline and one-year were made using Wilcoxon Signed
Ranks Test. Correlations were investigated using the Spearman Rank Correlation
Coefficient (r). Chi-squared tests were used to compare the frequency of developing
new lesions or developing MS in subgroups determined according to baseline MRI
features.
3.3 Results

Baseline

Eighty-one patients were studied, with a median age of 31 years (range 16 – 50 years). Forty-eight of the patients were women and 33 men. The presenting symptom was optic neuritis in 55 (bilateral simultaneous in two), an optic tract lesion in one, a brainstem syndrome in 18 and a spinal cord syndrome in seven patients. The median EDSS as a result of the CIS at the time of the first examination was 1 (range 0 – 8). The baseline MRI scan was performed a median of five weeks from the onset of symptoms (range 1 – 12 weeks). The initial findings of the baseline imaging in 33 patients have been published previously [O'Riordan et al. 1998c]. The symptomatic lesion was identified on 9/18 patients with a brainstem syndrome and 4/7 with spinal cord syndromes, as well as in the patient with the optic tract lesion. The optic nerves were not imaged as part of this study.

Brain MRI at baseline was abnormal, with one or more asymptomatic T2 lesions identified using the FSE sequence, in 56 (69%) patients. Callosal lesions were seen in 22 (27%) patients. The median number of lesions per patient was 4 (mean 11.5, range 0 – 76) and the median T2 lesion volume was 0.31cm³ (mean 1.7 cm³, range 0 – 13.9 cm³) (Table 3.1). One or more T2 lesion appeared hypointense on the T1-weighted images in 32 (40%) patients (median 0, mean 1.5, range 0 – 19) but the mean T1 / T2 lesion ratio in patients with lesions was only 14%. The median hypointense T1 lesion volume was 0cm³ (mean 0.3 cm³, range 0 – 4.5 cm³). The T2 lesion volume significantly correlated with T1 lesion volume (r = 0.74, p < 0.01).
Contrast-enhancing lesions were identified in the brain in 25 (31%) patients (median 0, mean 1.4, range 0 – 21). One or more asymptomatic spinal cord T2 lesions were found in 29 (36%) patients (median 0, mean 0.85, range 0 – 7). In two cases, T2 lesions were seen in the spinal cord but not the brain. Contrast-enhancing cord lesions occurred in eight (10%) patients (median 0, mean 0.12, range 0 – 3).

**FSE versus fFLAIR:** In a subgroup of 70 patients both a FSE and fFLAIR sequences were performed at baseline. In only one patient did the images appear normal using one sequence (fFLAIR) and abnormal using the other (FSE). Overall, images acquired using FSE were abnormal in 50 (71%) of patients and using fFLAIR in 49 (70%) patients. Significantly more T2 lesions were identified using the FSE sequence in the posterior fossa and around the ventricles (Table 3.2).

**One year follow up**

Imaging was repeated in 70 (86%) of the patients a mean of 12.5 months after baseline (range 11 – 19 months). The other 11 patients refused to have further imaging. Fifteen of the 70 patients seen after one year had developed CD and four CP MS; their median EDSS was 2 (range 0 – 8). In the patients who had an MRI examination performed at both time-points, new T2 lesions had developed in the brain in 39 (56%) cases (median 1 new T2 lesion, mean 4.8, range 0 – 128). New enhancing brain lesions were present in 23 (33%) patients (median 0 contrast-enhancing lesions, mean 1.2, range 0 – 26).

New lesions were more likely to occur in patients who had T2 lesions in both the brain and spinal cord at baseline (19/22; 86%), than those with brain (19/27; 70%) or
spinal cord (1/2; 50%) T2 lesions alone (Table 3.3). Only 4/19 patients with a normal brain and cord at baseline developed new lesions at follow-up – of interest, the new lesions were in the cord in three patients, of whom two developed clinical MS. Patients who had contrast-enhancing brain lesions at baseline were more likely to develop new brain or cord T2 lesions (20/22; 91%) than those with cerebral T2 lesions that did not enhance (18/27; 67%; p < 0.05) (Table 3.4).

The cerebral T2 lesion volume increased significantly, from a median of 0.35 cm$^3$ (mean 1.8 cm$^3$, range 0 – 13.9 cm$^3$) to 0.44 cm$^3$ (mean 2.8 cm$^3$, range 0 – 38.5 cm$^3$; p = 0.01). There was no significant correlation between T2 lesion volume at follow up and EDSS for all patients (r = 0.22, p = 0.07). New hypointense T1 lesions developed in the brain in 15 (21%) patients (median 0 new T1 hypointense lesions, mean 0.7, range 0 – 31). The mean cerebral hypointense T1 lesion volume increased from 0.39 cm$^3$ (range 0 – 4.5 cm$^3$) to 0.48 cm$^3$ (range 0 – 8.5 cm$^3$), although this increase did not reach significance (p = 0.5). The mean T1 / T2 lesion load remained constant (baseline 16.6%, 1 year 15.7%; p = 0.8).

The T2 lesion volume at baseline did not significantly correlate with the change in T2 lesion volume or hypointense T1 lesion volume over the subsequent year. The T1 lesion volume at baseline did not correlate with the change in T2 lesion volume over the subsequent year although there was a weak correlation with the change in hypointense T1 lesion volume (r = -0.25, p = 0.04). The change in T2 lesion load did not significantly correlate with the change in hypointense T1 lesion load over one year.
In the spinal cord, new T2 lesions were seen in 15 (21%) patients and contrast-enhancing lesions in 3 (4%). Three of these 15 patients did not develop new brain T2 lesions, including one patient who previously had normal brain and cord imaging.

3.4 Discussion

Asymptomatic, disseminated, T2 lesions were found in 69% of CIS patients on 3mm thick FSE brain images. This compares with 80/132 (61%) in the previous study performed at 0.5 Tesla using CSE with 5 – 10 mm thick slices in our Unit [Ormerod et al. 1987]. These differences suggest improved detection of lesions with newer, high-resolution techniques. Lesions in the corpus callosum, a region characteristically affected in MS [Gean-Marton et al. 1991], were seen in 22 (27%) patients. Four or more cerebral lesions were found in 51% of patients. In 40% of patients, a proportion of the T2 lesions appeared as hypointense T1 lesions. This suggests that severe tissue damage was already present in these lesions even at this early stage, although the proportion was small as exemplified by the low T1 / T2 lesion ratio.

The median total lesion volume of our cohort was 0.31cm$^3$ at baseline compared with 0.43 cm$^3$ (range 0 – 13.7 cm$^3$) in the original London cohort, analysed using the same semi-automated contouring technique [Sailer et al. 1999]. The use of thinner slices and high field imaging in MS patients has previously been found to increase the T2 lesion load [Filippi et al. 1995b, Filippi et al. 1997]. This apparently lower volume using these newer techniques may result from the detection of small lesions in patients who would previously been reported as having normal imaging. The finding that the ranges in the two studies are comparable and the mean lesion volume are in fact higher using the newer techniques, supports this (mean T2 volume: original
cohort 1.48 cm$^3$, new cohort 1.65 cm$^3$). No significant differences in T2 lesion volume were found between CIS patients presenting with different syndromes.

The use of fFLAIR did not, as might have been expected, increase the number of T2 lesions detected (Figure 3.1). In fact, in our cohort we found fFLAIR to be slightly less sensitive than FSE, both above and below the tentorium. With the exception of one patient who had a single posterior fossa lesion detected using FSE, which was not seen on fFLAIR images, both sequences detected abnormalities in the same patients.

The lower sensitivity of fFLAIR in the posterior cranial fossa is consistent with previous studies in established MS [Filippi et al. 1996, Bastianello et al. 1997, Gawne-Cain et al. 1997]; however, these same studies showed fFLAIR to be the more sensitive sequence in the supratentorial region. There could be several explanations for our different finding: (i) we used thinner slices than previous studies (3mm versus 5mm) which may improve detection of smaller lesion more so on FSE than fFLAIR; (ii) with the generally small lesion load in patients with CIS, detection of subtle high-signal foci on FSE is likely to be more accurate; and (iii) the analysis of FSE and fFLAIR images side by side (unlike the independent analyses in previous studies) sometimes highlighted lesions which were subtle on FSE but more clearly seen on fFLAIR. However, the reverse was also true. The addition of fFLAIR did not reveal any lesions in patients judged to have a normal FSE study. In the light of these results, it would appear that there is no need to perform fFLAIR in addition to thin slice FSE in the investigation of patients with CIS.

Focal contrast-enhancement following the administration of intravenous gadolinium-DTPA was seen in 31% of patients at baseline (Figure 3.2). All contrast-enhancing
lesions were also seen as high signal lesions on T2-weighted images. Our results are in keeping with earlier reports of contrast-enhancement in 27% - 38% of CIS patients with abnormal imaging in comparable groups of patients [Christiansen et al. 1992, Barkhof et al. 1997]. However, there are two potential reasons why this study may have underestimated the frequency of contrast-enhancing lesions. (i) For practical reasons, it was not always possible to scan the patients within the first month of their symptoms. Contrast-enhancing lesions usually persist for between 2 – 8 weeks [Miller et al. 1988b] and so it is possible that some that had occurred at the time of the clinical symptoms may have already resolved. However, the frequency of enhancing lesions was similar in the 48% of the cohort imaged within four weeks of the onset of their symptoms (33%) and the 89% of the cohort imaged within eight weeks (31%) as in the total group. (ii) A small number of patients (10%) received steroid treatment as a treatment for their initial symptoms. Steroids have been shown to reduce the frequency of contrast-enhancing lesions in MS [Frequin et al. 1992], albeit temporarily [Miller et al. 1992b].

Asymptomatic high signal lesions were detected on FSE images of the spinal cord in 29 (36%) patients (Figure 3.3), eight of whom also exhibited contrast-enhancement in one or more lesion. In two cases, the T2 lesions in the spinal cord were not associated with abnormalities in the brain. This finding is recognised in established MS [Thorpe et al. 1996], but has not previously been reported in other cohorts of CIS patients. Somatosensory evoked potentials (SEPs) have been shown to be abnormal in approximately 10 – 20% of CIS patients [Frederiksen et al. 1991, Martinelli et al. 1991, Filippini et al. 1994, Frederiksen et al. 1996, Ghezzi et al. 1999], which would be in keeping with the identification of such lesions in the present study. Spinal cord
imaging in CIS patients, in addition to brain imaging, may further help to identify patients at risk from the future development of MS.

The development of new brain T2 lesion was seen in 39 (56%) of patients after one year, of whom only one had normal imaging at baseline. In a further 3 (4%) patients, new spinal cord T2 lesions, in the absence of new brain lesions developed. By contrast, new clinical symptoms leading to diagnosis of CD MS occurred in only 15 (21%) and CP MS in 4 (6%). This is in keeping with the observation in established MS that MRI is a sensitive measure of disease activity with new lesions frequently occurring despite clinical stability [Isaac et al. 1988, Willoughby et al. 1989]. The presence of widely disseminated lesions (in both the brain and spinal cord) at baseline was associated with an even higher risk (86%) of new T2 lesion formation. The greatest risk, however, was in patients with contrast-enhancing brain lesion at baseline, of whom 91% developed new T2 lesions, supporting the view that the combination of contrast-enhancing lesions with non-enhancing lesions on a single image is highly suggestive of dissemination of disease in time as well as space.

Overall, there was a significant increase of 26% in the median T2 volume in our cohort during the year. This compares with a median annual increase of 6 - 12% in the relapsing remitting stage of MS [Simon et al. 1998, Li et al. 1999] and 2 – 10% in the secondary progressive stage [Miller et al. 1999]. This decreasing percentage with disease progression at least partly reflects the increasing absolute T2 lesion load as the condition advances.
Only one patient in the cohort received treatment with disease-modifying drug (interferon beta) during the study. Treatment with interferon beta has been shown to affect the natural history of the development of MRI lesions [Paty et al. 1993, Simon et al. 1998, Miller et al. 1999, Li et al. 1999, Zhao et al. 2000]. It is, therefore, likely that our study is closer to a natural history study of the first year after CIS than will be possible in the future, since the widespread use of these drugs, even in this early stage, is beginning to occur in many countries encouraged by a positive recent trial [Jacobs et al. 2000].

In summary, this study confirms that MRI is a sensitive method of providing evidence of dissemination of demyelinating disease in space in patients who have had only a single clinical event and in whom, therefore, the prognosis is uncertain. The use of new MRI techniques enabled the increased detection of lesions in the brain and the identification of clinically silent lesions in the spinal cord, which in some cases was the only evidence of disseminated disease. Serial imaging of these patients showed new lesions to develop, indicating dissemination of disease in time, not infrequently in the absence of clinical symptoms. The presence at baseline of either contrast-enhancing brain lesion or a combination of T2 brain and cord lesions had a particularly high likelihood for dissemination in time, suggesting the pathological processes of MS. Such baseline imaging characteristics may prove useful in developing revised criteria for an earlier diagnosis of MS.
Table 3.1  T2 lesion (FSE) brain volume (cm$^3$) measurements in patients presenting with CIS

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>All clinically isolated syndromes</td>
<td>81</td>
<td>1.7</td>
<td>0.31</td>
<td>0 - 13.9</td>
</tr>
<tr>
<td>Optic Neuritis</td>
<td>55</td>
<td>1.5</td>
<td>0.3</td>
<td>0 - 13.9</td>
</tr>
<tr>
<td>Brainstem syndrome</td>
<td>18</td>
<td>2.4</td>
<td>0.4</td>
<td>0 - 12.0</td>
</tr>
<tr>
<td>Spinal cord syndrome</td>
<td>7</td>
<td>0.8</td>
<td>0.06</td>
<td>0 - 5.0</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>*Abnormal MRI</td>
<td>56</td>
<td>2.4</td>
<td>1.0</td>
<td>0.03 - 13.9</td>
</tr>
<tr>
<td>Four or more T2 lesions on FSE</td>
<td>41</td>
<td>3.2</td>
<td>1.7</td>
<td>0.2 - 13.9</td>
</tr>
</tbody>
</table>

* At least one asymptomatic T2 lesion on brain FSE
Table 3.2  Comparison of T2 lesion number detected using FSE and fFLAIR sequences in CIS patients at presentation (n = 70).

<table>
<thead>
<tr>
<th>Brain region</th>
<th>FSE</th>
<th>fFLAIR</th>
<th>#p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(mean, median, sum)</td>
<td>(mean, median, sum)</td>
<td></td>
</tr>
<tr>
<td>Posterior fossa</td>
<td>0.6 / 0 / 45</td>
<td>0.4 / 0 / 30</td>
<td>0.001</td>
</tr>
<tr>
<td>Discrete</td>
<td>2.1 / 0 / 150</td>
<td>2.2 / 0 / 154</td>
<td>0.7</td>
</tr>
<tr>
<td>Periventricular</td>
<td>4.9 / 1 / 345</td>
<td>4.4 / 1 / 308</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cortical/subcortical</td>
<td>3.6 / 1 / 252</td>
<td>3.2 / 1 / 227</td>
<td>0.3</td>
</tr>
<tr>
<td>Total</td>
<td>11.3 / 4.5 / 792</td>
<td>10.2 / 3.5 / 719</td>
<td>0.12</td>
</tr>
</tbody>
</table>

# Wilcoxon signed ranks test
Table 3.3  T2 lesions in CNS (brain and cord) at presentation with a CIS and new T2 lesions 12 months later: relationship between baseline and follow-up MRI and the development of MS.

<table>
<thead>
<tr>
<th>Baseline (n= 70)</th>
<th>12-month follow-up (n = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Site of new MRI lesions</td>
</tr>
<tr>
<td>Brain + Cord +</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain + Cord -</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain - Cord +</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain - Cord -</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abnormal MRI**

| New lesions + | 39 | 16 |
| New lesions - | 12 | 1  |

**Normal MRI**

| New lesions + | 4  | 2  |
| New lesions - | 15 | 0  |

+ / - = T2 lesions present / absent at baseline or new lesions present / absent at follow-up
Table 3.4  Predictive value of the combination of contrast-enhancing and T2 lesions for the development of new T2 lesions after 1 year

<table>
<thead>
<tr>
<th>Baseline Brain MRI (n = 70)</th>
<th>New brain or cord lesions after one year follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Contrast-enhancing T2 lesions +</td>
<td>T2 lesions +</td>
</tr>
<tr>
<td>Contrast-enhancing T2 lesions -</td>
<td>T2 lesions -</td>
</tr>
<tr>
<td>Contrast-enhancing lesions -</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>T2 lesions +</td>
</tr>
<tr>
<td></td>
<td>T2 lesions -</td>
</tr>
</tbody>
</table>

+ / - = presence / absence of lesions
Figure 3.1  Comparison of (a) PD-weighted FSE and (b) FLAIR in CIS
Taken from a 24 year old lady (JC) three weeks following an episode of optic neuritis
Figure 3.2 Contrast-enhancing lesions in CIS
(a) Axial PD-weighted and (b) contrast-enhanced T1-weighted images from a 32 year old lady (LF) six weeks following the onset of an isolated unilateral episode of optic neuritis. Several T2 lesions can be seen, two of which show contrast-enhancement on the T1-weighted images.
Figure 3.3 Spinal cord T2 lesions in CIS
Imaging of the spinal cord in a 31-year-old lady (SC) six weeks following presenting with a left sixth nerve palsy due to an isolated brainstem syndrome. A high signal lesion can be seen on the PD-weighted images (a) at C7, which enhanced on the T1-weighted images following the administration of intravenous gadolinium-DTPA (b).
CHAPTER 4
Predictive Value of MRI for the Early Development of MS

4.1 Aims
The aim of this study was to assess the relative positive predictive value (PPV), sensitivity and specificity for the development of early MS of MRI parameters identified in CIS patients from two MRI examinations, one performed at presentation and the second three months later.

4.2 Methods
The baseline and three-month follow-up T2- and T1-weighted MRI examinations of all the patients I had clinically assessed at one year were reviewed by an experienced neuroradiologist (Dr Miszkiel), who was blinded to the clinical state. In each patient, the number of T2 and contrast-enhancing lesions were recorded - in the brain at both time-points, and in the spinal cord at baseline only. The diagnosis of MS was made using clinical criteria alone.

Statistical analysis
Based on the outcome at one year (either CD or CP MS diagnosed using only clinical criteria or patients remains as a CIS) the number of true positives (TP; test abnormal, MS diagnosed), true negatives (TN; test normal, no MS), false positives (FP; test abnormal, no MS) and false negatives (FN; test normal, MS diagnosed) were calculated for each parameter and used to determine the positive predictive value (PPV) (TP/(TP + FP)), sensitivity (TP / (TP + FN)) and specificity (TN / (TN + FP)).
The chi-squared test was used to compare the frequency of developing MS in subgroups determined by their MRI findings.

4.3 Results

All three visits were attended by 68 (84%) of the CIS cohort. There were 39 women and 29 men. The median age at presentation was 31 years (range 17 - 50 years). The presenting symptom was optic neuritis in 45 (one bilateral simultaneous), a brainstem syndrome in 16, a spinal cord syndrome in six and an optic tract lesion in one patient. The first MRI examination was performed after a median of five weeks (range 1 - 12 weeks) following the onset of symptoms, the three-month follow-up MRI examination after a further 13 weeks (range 8 - 20) and the clinical assessment after a median of 12 months (range 11 - 19 months) from baseline. After one year, 18 (26%) had developed CD (14) or CP (4) MS.

Baseline (Table 4.1)

Overall asymptomatic T2 lesions were found in both the brain and spinal cord in 21 (31%), the brain alone in 27 (40%) and the spinal cord alone in two (3%) patients. Contrast-enhancing brain lesions were seen in 21 (31%) patients and contrast-enhancing cord lesions in 7 (10%). The most predictive parameter for the development of MS from the baseline images alone was the presence of one or more contrast-enhancing lesion in the brain (PPV 52%). This had high specificity (80%) but a relatively low sensitivity (61%) for the development of MS after one year. The presence of one or more asymptomatic T2 lesions in the brain was very sensitive, being present in 16 (89%) of the patients who subsequently developed MS, but had a poor specificity (36%) and PPV (33%); increasing the number of T2 lesions required
improved specificity and PPV, but at the expense of sensitivity. The presence of one or more asymptomatic T2 lesions in the spinal cord had a poor sensitivity (50%) and PPV (39%) for development of MS, as did the presence of contrast-enhancing cord lesions (PPV 29%, sensitivity 11%), but both had a better specificity than equivalent findings in the brain.

Patients with T2 lesions in both the brain and spinal cord had a greater risk of developing MS after one year than patients with brain lesions alone, although this difference did not achieve statistical significance (43% and 26% respectively; p > 0.1). Neither of the patients with T2 lesions only in the spinal cord developed MS. Two (10%) of the patients with normal imaging of both the brain and spinal cord at baseline developed MS during the follow-up.

Serial MRI (Table 4.2)
The combination of baseline T2 lesions with new T2 lesions at follow-up gave the most robust overall prognostic data, with a PPV of 55% and both a high sensitivity (83%) and specificity (76%) for the development of MS. The presence or absence of new T2 lesions at follow-up in patients with an abnormal baseline T2-weighted brain MRI examinations significantly altered the risk of developing MS (15/27 (55%) and 1/21 (5%) respectively; p < 0.001). The median number of T2 lesions at presentation in the former group was 20 (range 1 - 76) and in the latter 5 (range 1 - 20). The combination of contrast-enhancing lesions on the T1-weighted images of both examinations had the highest PPV (70%) and specificity (94%), but it had a low sensitivity detecting only 7/18 (39%) patients who subsequently developed MS.
4.4 Discussion

This study has shown that the predictive value of MRI in determining the risk of a patient presenting with CIS developing CD or CP MS within a year, can be improved by performing a second MRI examination of the brain several months after presentation. Thus, the presence of an abnormal baseline T2-weighted brain image combined with new T2 lesions at follow-up had a better combination of PPV, sensitivity and specificity than any lesion parameter obtained from a single MRI examination. Such a combination is desirable for optimal patient selection for treatment trials or for therapeutic intervention aimed at preventing the development of MS. The high PPV, i.e. risk for MS, in untreated patients means that a placebo-controlled trial will have a good power to demonstrate a reduction in the proportions developing MS in the active treatment arm. A high sensitivity means that few patients who will go on to develop MS would be excluded from the trial. A high specificity means that few of the patients not developing MS would be included in the study.

Abnormalities found on a single MRI examination have been recently used to select patients for clinical trials of interferon beta aimed at delaying the conversion from CIS to CD MS [Comi et al. 2000, Jacobs et al. 2000]. Our new serial MRI data suggests it may be possible to identify a sub-group of patients with a low risk for MS in spite of an abnormal baseline T2-weighted MRI examination - only 5% who did not develop new T2 lesions at three months went on to develop clinical MS at one year. Serial MRI criteria may thus identify patients with an abnormal baseline MRI who are less suitable for early treatment or clinical trial participation. However, the follow-up period needs to be extended before the risks for MS can be more accurately determined.
As with previous studies [Barkhof et al. 1997], the presence of contrast-enhancement was the most predictive parameter from a single brain image. The presence of contrast-enhancing lesions on both baseline and three-month follow-up MRI further improved PPV and specificity. This combination almost certainly reflects new lesion formation at different time-points, strongly suggesting MS as the underlying pathology. The usefulness of such a combination for selection of patients for clinical trials is limited however by its low sensitivity. It might have a role if one wanted to identify a subgroup who appeared to have a particularly high risk for the early development of MS (70% did so in this study).

The presence of T2 lesions in the spinal cord at presentation had a similar PPV as brain T2 lesions. Only half the patients developing MS, however, were found to have cord lesions. In two cases, the presence of lesions on T2-weighted imaging of the spinal cord was the only evidence of disseminated disease although in neither instance did these patients develop MS within the follow-up period. Patients who were found to have more widely disseminated disease, with T2 lesions in both the brain and spinal cord, appeared more likely to develop MS than those with brain lesions alone, although this difference did not reach statistical significance.

Two patients (10%) with normal imaging at both baseline and three-month follow-up developed MS during the study. Both presented with optic neuritis with one developing a spinal cord syndrome and one a brainstem syndrome. This emphasises the fact that patients with normal brain imaging at presentation are still at risk from further episodes, although numerous studies have shown that this risk, even in the
long term, is substantially less than for those who have abnormal imaging at presentation (see Chapter 2).

Our study investigated the predictive value of only two serial MRI examinations. It is possible that more extensive serial MRI, e.g. monthly for 6 months, or 3-monthly for one year, will provide better prognostic data. Further studies using such protocols are required.

Although this cohort of patients has only been followed for a relatively short period of time, some natural history studies have found in relapsing-remitting MS patients, that early disease activity may have a major influence on future disability (see Chapter 1). Further follow-up is necessary to consolidate these observations, but serial MRI over a short time does appear to have advantages over a single examination in identifying patients at the greatest risk of developing clinical MS early on and thereby should allow more reliable selection of patients for clinical trials or therapeutic interventions to delay evolution to CD MS.
### Table 4.1  Relationship between MRI findings at presentation with CIS (n = 68) and clinical outcome after a year

<table>
<thead>
<tr>
<th>MRI parameter</th>
<th>Minimum number</th>
<th>Prevalence n (%)</th>
<th>*MS n</th>
<th>PPV %</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesions on T2-weighted imaging</td>
<td>1</td>
<td>48 (71)</td>
<td>16</td>
<td>33</td>
<td>89</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>37 (54)</td>
<td>14</td>
<td>38</td>
<td>78</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>25 (37)</td>
<td>11</td>
<td>44</td>
<td>61</td>
<td>72</td>
</tr>
<tr>
<td>Contrast-enhancing lesions</td>
<td>1</td>
<td>21 (31)</td>
<td>11</td>
<td>52</td>
<td>61</td>
<td>80</td>
</tr>
<tr>
<td><strong>Cord</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesions on T2-weighted imaging</td>
<td>1</td>
<td>23 (34)</td>
<td>9</td>
<td>39</td>
<td>50</td>
<td>72</td>
</tr>
<tr>
<td>Contrast-enhancing lesions</td>
<td>1</td>
<td>7 (10)</td>
<td>2</td>
<td>29</td>
<td>11</td>
<td>90</td>
</tr>
<tr>
<td><strong>Combined Risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesions on T2-weighted images of brain and cord</td>
<td>1</td>
<td>21 (31)</td>
<td>9</td>
<td>43</td>
<td>50</td>
<td>76</td>
</tr>
<tr>
<td>Lesions on T2-weighted images of brain only</td>
<td>1</td>
<td>27 (40)</td>
<td>7</td>
<td>26</td>
<td>39</td>
<td>60</td>
</tr>
</tbody>
</table>

*18 patients developed CD or CP MS
Table 4.2  Relationship between serial early MRI findings in CIS (n = 68) and clinical outcome after a year

<table>
<thead>
<tr>
<th>MRI parameter</th>
<th>Minimum number</th>
<th>Prevalence n (%)</th>
<th>*MS n</th>
<th>PPV %</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brain only</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesions on T2-weighted imaging at baseline</td>
<td>1</td>
<td>27 (40)</td>
<td>15</td>
<td>55</td>
<td>83</td>
<td>76</td>
</tr>
<tr>
<td>and new T2 lesions at follow up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contrast-enhancing lesions at baseline</td>
<td>1</td>
<td>10 (15)</td>
<td>7</td>
<td>70</td>
<td>39</td>
<td>94</td>
</tr>
<tr>
<td>and new contrast-enhancing lesions at follow up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

* 18 patients developed CD or CP MS
CHAPTER 5
The assessment of brain tissue in CIS using MR techniques

5.0 Aims
In the following two studies I used single-voxel $^1$H-MR spectroscopy and MTI, to assess brain tissue in regions of NAWM and in lesions. My aim was to determine whether or not abnormalities that have been reported in established MS were detectable in patients presenting with CIS.

5.1 Single-voxel proton magnetic resonance ($^1$H-MR) spectroscopy

5.1.1 Methods

Patients
Single-voxel $^1$H-MR spectroscopy was performed at the three-month visit on all patients recruited into the CIS cohort after May 1997. Twenty age- and sex-matched control subjects were also studied for comparison.

$^1$H-MR spectroscopy sequence
Following an FSE axial localising sequence (TR 3000 ms, TE 14/84 ms, ETL 8, matrix 256 x 192, FOV 24 cm, NEX 1, 19 x 5 mm slices with a 1.5 mm gap; acquisition time 2 minutes), a single-voxel spectrum was acquired from parietal NAWM at the level of the lateral ventricles (Figure 5.1). Care was taken to position the voxel as far as possible away from any visible lesions, making it as large as possible whilst excluding CSF and grey matter. A PRESS sequence (TR 3000 ms, TE 30 ms, 192 averages and 8 phase cycles; acquisition time 10 minutes) was used. Automatic shimming and water suppression was performed using the PROBE
proprietary software (GE Medical Systems). When possible, spectra were also obtained from lesions occurring in a similar region that were large enough to fill more than half of a voxel (Figure 5.2).

Data analysis

I quantified the metabolic concentrations of tNAA, choline-containing compounds (Cho), creatine / phosphocreatine (Cre) and myo-inositol (Ins) using the LCModel [Provencher 1993]. Input variables were fixed in order to minimise user variability. Regular quality assurance was performed in the Unit to produce the necessary calibration factor and ensured the results were consistent over time.

Statistical analysis

Comparison between the metabolite concentrations in the groups was made using a two-sample t-test. Comparisons between voxel dimensions were made using the Mann-Whitney Test. Due to the number of comparisons performed a p-value < 0.01 was regarded as significant and ≤ 0.05 as only a trend.

5.1.2 Results

$^1$H-MR spectroscopy of NAWM was performed in 39 patients, a median of 18 weeks (range 13 – 24 weeks) from the onset of symptoms. In addition, lesions were studied in eight patients none of which displayed contrast-enhancement. In the other patients, lesions were either not present in the appropriate region or were too small to study. The median age of patients studied was 32 years (range 18 – 50 years); 21 patients were women and 18 men. The presenting syndrome was optic neuritis in 32 (one bilateral simultaneous), a brain-stem syndrome in six and a spinal cord syndrome in
two cases. Abnormal baseline T2-weighted MRI examinations were present in 26 (67%) of the patients (median number of lesions 4, range 0 - 76).

The median size of the NAWM voxels was 2.1 ml (range 1.3 – 5.7 ml) in patients compared to 2.4 ml (range 1.1 – 7.4 ml) in controls (p = 0.4). The wide range of voxel sizes was due to anatomical variation between subjects. Comparison of patient with control NAWM did not show any significant difference in the concentrations of tNAA either in the total patient group or in patients with T2 lesions on brain MRI. Similarly there were no significant differences in the other studied metabolites (Table 5.1). There was no correlation between tNAA in the patient NAWM and either (a) number of lesions or lesion volume on T2-weighted MRI, or (b) the number of enhancing lesions at baseline. The median size of the lesion voxels was 1.4 cm$^3$ (range 1 – 2.2 cm$^3$). A significantly lower tNAA concentration was found in the lesions compared to control NAWM. Absolute values of Cho and Ins were significantly raised in lesions, compared to control NAWM, and there was a trend towards an increase in Cre (Table 5.1).

After 12 months follow-up, CD MS had developed in eight (21%) patients and CP MS in a further one (3%). When this sub-group of patients was compared controls, there were still no significant differences in the tNAA concentration in NAWM voxels (Table 5.1).

5.1.3 Discussion

This study found a reduction in tNAA concentration in lesions but not in NAWM in a cohort of CIS patients. This suggests that there was focal axonal loss / damage in
lesions (see Chapter 2) in these patients but the evidence for widespread axonal
damage found in established MS was not detectable.

The reduction in NAA concentrations can be partially reversible in acute MS lesions
However, none of the lesions studied displayed contrast-enhancement (the presence of
which indicates a defect in the blood-brain-barrier with the potential for vasogenic
oedema); thus it is unlikely the reduction in tNAA concentration found is a dilutional
effect due to oedema. In addition, the MRI examinations performed three months
earlier had revealed that all the lesions studied were already present at that time.
Therefore, the lesions were at least three months old, and so it is likely that the
reduction in tNAA concentration will be at least partially irreversible, suggesting that
focal axonal loss or permanent damage has already occurred in some lesions when
patients present with CIS.

We found the tNAA of NAWM to be normal, even in patients with abnormal MRI
brain examinations. These latter patients have a high risk of further relapses and many
are in the earliest clinical stages of MS (Chapter 2). A retrospective analysis in the
sub-group of patients who did develop MS within a year of this study has confirmed
that the baseline tNAA concentration in the NAWM of these patients did not
significantly differ from controls. Our results are compatible with the study by
Tourbah and colleagues who found no significant difference between NAA
concentrations in the NAWM from patients with clinically isolated optic neuritis and
controls NAWM [Tourbah et al. 1999]. These findings suggest that the reduced NAA
concentration seen in the NAWM in established MS is likely to occur as a result of
later accumulation of damage, possibly as a consequence of further inflammatory episodes, rather than being due to an inherent pre-existing defect in the white matter. This would be consistent with the finding that the concentration of NAA falls in association with disease progression [Arnold et al. 1994] and is lower in patients in more advanced stages of the disease [Fu et al. 1998].

The concentrations of Cho and Ins were increased, compared to control NAWM, in the lesions but not NAWM in CIS patients. There was also a trend towards an increase in Cre. These findings have all been reported in studies of MS lesions. Creatine is found in all brain cells, but its concentration is higher in astrocytes than in neurones and so increases might be expected with gliosis or with astrocyte hyperplasia [Urenjak et al. 1993]. A rise in phospho-creatine can be caused by microglia [Macouillard et al. 1995]. The concentration of Cho has been shown to be increased in acute [Miller et al. 1991, Arnold et al. 1992, Davie et al. 1994, De Stefano et al. 1995, Narayana et al. 1998] and chronic lesions [Miller et al. 1991, Husted et al. 1994] as well as in NAWM [Husted et al. 1994]. It has been suggested that this may imply active or recent demyelination because of the abundance of Cho in myelin [Arnold et al. 1992, Davie et al. 1994]. Cho is, however, also present in all cell membranes and elevations could be due to the increased turnover of cells involved in the inflammatory process [Brenner et al. 1993]. The concentration of Ins has been observed to be elevated in MS lesions in previous studies [Davie et al. 1994, De Stefano et al. 1995, Koopmans et al. 1993], with the concentration being higher in hypointense T1 lesions than those visible only on T2-weighted images [van Walderveen et al. 1999, Brex et al. 2000]. Ins is an osmolyte but its function is unknown. It has been proposed to be a glia-specific marker [Brand et al. 1993]
because of its high concentration in astrocytes [Thurston et al. 1989, Strange et al. 1994] but, as with Cho, it may also be increased due to the turnover of membrane constituents.

Further follow-up is needed to understand when and how NAWM develops a low NAA concentration in MS: does it relate to the number and site of new inflammatory foci (contrast-enhancing lesions) or to the degree of axonal damage in new lesions (as determined by their NAA concentration), or is it independent of focal lesion pathology? This will also determine the utility of $^1$H-MR spectroscopy to monitor the evolving disease and whether it can be used as a predictive tool in helping to identify which patients are likely to develop further disability.
Table 5.1  Comparison of absolute metabolic concentrations in CIS and controls

<table>
<thead>
<tr>
<th></th>
<th>Control NAWM</th>
<th>CIS NAWM</th>
<th>CIS lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>≥ 1 lesions</td>
<td>#MS group</td>
</tr>
<tr>
<td>Number</td>
<td>20</td>
<td>39</td>
<td>26</td>
</tr>
<tr>
<td>Sex (Female/Male)</td>
<td>11 / 9</td>
<td>21 / 18</td>
<td>16 / 10</td>
</tr>
<tr>
<td>Age, years: median (range)</td>
<td>29 (22 – 49)</td>
<td>32 (18 – 50)</td>
<td>32 (18 – 49)</td>
</tr>
<tr>
<td>Voxel size, cm³: median (range)</td>
<td>2.4 (1.1 – 7.4)</td>
<td>2.1 (1.3 – 5.7)</td>
<td>2.1 (1.3 – 5.7)</td>
</tr>
<tr>
<td>Metabolite concentration (mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cho; mean (SD)</td>
<td>1.3 (0.2)</td>
<td>1.4 (0.2)</td>
<td>1.4 (0.3)</td>
</tr>
<tr>
<td>Cre; mean (SD)</td>
<td>4.4 (0.5)</td>
<td>4.4 (0.6)</td>
<td>4.4 (0.6)</td>
</tr>
<tr>
<td>Ins; mean (SD)</td>
<td>3.8 (1.1)</td>
<td>4.1 (1.2)</td>
<td>4.2 (1.2)</td>
</tr>
<tr>
<td>tNAA; mean (SD)</td>
<td>9.1 (0.9)</td>
<td>9.0 (1.2)</td>
<td>8.9 (1.0)</td>
</tr>
</tbody>
</table>

* p ≤ 0.05 (trend), ** p < 0.01, ***p < 0.001

# Patients who developed CD or CP MS within 1 year of presentation
Figure 5.1  Spectrum from NAWM in CIS
An axial image from a FSE of a 49 year old lady (LG) with acute optic neuritis, showing the voxel (volume 3.8ml) placed over an area of NAWM. The spectrum from the voxel, showing both raw data and a fitted line, generated by the LCModel. Values of the concentrations of the main metabolites were tNAA 9.9mmol/l, Cr 5.7mmol/l, Cho 1.6 mmol/l and Ins 3.3 mmol/l.
Figure 5.2 Spectrum from a lesion in CIS
An axial image from a FSE of a 49 year old lady (LG) with acute optic neuritis, showing the voxel (volume 2.2ml) placed over a lesion. The spectrum from the voxel, showing both raw data and a fitted line, generated by the LCModel. Values of the concentrations of the main metabolites were tNAA 7.9 mmol/l, Cr 5.9 mmol/l, Cho 1.8 mmol/l and Ins 7.4 mmol/l.
5.2 Magnetisation Transfer Imaging (MTI)

5.2.1 Methods

Patients

MTI was performed on all the patients recruited into the CIS cohort after January 1998 at their three-month follow up visit. Twenty-seven CIS patients were studied. The NAWM of 13 age- and sex-matched control subjects was also examined for comparison.

MTI sequence

A dual-echo SE sequence was performed with and without pre-saturation pulses. (TR 1720 ms, TE 30/80 ms, matrix 256 x 128, FOV 24 cm x 18 cm, NEX 0.75, 28 x 5 mm axial slices; acquisition time 20 minutes) [Barker et al. 1996]. The pre-saturation pulse was a Hamming apodised three lobe sinc pulse, with a duration of 16 ms and a peak amplitude of 23.2 μT, giving a nominal bandwidth of 250 Hz, applied 1 kHz off-water resonance. A computer programme calculated the MTR for each pixel using the formula provided in Chapter 2. The resulting PD- and T2-weighted and inherently co-registered MTR images were then displayed on a Sun workstation (Sun Microsystems Inc., Mountain View, CA) using image display software [Plummer 1992].

NAWM MTR analysis

I performed the analysis after the blinding of all 40 images. Regions of interest (ROI) were outlined on the PD-weighted images (TE 30 ms) with reference to the T2-weighted images (TE 80 ms). A standard template was used to ensure the amount of white matter studied in each region of the brain was the same for each subject. The ROIs were positioned in each designated region of white matter taking care not to
include CSF or grey matter (or lesions in the case of patients) and leaving a surrounding rim of white matter to minimise partial volume effects. Adjacent slices were examined to ensure the ROI was completely in the white matter. The ROI size was 77.3 mm$^2$ in the pons and 22.9 mm$^2$ in the genu of the corpus callosum. For bilateral regions, the mean ROI size was 40.9 mm$^2$ in parieto-occipital white matter, 49.2 mm$^2$ in frontal white matter, 59.8 mm$^2$ in the posterior limb of the internal capsule and 77.3 mm$^2$ in the centrum semi-ovale. Once all the ROIs had been identified, they were applied to the MTR images (Figure 5.3). For bilateral regions of white matter, the mean of the measurements from the right and left hemisphere was taken to average any (minimal) effects of asymmetry between the hemispheres [Silver et al. 1997]. The reproducibility of the technique was assessed by duplicating the blinded images of five subjects prior to the blinding process and comparing the MTR values of each pair following unblinding.

**Lesion identification and MTR analysis**

Lesions, when present, were contoured on the PD-weighted images, with reference to the T2-weighted images, using a semi-automated local thresholding technique [Plummer 1992]. Lesion volumes were calculated automatically as the computed area multiplied by the slice thickness (5 mm). The regions were then applied to the inherently co-registered MTR image allowing the mean lesion MTR to be calculated for each patient.

**Statistical analysis**

The CoV was used to quantify reproducibility, after determining the mean and standard deviation of the duplicate measurements of NAWM MTR. Comparison of
the MTR in patient NAWM and lesions were made with the MTR of the NAWM in control subjects using two sample t-tests. Due to the number of statistical comparisons performed a p-value < 0.01 was considered to be significant.

5.2.2 Results

MTI was performed in 27 patients, a median of 18 weeks (range 14 - 24 weeks) after the onset of symptoms. Fourteen of the patients were women and 13 men. The median age was 34 years (range 21 - 51). Seventeen (63%) of the patients had lesions on PD- and T2-weighted images. The median total lesion volume for all patients was 0.3 cm$^3$ (range 0 - 6.8 cm$^3$). The control patients were age- and sex-matched comprising of 6 men and 7 women with a median age of 34 years (range 25 - 47). The mean CoV of the technique was calculated as 0.6%.

In the control subjects, significant differences were found in the MTR between the different regions of the brain with the highest MTR being recorded in the corpus callosum. This probably reflects the different sizes and concentrations of myelinated nerve fibres throughout the brain. There were no significant differences between the MTR in controls and patients in any of the white matter regions or in the overall mean values for white matter. Comparison of control NAWM with the NAWM of the sub-groups of patients with one or more T2 lesions and four or more T2 lesions also did not reveal any statistically significant differences (Table 5.2). In the 17 patients with lesions (median 6, range 1 - 51), the mean MTR of the lesions was significantly lower than control NAWM (Table 5.2).
To date, the median follow-up is 12 months (range 11 – 15 months) and at this time seven patients (26%) have developed CD (4) or CP (3) MS. As in other studies, progression was most likely in those with a greater number of T2 lesions (5/13 with ≥ 4 lesions developed MS), although two of the patients who developed MS had normal baseline imaging. The NAWM MTR of those developing MS was not significantly different from that of the controls (Table 5.2).

5.2.3 Discussion

In contrast with findings in established MS using similar techniques [Dousset et al. 1992, Loevner et al. 1995, Filippi et al. 1995c, Leary et al. 1999a], the MTR in the NAWM of patients with CIS was not found in our study to be reduced. In particular, using an identical MTI sequence and ROI approach in our Unit, significant reductions have been found in the NAWM MTR of patients with primary progressive MS [Leary et al. 1999a], and patients with early relapsing-remitting MS [Griffin et al. 2000]. By contrast, in only one patient in the present CIS study was the mean MTR value of NAWM below the 95% confidence interval of control NAWM MTR.

The sub-group of CIS patients in this study was representative of the total cohort in terms of the frequency and extent of T2 lesions on brain MRI at presentation. As has been discussed, CIS patients with T2 lesions have a high risk of developing CD MS. Our finding of a normal NAWM MTR in this high-risk group, and in those who developed clinical MS in the short follow-up period, suggest that widespread NAWM tissue damage is not usually present at the earliest clinical stages of MS. These results are consistent with the findings in our ¹H-MRS study, described previously, which found the major metabolites, including NAA, to be normal in NAWM.
The MTR of cerebral white matter is not homogenous and the regions sampled were selected to include several anatomical areas, using information from a normative database using the same sequence [Silver et al. 1997]. The findings in our control patients mirror those of the earlier study, with the highest MTR recorded in the corpus callosum. Careful matching of the patient and control groups for age and the use of mean MTR from bilateral regions of white matter should have avoided any errors due to the previously reported effects of age or hemispheric differences on MTR [Silver et al. 1997]. The two groups were also sex matched, although sex differences in MTR have not been previously reported.

A limitation of selecting regions of white matter is that only a small percentage of the total white matter is examined. A more comprehensive assessment of tissue MTR can be achieved using a histogram analysis technique [van Buchem et al. 1998, Rovaris et al. 1998, Phillips et al. 1998]. Such studies have been performed including CIS patients, but with conflicting results [Filippi et al. 1999b, Iannucci et al. 2000, Kaiser et al. 2000]. Two of these studies, both performed by the same group of investigators, selected only CIS patients with at least four T2 lesions, thus concentrating on a group with a high likelihood of developing CD MS. In the first of their studies, 21 CIS patients were seen within three months of symptom onset [Filippi et al. 1999b]. Global whole brain histogram analysis showed no significant difference between CIS patients and 20 aged and sex matched controls. However, in their second study, they analysed MT histograms of segmented normal-appearing brain tissue (incorporating white and grey matter following the extraction of lesions) of 24 CIS patients and found that the average MTR and peak position were significantly lower in patients than controls [Iannucci et al. 2000], suggesting that small focal abnormalities, beyond
the resolution of conventional imaging, might be present. It is unexpected that in the second study abnormalities were detected when in the first study, which included lesions (that have a lower MTR than normal appearing tissues) they were not. Another group of investigators have also looked at this issue, and in a study of 11 CIS patients (median lesion load 1.0 cm³, range 0 – 7.6 cm³) they found no differences between MT histogram parameters in patients and controls [Kaiser et al. 2000].

The difference between the study of Iannucci and colleagues, which reported abnormal MTR histograms, and our study, which found normal NAWM MTR using an ROI approach, may have several explanations. First, we did not examine the MTR of grey matter, so it could be that this is where these subtle changes lie. Secondly, the histogram method is more prone to partial volume influences from CSF and lesion edges, which may be sufficient to introduce minor abnormalities in the presence of atrophy (which has been detected in the early follow up of CIS patients (see chapter 6) or a significant T2 lesion load. Partial volume effects were less likely in our study due to the careful placing of the region of interest. Thirdly, the lesion volumes in the present study were much smaller, even when only patients with four or more lesions are considered (median T2 lesion volume: present study 1.1 cm³, Iannucci et al 5.1 cm³ [Iannucci et al. 2000]), suggesting that the latter study includes patients with a more pathologically advanced disease.

The MTR of the T2 lesions was significantly reduced compared to control NAWM. For individual patients, the mean lesion MTR ranged from 26.5 to 36.8 pu, implying histologic heterogeneity between patients. Whether patients with a lower mean lesion MTR (which implies more tissue damage such as demyelination and axonal loss [van
Waesberghe et al. (1999)) will have a poorer prognosis will need to be determined by further follow up; the study by Iannucci and colleagues suggested after a mean of 33 months follow-up that it did not [Iannucci et al. 2000].

In conclusion, the present study suggests that focal lesions are the predominant pathological feature in CIS patients, many of whom are in the early stages of MS. This would be consistent with a hypothesis that focal lesions rather than diffuse NAWM pathology are the primary event in MS patients who present with CIS. However, it is possible that MTR is insensitive to subtle NAWM pathological changes and the study of NAWM in CIS with other modalities e.g. T1 relaxation, or diffusion-weighted imaging, would be of interest. It is also possible that subtle focal NAWM changes occur which precede the frank appearance of a lesion as has been suggested by the occurrence of MTR and diffusion abnormalities for several weeks or months prior to lesion appearance in patients with CD MS [Filippi et al. 1998b, Goodkin et al. 1998, Werring et al. 2000]. Continued follow up of CIS patients is necessary to determine when the widespread decrease in NAWM MTR that has been found in established MS occurs and whether its development correlates with the extent and nature of focal lesion pathology. The prognostic value of lesion MTR at this early stage needs also to be determined by follow up. Finally, the fact that CIS NAWM appears normal using quantitative values such as MTR and $^1$H-MRS metabolite concentrations, indicates that therapeutic trials at this stage of the disease might usefully incorporate such assessments of the NAWM in order to determine whether the appearance of abnormality is prevented or delayed.
<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>CIS (total)</th>
<th>CIS (&gt;1 T2)</th>
<th>CIS (&gt;4 T2)</th>
<th>CIS (MS group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>13</td>
<td>27</td>
<td>17</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Sex</td>
<td>6M / 7F</td>
<td>13M / 14F</td>
<td>7M / 10F</td>
<td>5M / 8F</td>
<td>2M / 5F</td>
</tr>
<tr>
<td>Age, years: mean (range)</td>
<td>34 (25 - 47)</td>
<td>34 (21 - 51)</td>
<td>35 (21 - 48)</td>
<td>37 (21 - 48)</td>
<td>36 (26 - 46)</td>
</tr>
<tr>
<td>Lesion volume, cm³: mean (range)</td>
<td>_</td>
<td>0.3 (0 - 6.8)</td>
<td>0.5 (0.01 - 6.9)</td>
<td>1.1 (0.2 - 6.8)</td>
<td>1.7 (0 - 6.8)</td>
</tr>
<tr>
<td>MTR, pu: mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pons</td>
<td>38.8 (0.7)</td>
<td>38.6 (1.1)</td>
<td>38.7 (0.9)</td>
<td>38.8 (0.9)</td>
<td>38.6 (0.5)</td>
</tr>
<tr>
<td>Parieto-occipital</td>
<td>37.0 (0.7)</td>
<td>37.4 (0.6)</td>
<td>37.4 (0.5)</td>
<td>37.5 (0.5)</td>
<td>37.7 (0.5)</td>
</tr>
<tr>
<td>Frontal</td>
<td>39.5 (0.7)</td>
<td>39.4 (0.6)</td>
<td>39.4 (0.6)</td>
<td>39.3 (0.7)</td>
<td>39.6 (0.4)</td>
</tr>
<tr>
<td>Posterior internal. capsule</td>
<td>37.1 (0.7)</td>
<td>36.9 (0.7)</td>
<td>36.8 (0.5)</td>
<td>36.8 (0.6)</td>
<td>36.7 (0.2)</td>
</tr>
<tr>
<td>Corpus callosum</td>
<td>41.0 (0.9)</td>
<td>40.4 (0.9)</td>
<td>40.5 (0.9)</td>
<td>40.3 (1.0)</td>
<td>40.6 (0.7)</td>
</tr>
<tr>
<td>Centrum semi-ovale</td>
<td>37.8 (0.5)</td>
<td>37.9 (0.9)</td>
<td>38.1 (0.9)</td>
<td>37.9 (0.9)</td>
<td>38.0 (0.8)</td>
</tr>
<tr>
<td>NAWM (total)</td>
<td>38.5 (0.6)</td>
<td>38.4 (0.5)</td>
<td>38.5 (0.4)</td>
<td>38.4 (0.4)</td>
<td>38.5 (0.3)</td>
</tr>
<tr>
<td>Lesions (total)</td>
<td>NA</td>
<td>NA</td>
<td>33.1 (2.3)*</td>
<td>33.9 (1.2)*</td>
<td>34.1 (0.8)*</td>
</tr>
</tbody>
</table>

* p < 0.001

(T2, lesion visible on T2-weighted brain MRI; SD, standard deviation; M, male; F, female)
Figure 5.3  Example of the positioning of NAWM ROIs on the MT image.
(A) pons, (B) parioto-occipital (bilateral), (C) frontal (bilateral), (D) genu of corpus callosum, (E) posterior internal capsule, (F) centrum semi-ovale (bilateral).
CHAPTER 6
Serial measurement of brain and cord atrophy in CIS

6.0 Aims
In the following two studies I investigated whether atrophy could be detected in patients with CIS using quantitative MRI techniques. In Chapter 6.1, a preliminary study of brain atrophy in a small group of CIS patients is presented. This was performed in collaboration with members of the Dementia Research Group, Institute of Neurology, who have devised an analysis package for measuring brain atrophy. The measurement of ventricular volume was used as a marker of brain atrophy. This is a sensitive method of detecting tissue loss in MS, where pathology often occurs around the ventricles, and has been found to correlate with brain atrophy [Fox et al. 2000]. In Chapter 6.2, cord atrophy was assessed in a larger group of unselected CIS patients by the measurement at presentation and one year later of cross-sectional cord area at the level of C2.

6.1 Measurement of ventricular volumes
6.1.1 Methods

Patients
After the first year of follow up was completed I retrospectively selected two age- and sex-matched groups of patients from the total CIS cohort. The first consisted of the first nine patients who had suffered a relapse, separated in time (greater than three months) and space from their initial symptoms (four optic neuritis, one optic tract lesion, two brainstem and two spinal cord syndromes), thereby leading to a diagnosis of CD MS [Poser et al. 1984]. All these patients had one or more areas of high signal
suggestive of disseminated disease on their baseline T2-weighted brain images. The second group consisted of eight patients from the CIS cohort (three optic neuritis, three brainstem and two spinal cord syndromes), who had either normal imaging or only the symptomatic lesion visible at baseline and no further symptoms at follow up; these patients were studied for comparison.

**Image analysis**

Post-contrast T1-weighted images acquired at baseline and one year were analysed using an interactive image analysis package (MIDAS) [Freeborough et al. 1997]. Measurements were performed retrospectively, in a randomised and blinded fashion by a member of the Dementia Research Group experienced with the technique (Mrs R Gordon). Whole brain volumes were obtained using semi-automated iterative morphological techniques originally developed for three-dimensional volumetric scans. Mean signal intensity over these brain regions was calculated. Ventricular regions were outlined using a thresholding technique with the ventricular-brain boundary set at 60% of whole brain signal intensity. As the technique uses signal intensity for thresholding, high signal structures within the ventricles on the enhanced images e.g. blood vessels, were excluded. The ventricular region consisted of the lateral ventricles including the temporal horns but excluding the third and fourth ventricles. Ventricular volumes were automatically calculated from the outlined regions by multiplying total area outlined by slice thickness and were used to determine the change over the year.
Reproducibility

Five randomly chosen individuals had ventricular volumes measured twice by a single operator blind to subject details. The mean CoV for intra-rater reproducibility of the ventricular volumes was calculated.

Statistics

Comparisons between ventricular volumes measured in the groups of patients were performed using a Mann-Whitney Test. Measurements of change within groups was calculated using Wilcoxon Signed Ranks Test.

6.1.2 Results

The two groups were matched for age, sex and presenting syndromes. At baseline, the CIS patients that would go on to develop early MS had a median of 25 high-signal lesions on T2-weighted imaging (range 2 – 71) and eight contrast-enhancing lesions (range 0 – 10). In the other group of CIS patients, only one symptomatic lesion was seen in one patient who had a brainstem presentation.

After one year of follow up, the patients who developed MS had a median of five new T2 lesions (range 0 – 28). The median number of new contrast-enhancing lesions was only 1 (range 0 – 10), but overall the difference from baseline was not significant (p = 0.18). None of the patients in the matched group had developed either new T2 or enhancing lesions.

The CoV for intra-rater reproducibility of the ventricular volumes was 0.13% (range 0.02 – 0.23). Ventricular enlargement occurred at a significantly greater rate in the
patients developing MS than in those without further symptoms (Table 6.1). Using the matched group as "controls" to determine the expected rate of atrophy in this population, 95% confidence limits were calculated. Five of the nine (56%) patients who developed MS had an increase in ventricular volume in excess of this whereas none of the matched group showed such an increase.

6.1.3 Discussion

This study detected a significant, albeit small, increase in ventricular size in a small group of patients in the earliest clinical stage of MS. Such a change was not seen in a matched group of CIS patients differing in that they had no evidence of disseminated disease on their baseline T2-weighted images and had no further symptoms during the follow-up period. This latter group is known to have a much lower risk of developing MS compared with patients with evidence of disseminated disease at presentation (see Chapter 2). The findings indicate that atrophy is not an end-stage event in MS but reflects on-going pathology and can be detected in patients very early in the disease using these highly reproducible techniques.

What is the pathological basis of the atrophy observed? The \(^1\)H-MR spectroscopy study described in Chapter 5.1, whilst demonstrating evidence for focal axonal loss or damage, did not detect a reduction in the NAA concentration in cerebral NAWM in CIS. A reduction in the concentration of NAWM NAA has been reported in patients with established MS [Arnold et al. 1992, Husted et al. 1994, Davie et al. 1994, Rooney et al. 1997] and in secondary progressive MS the NAA concentration has been found to correlate with brain atrophy [Coles et al. 1999]. This implies that in CIS patients, axonal loss or damage has either not occurred in NAWM, or that there is
only mild damage that is below the level that can be detected using this technique. It is unlikely, therefore, that the ventricular enlargement found results purely from widespread axonal loss in NAWM. It may be that it results solely from the focal axonal damage in lesions with secondary Wallerian degeneration. In a study by Hickman and colleagues, a 15% reduction in optic nerve cross-sectional area was seen after a single episode of optic neuritis [Hickman et al. 2000]; focal lesions therefore have the potential to cause atrophy.

Other factors must also be considered as causes for mild atrophy. Demyelination itself will result in loss of tissue and also leads to a reduction of axonal diameter; furthermore, the myelin in remyelinated fibres is thinner than normal fibre [Harrison et al. 1972, McDonald 1974, Prineas et al. 1979]. However, we have also shown that the MTR of the cerebral NAWM in CIS patients does not differ significantly from controls (chapter 5.2), suggesting that widespread demyelination has not occurred. Reactive gliosis, which might cause contraction of the tissue with a resulting increase in the size of the ventricles, should also be considered as a potential cause of the small amount atrophy seen this early in the disease. Differences in the amount of oedema and inflammation at the two time-points could lead to an apparent change in volume. This was monitored indirectly by recording the number of contrast-enhancing lesions, which did not differ significantly between the two examinations. Drugs, illness, dehydration, pregnancy, poor diet and alcohol abuse must also be considered in any study of cerebral atrophy. None of these are applicable to this cohort, with the exception of one patient who received a short course of steroids and started interferon beta-1b between the two scans. Analysis excluding this one case still revealed a significantly greater rate of atrophy in the early MS group.
Future studies are required, optimising acquisition and image analysis; registration of pre-contrast three-dimensional T1-weighted images will permit more accurate measures of cerebral atrophy. Larger patient groups with longer, prospective follow-up need to be studied to determine if a relationship exists between atrophy, which is thought to predominantly represent axonal loss, and other markers of disease in MS, and to determine if the rate of atrophy predicts future clinical course.
<table>
<thead>
<tr>
<th></th>
<th>Clinically isolated syndrome</th>
<th>p-value</th>
<th>#p-value</th>
<th>#p-value between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early MS</td>
<td>Asymptomatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>M = male, F = female</td>
<td>4M / 5F</td>
<td>3M / 5F</td>
<td>0.8</td>
</tr>
<tr>
<td>Age</td>
<td>Median (range), years</td>
<td>32 (17 – 46)</td>
<td>31 (25 – 34)</td>
<td>0.9</td>
</tr>
<tr>
<td>Baseline ventricular volume</td>
<td>Median (range), cm³</td>
<td>4.1 (2.9 – 25.7)</td>
<td>3.2 (1.1 – 17.4)</td>
<td>0.2</td>
</tr>
<tr>
<td>Follow up</td>
<td>Delay: median (range), months</td>
<td>12 (12 – 12)</td>
<td>12 (12 – 14)</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>Ventricular volume: median (range), cm³</td>
<td>5.1 (3.5 – 26.5)</td>
<td>3.3 (1.2 – 16.7)</td>
<td>0.036*</td>
</tr>
<tr>
<td>Rate of change in ventricular volume</td>
<td>Median, cm³</td>
<td>+0.8</td>
<td>-0.1</td>
<td>0.021*</td>
</tr>
<tr>
<td>p value for change within group</td>
<td>0.036*</td>
<td>0.4</td>
<td>* significance level p&lt;0.05</td>
<td></td>
</tr>
</tbody>
</table>
6.2 Measurement of cross-sectional spinal cord area

6.2.1 Methods

Patients

Forty-three unselected CIS patients were studied at presentation and after one year. In
addition a group of 15 age- and sex-matched healthy controls were studied for
comparison.

MRI Sequence

A volume-acquired inversion-prepared fast spoiled gradient echo (FSPGR) of the
spinal cord was acquired using phased-array coils at baseline and at the one-year
follow-up MRI examination (TR 15.6 ms, TE 4.2 ms, TI 450 ms, flip angle 20°,
matrix 2562, FOV 25 cm, NEX 1, 60 x 1 mm sagittal slices; acquisition time 6
minutes)

Image analysis

A series of five contiguous 3 mm pseudo-axial slices were reformatted from the
volume data set on the Signa using the centre of the C2/C3 intervertebral disc as a
caudal landmark, with the slices perpendicular to the spinal cord. The images were
then transferred to a Sun workstation (Sun Microsystems, Inc., Mountain View, CA)
and uniformity corrected. Using an automated program the images were then
allocated random filenames. Following blinding to both the patient details and the
scan acquisition order I calculated the mean area of the slices using a technique
described by Losseff and colleagues [Losseff et al. 1996a]. A programme of quality
assurance operated in the department, which involved the serial imaging of control
subjects to ensure reproducibility of the quantitative measurement of cord area over time [Leary et al. 1999b].

Reproducibility

In five CIS patients and five controls the spinal cord images were duplicated prior to the blinding process. Following unblinding, the pairs of independently acquired spinal cord area measurements for these ten patients were used to calculate the CoV.

Statistics

Changes of cord area within groups of patients were compared using a paired t-test. Comparison between patients and controls were performed using a two-sample t-test.

6.2.2 Results (Table 6.2)

Serial imaging was available in 43 CIS patients. Imaging was performed at baseline and again after a median of 12 months (range 11 – 17 months). The median age of the patients studied was 31 years (range 18 – 50 years). Twenty-four of the patients were women. Twenty-nine presented with optic neuritis (all unilateral), nine with a brainstem syndrome and five with a spinal cord syndrome. One or more asymptomatic lesions were present on T2-weighted images of the brain in 32 (74%) patients (median 5, range 1 – 70). In 2 / 5 patients presenting with a spinal cord syndrome, the symptomatic lesion was seen on spinal cord imaging. In one case, the symptomatic lesion was in the cervical area and was associated with contrast-enhancement. Fifteen healthy controls (eight women, seven men) with median age 29 years (range 23 – 49 years) were also studied on two occasions a median of 12 months.
(range 9 – 14 months) apart. The CoV for the measurement of spinal cord area using this technique was 1.4%.

At baseline, the spinal cord area was significantly smaller than controls in the sub-group of CIS patients with an abnormal brain MRI (mean area: controls 78.1 cm\(^3\), patients 73.9 cm\(^3\); p = 0.03). Cord area in CIS patients with normal brain MRI at presentation did not differ significantly from controls (mean area 76.5 cm\(^3\); p = 0.46). The cross-sectional area of the cord did not correlate with the T2 brain lesion number or volume, the number of enhancing brain lesions at baseline, or the number of asymptomatic cord T2 lesions.

When the 5 patients with spinal cord syndromes were excluded from the analysis, the difference in cord area between patients with brain lesions versus controls remained significant (mean 74.0 mm\(^2\) versus 78.1 mm\(^2\); p = 0.04).

One or more asymptomatic T2 lesion was seen on sagittal FSE images of the spinal cord in 14/43 (33%) patients. There was no difference in cord area between these patients with (mean area 74.5 mm\(^2\)) and those without (mean area 74.7 mm\(^2\)) cord lesions.

After one year of follow-up, 13 (30%) of the patients had further symptoms leading to a diagnosis of CP or CD MS. All of these patients had at least one high signal lesion on T2-weighted imaging of the brain. It was not possible to detect a significant change in the spinal cord area over the follow-up period in either the CIS patients (with or without lesions on T2-weighted brain imaging) or in patients who developed
MS. Comparison of spinal cord area between the groups and sub-groups had similar findings after one year (Table 6.2).

6.2.3 Discussion

Cross-sectional spinal cord area at the level of C2 was significantly smaller in the 74% of patients presenting with clinically isolated syndrome who had one or more T2 lesions on brain MRI than in a matched control group. This is the group who have the highest risk of developing MS and it is likely that in the majority of cases we were studying MS at its earliest clinical stage. The baseline cord area in the patients who went on to develop MS within the year was also found to be reduced (mean area 74 mm$^2$) compared with controls, but this did not achieve significance, perhaps due to the smaller sample size.

The patient group with T2 brain lesions had a slightly higher proportion of females than the controls (63% versus 53%). This might raise the question whether gender differences in cord area per se have influenced the results. However, a previous evaluation of 15 males and 15 females using the same method, though showing a trend to smaller cord sizes in females, did not reveal a significant gender difference [Losseff et al. 1996]. Furthermore, our patient group with normal brain MRI has an excess of males but does not exhibit a higher cord area than controls. It is unlikely, therefore, that the minor gender differences in our subgroups can account for the results.

The practicalities of recruitment lead to baseline scans being performed over a range of one to 11 weeks following the onset of the presenting syndrome. It is most unlikely
that the baseline findings would have been different had they been obtained closer to
the clinical episode, since measurable atrophy changes probably evolve over a longer
period — the lack of change over the next year suggests this was indeed the case.

Patients presenting with a spinal cord syndrome made up 12% of the cohort. In only
one of these cases was the symptomatic lesion seen in the cervical region in which the
cord area was measured. Although this lesion enhanced following contrast
administration, there did not appear to be swelling or focal atrophy associated with the
lesion, and exclusion of this patient did not affect the results. The acquisition of spinal
cord area measurements in images obtained following contrast administration in
patients but not in controls, is a potential source of error in this study but it is thought
to have been unlikely to affect the result. Notably, the signal contrast between the
cord and the surrounding CSF, which is the critical feature enabling reproducible
segmentation, appeared to be the same in both groups. This also ensured that blinding
was preserved.

The rate of cord atrophy did not differ significantly from controls over the one year of
follow up using the technique described, and in fact significant tissue loss over this
period was not detected. This is likely due to the small amount of atrophy occurring
over this short time period being counterbalanced by limitations in the sensitivity of
the methods used. However, the reduction in cord area in these patients at
presentation implies that atrophy has already begun to occur at and prior to this early
clinical stage, at least in some patients. It is possible that the cervical cord measure of
atrophy is particularly sensitive because of the length of the projection axons sampled.
These findings are consistent with the previous CIS study, measuring ventricular volumes, and provides further evidence that atrophy may occur early in MS. In both the present study and the study of ventricular volume, the amount of atrophy detected was small. In addition, the finding of atrophy in the spinal cord arose only in a sub-group analysis of CIS patients and therefore this finding does need to be interpreted with some caution. Further studies are also needed to explore the relationship between cord and brain atrophy CIS patients.

Axonal loss may be a contributing cause to the cord atrophy observed and has been found in post-mortem studies to occur in this region of the spinal cord early in MS [Ganter et al. 1999]. However, although they both occur [Evangelou et al. 2000], axonal loss and atrophy may not necessarily proceed together. Despite MR spectroscopy and magnetisation transfer imaging studies having found evidence compatible with focal tissue and axonal damage in the lesions of patients with CIS, studies of brain normal appearing white matter suggest that widespread tissue and axonal damage is either mild or absent at this stage of the disease [Chapter 5]. Demyelination per se, with or without thin remyelinated fibres, should also be considered a potential cause of such mild atrophy.

The small amount of atrophy found over the one year of this study contrasts with the rate of atrophy previously been reported in established MS [Stevenson et al. 1998] Stevenson et al, using the same technique as we have used, detected a mean reduction in cord area of 2.98mm² in six patients with relapsing remitting MS in one year. The mean disease duration in these patients was 5.6 years (range 2 – 9 years). Larger, serial MRI studies of patients with early relapsing remitting MS are required to
determine when the rate of atrophy increases. The mechanisms of atrophy are also uncertain. For example, is it due to Wallerian degeneration secondary to axonal transection in lesions or to pathological events occurring in the normal appearing tissues, which are independent of lesions? Understanding the mechanisms of atrophy will enable more rational targeting and timing of therapeutic interventions, which aim to prevent these widespread destructive changes. The use of serial multi-sequence MR investigations, which characterise different aspects of the evolving pathology, will be an important means of elucidating the basis of progressive atrophy.
Table 6.2  Cross-sectional cord area measurements in CIS and controls

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Clinically Isolated Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>No brain lesions</td>
</tr>
<tr>
<td>Number</td>
<td>15</td>
<td>43</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>31</td>
<td>31.4</td>
</tr>
<tr>
<td>Median</td>
<td>29</td>
<td>31</td>
</tr>
<tr>
<td>Sex (male / female)</td>
<td>7 / 8</td>
<td>19 / 24</td>
</tr>
</tbody>
</table>

**Baseline cord area (mm²)**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Clinically Isolated Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>78.1 (5.2)</td>
<td>74.6 (6.2)</td>
</tr>
<tr>
<td>Range</td>
<td>70.1 - 86.1</td>
<td>63.2 - 91.1</td>
</tr>
<tr>
<td>#p = from control</td>
<td>0.06</td>
<td>0.5</td>
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</table>

**Follow up cord area (mm²)**

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>78.1 (5.5)</td>
<td>74.4 (7.0)</td>
</tr>
<tr>
<td>Range</td>
<td>69.7 - 88.4</td>
<td>62.8 - 92.8</td>
</tr>
<tr>
<td>#p = from control</td>
<td>0.07</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**Atrophy / year (mm²)**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Clinically Isolated Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>-0.1 (2.3)</td>
<td>-0.02 (3.1)</td>
</tr>
<tr>
<td>Range</td>
<td>-5.4 - 4.3</td>
<td>-9.2 - 6.2</td>
</tr>
<tr>
<td>*p = within group</td>
<td>0.99</td>
<td>0.67</td>
</tr>
<tr>
<td>#p = from controls</td>
<td>0.9</td>
<td>0.96</td>
</tr>
</tbody>
</table>

# Two-sample t-test  (comparison with controls)

*Paired sample t-test (comparison between time-points within groups / sub-groups)
PART 3

THE LONG-TERM PREDICTIVE VALUE OF MRI IN

CLINICALLY ISOLATED SYNDROMES
CHAPTER 7

The Long-Term Follow-Up of Clinically Isolated Syndromes:
An MRI Study with Emphasis on the Relationship with Disability

7.1 Introduction

In Chapter 2, the results of several prospective MRI studies were presented which demonstrated that the presence of one or more asymptomatic T2 brain lesion significantly increase the risk of a CIS patient developing MS over the subsequent 1 – 5 years following presentation. However, due to the relatively short duration of most of these MRI studies, the relationship between early MRI findings in CIS patients and subsequent disability is less well documented. The long duration of MS, with its markedly varied clinical course means that large groups of patients need to be followed for many years for this information to be acquired. Such follow-up would also enable the detection of those patients who have long symptom-free intervals before a second MS-defining attack.

In this study I assessed a cohort of CIS patients after a mean of 14.1 years from presentation. The patients had previously had clinical and MRI examinations at presentation, 1 year, 5 years and 10 years. In this latest follow-up, a clinical assessment was performed which included the measurement of disability using the EDSS [Kurtzke 1983] and when possible, a further MRI was acquired. This study afforded the opportunity to evaluate the relationship between clinical and MRI evolution over a uniquely long period of time.
7.2 Methods

Patients.

All the patients had presented with CIS to the wards and clinics of The National Hospital, Queen Square, London or the Physicians’ Clinic at Moorfields Eye Hospital, London between 1984 and 1987. Men and women aged between 10 and 50 years had been considered for inclusion after appropriate investigations had been performed to exclude alternative causes when indicated. Patients were initially recruited for a clinical and MRI examinations at baseline and after approximately one year. During this period, 109 patients were studied at both time points [Miller et al. 1988a, Miller et al. 1989]. Further assessments took place after approximately five years (89 patients) [Morrissey et al. 1993, Filippi et al. 1994] and 10 years (81 patients) [O’Riordan et al. 1998, Sailer et al. 1999]. During the course of the first 10 years, four patients were excluded, as alternative causes for the presenting symptoms were determined at follow-up (myaesthenia gravis, cerebrovascular disease, HIV-related complications, systemic lupus erythematosus). Two patients died from causes unrelated to MS. One additional patient died as a result of complications of MS between the 5 and 10-year follow-up, and was included in the total denominator of 81 patients for whom clinical data was available at 10 years [O’Riordan et al. 1998].

For this study, I invited the 80 surviving patients seen at the 10-year follow-up back for a further clinical assessment. Initially a letter was sent to each patient. If there was no response to this, a second letter was sent and I tried to contact them by telephone. If none of these approaches were successful, the patients’ details were sent to the Office of National Statistics who forwarded letters on to the patient via their Health Authority and General Practitioner.
Patients who responded were invited to attend for a clinical and MRI examination. Patients who were unwilling or unable, to attend were assessed via a standardised telephone interview.

Progression to CD or CP MS was defined using the Poser criteria [Poser et al. 1983] solely on clinical grounds. An interval of at least six months was required between the presenting symptom and any subsequent event to reduce the chance of including a case of slowly evolving ADEM. In those patients diagnosed as having MS, disease subtypes were classified as relapsing-remitting or secondary-progressive [Lublin & Reingold 1996]. A period of 6 months progressive neurological deterioration was required in patients classed as having secondary progressive MS. Disability was scored on the EDSS, either following a neurological examination or by using a standardised telephone questionnaire. The questionnaire used for this interview had been previously validated in a study of 110 MS patients comparing the EDSS score achieved via the telephone with that achieved by physical examination. The intra-class correlation coefficient for the two measurements was 94.8% [L. Kappos, personal communication].

**MRI**

At baseline and 5-years, imaging was performed on a Picker 0.5 T super-conducting imager. Contiguous axial slices of the brain were obtained using a SE sequence (TR 2000 ms, TE 60 ms). The slice thickness was 10mm in some of the very early baseline images and 5mm thereafter. MRI was also performed on this cohort one year after presentation, but as none of these images were available in an electronic format on which quantitative analysis of lesion volume could be performed and some of the
hard-copy images were unavailable, these data could not be incorporated into the present study. For the 10-year follow-up, imaging took place on a 1.5 Tesla Signa (General Electric, Milwaukee, WI, USA) imager and a dual-echo CSE sequence (TR 2000 ms, TE 30 / 90 ms, 5 mm slice thickness) was used. The methods of lesion counting and quantifying the T2 lesion load over the first ten years have been described previously [O'Riordan et al. 1998, Sailer et al. 1999].

In the present study, imaging took place at 1.5 T, using a dual-echo FSE sequence (TR 2000 ms, effective TE 19 / 95 ms, 5 mm slice thickness). Contiguous axial images of the brain were acquired using standard head-coils. T2 lesions were identified on hardcopy images by an experienced observer blinded to clinical details (Dr O Ciccarelli). Images were reported as normal if there were no high-signal lesions visible or, in the case of a brainstem syndrome, if only the symptomatic lesion could be seen. The images were then transferred to a Sun workstation (Sun Microsystem Inc., Mountain View, CA, USA) and displayed using image display software. Dr Ciccarelli then quantified lesion volume using a semi-automated local thresholding technique [Plummer 1992].

Reproducibility

To ensure reproducibility of lesion volume quantification in the present analysis, the T2 lesion loads from eight patients, with a range of lesion volumes, were measured in a blinded fashion on two occasions a week apart. The coefficient of variation was 3.7% (range 0.5 – 8.7%).
Comparison between groups was performed using Chi-squared or Mann-Whitney tests. The Spearman Rank Correlation coefficient ($r$) was calculated to determine the relationship between MRI and clinical parameters.

### 7.3 Results

Clinical information was obtained on 72 of the 81 patients included in the 10-year follow-up. I examined 56 patients (at which stage, one was excluded from the cohort because, in retrospect, his initial symptoms were attributed to cerebrovascular disease), whilst 13 were unable or unwilling to attend the hospital for an examination but agreed to have an assessment performed via the telephone. A further two patients had died as a result of their MS between the 10 year- and the present follow-up, making three MS-related deaths over the whole follow-up period from onset. The remaining patients declined to take part (1), had moved abroad and were not contactable (1) or were not able to traced (7).

The demographics of the remaining 71 CIS patients in this study (including the 3 who had died as a result of their MS) did not significantly differ - with respect to presenting symptom, male / female ratio and proportion with an abnormal baseline MRI - from the original cohort, suggesting this was a representative group (Table 7.1). The presenting syndrome had been optic neuritis in 36 cases, a brainstem syndrome in 14 and a spinal cord syndrome in 21. There were 49 females and 22 males. The brain MRI at baseline had been abnormal in 50 (70%). The surviving patients were assessed after a mean follow-up period of 14 years (range 12.5 – 16.75 years) when their mean age was 45 years (range 33 – 64 years).
Relationship between CIS and MS

CD MS had developed in 48 (68%) of the CIS patients and CP MS in a further five (7%). The relationship between CD MS and each different presenting syndrome was similar (optic neuritis 25/36 (69%), brainstem syndrome 9/14 (64%) and spinal cord syndrome 14/21 (67%)). Disease-modifying treatments (interferon beta) had been prescribed in only three patients, one of whom was continuing with treatment, whilst the other two had stopped treatment after a brief period.

The median EDSS of the patients with CD MS was 3.25 (range 0 – 10); > 3 in 24 (50%) patients, ≥ 6 in 15 (31%) patients and 10 (died from MS) in 3 (6%) patients. The T2 lesion volume at baseline correlated significantly with EDSS (r = 0.48, p < 0.001) and T2 lesion volume (r = 0.76, p < 0.001) at 14-years. The median T2 lesion volume in the 42 patients with CD or CP MS imaged at 14 years was 12.5 cm³ (range 0.55 – 70.3 cm³); this correlated significantly with the EDSS at 14 years (r = 0.58, p < 0.001).

Outcome related to baseline MRI findings (Table 7.2)

(a) Normal baseline MRI (n = 21).

Four (19%) of the patients had developed CD MS (all relapsing-remitting) with a median EDSS of 1.75 (range 1 – 2). The median time to the second (MS-defining) demyelinating episode was 7.5 years (range 5 – 11 years). One (5%) further patient developed CP MS. Eight of the patients had developed T2 lesions over the 14 year follow-up period. These included all five of the patients who had developed clinical MS (median volume 9.2 cm³, range 1.5 – 19 cm³) and three patients who had not had any further clinical symptoms (median volume 0.5 cm³, range 0.4 – 5.5 cm³). Two
further patients not imaged at this assessment had been noted to develop T2 lesions in the previous studies in the absence of clinical symptoms. Thus, 10/21 (48%) exhibited clinical or neurological evidence of multi-phasic disease.

(b) Abnormal baseline MRI (n = 50).

CD MS had developed in 44 (88%) patients; 27 had relapsing-remitting MS (20 with an EDSS ≤ 3 and 7 with an EDSS > 3) and 17 had developed secondary progressive MS (3 of whom died as a result of the disease). The median EDSS of this CD MS group at follow-up was 3.5 (range 0 – 10). The median time to the MS-defining demyelinating episode was significantly shorter than for patients with a normal baseline MRI (median 2 years, range 0.5 – 12 years; p = 0.003). A further four (8%) patients had developed CP MS. One of the two patients remaining with a diagnosis of CIS did have evidence of new lesions on MRI whilst the other (who had > 10 lesions at baseline) had refused to re-attend or to have any of the follow-up imaging. Overall, 49/50 (98%) exhibited clinical or radiological evidence of multi-phasic disease. The median T2 lesion volume in the 38 patients imaged at 14 years was 12.5 cm³ (range 0.5 – 70.3 cm³). This correlated with EDSS at 14 years (r = 0.63, p < 0.001).

Relationship between earlier MRI findings and disability after 14 years (Table 7.3)

The strongest correlation with the EDSS at 14-years was found with the change in the T2 lesion volume over the first 5 years (r = 0.61, p < 0.001) and the T2 lesion volume at 5-years (r = 0.60, p < 0.001) (Table 7.3). These correlations were stronger than those found for baseline T2 volume, or for subsequent measures (T2 lesion volume at 10 years and change in T2 volume from years 5 – 10 and 10 – 14). Patients who had the worst clinical outcomes not only had larger T2 lesion loads at baseline, but also
had larger increases in their T2 lesion loads over subsequent years (Table 7.4); this is particularly apparent in the three patients who died as a result of their MS during the follow-up period.

**Correlations between change in T2 lesion volume and change in EDSS (Table 7.5)**
The change in T2 lesion volume correlated most strongly with the change in EDSS over the first 5-years of the study.

**Relationship between early and late disability**
The EDSS at 5 years and 10 years was strongly predictive of disability at 14 years (Table 7.3). Out of 12 CD MS patients who had an EDSS > 3 due to MS after 5 years, 11 (92%) had an EDSS ≥ 6 after 14 years, compared to only 3/31 (10%) who had an EDSS ≤ 3 at 5 years (p < 0.001) (two patients who had developed CD MS after 14 years were not assessed at 5 years).

7.4 Discussion
This study confirms previous reports from the 5 and 10 year follow-up of the same cohort of the importance of brain MRI at presentation in influencing the long-term prognosis of patients presenting with CIS, both in terms of the time to and the likelihood of developing MS and the level of disability that may occur [Morrissey et al. 1993, Filippi et al. 1994, O’Riordan et al. 1998, Sailer et al. 1999]. A new observation is the apparent importance of early MRI lesion load change in their association with long-term disability; the T2 lesion volume after 5 years and the change in volume over the first 5 year period both correlated more strongly with the
EDSS after 14 years than did baseline T2 lesion volume, or the T2 lesion volumes at later time points.

Relationship between CIS and MS

Overall, 68% of the CIS patients seen after 14 years developed CD MS is similar to the prediction made by Francis and colleagues using life-table analysis that 75% of a UK-based cohort of optic neuritis patients would develop CD MS after 15 years [Francis et al. 1987]; although in this earlier study not all the patients were recruited and followed-up prospectively which may have influenced the results. Other prospective studies of comparable length in other countries have reported lower frequencies of conversion in patients with isolated optic neuritis, the most studied of the CIS, with between 38 – 58% of patients developing MS after 13 – 15 years of follow-up [Rizzo & Lessell 1988, Sandberg-Wollheim et al. 1990, Frith et al. 2000]. The finding in our study of a similar proportion of patients developing MS (and disability) following a brainstem and spinal cord syndrome to that seen following optic neuritis implies that the inclusion of other CIS is unlikely to have accounted for the discrepancies in the results. The differences from other studies may alternatively be due to either geographical variations in disease course, or may result from the loss to follow-up of a number of patients in our original cohort. If it were assumed that all other patients from the original cohort not seen at this review (after exclusion of the 5 cases that have subsequently proven to have had an alternative diagnosis) had had no further symptoms then the clinical conversion rate would be 52/104 (50%). However, four patients lost to follow-up at 14 years, who had CD MS when seen at 10 years, indicate that the true figure must be higher than this.
The presence of T2 lesions on brain MRI at baseline significantly increased the likelihood that MS would develop; 88% of patients with an abnormal brain MRI developed CD MS, compared to only 19% with a normal brain MRI (p < 0.001). Median time to the second MS-defining attack was also significantly different (7.5 years and 2 years in the normal and abnormal MRI groups respectively). Only one patient with four or more T2 lesions at baseline did not have any further clinical symptoms. This was a 33-year-old woman who presented with a partial transverse myelitis and it may be that her condition was due to the less common monophasic illness, ADEM. Follow-up studies of ADEM suggest that partial resolution of lesions, without new lesion formation, is the rule in this condition [Kesselring et al. 1990, O’Riordan et al. 1999]. Unfortunately, this lady has only been assessed by telephone and has not had a further clinical assessment or MRI examination. It is therefore not known if new signs have developed or whether the T2 lesions have resolved.

Long-term disability in patients presenting with CIS

The median overall disability of the CIS patients was mild. The median EDSS of patients who developed CD MS was 3.25. By comparison natural history studies of patients with established MS have suggested that after 15 years, 50% of patients will require aid to walk (equivalent to an EDSS of 6) [Confavreux et al. 1980, Weinshenker et al. 1989, Runmarker & Andersen 1993]. There are several reasons why this difference may have arisen: (1) Patients with primary progressive MS were not included in this present study but have been in other studies [Confavreux et al. 1980, Runmarker & Andersen 1993]; this sub-group of MS patients has been shown to accumulate disability more rapidly than patients with relapsing-remitting MS [Confavreux et al. 2000]. (2) The largest sub-group of patients were those with optic
neuritis. This has been reported to be associated with a milder disease course [Hawkins & McDonnell 1999] (although this did not appear to have been the case in our study). The finding of this study are consistent with several reports that approximately 70 – 80% of optic neuritis patients remain unrestricted after mean follow-up periods of between 8 and 15 years [Bradley & Whitty 1968, Nikoskelainen & Riekkinen 1974, Hutchinson 1976, Rizzo & Lessell 1988]. (3) All traceable cases were followed prospectively, regardless of whether or not they developed further symptoms ensuring that patients with little or no disability were included. (4) A comprehensive and formal follow-up was performed reasonably frequently (1, 5, 10 and 14 years from onset), enabling milder relapses to be identified that may have gone undetected if there had been longer intervals between assessments. This may have resulted in patients being included in the MS groups who could have been misclassified as CIS had the intervals had been longer.

The T2 lesion number and volume on the presenting MRI identified patients who were more likely to become disabled. Patients in this study who developed MS and had at least four T2 lesions at baseline accounted for 75% of those with an EDSS > 3 (including all three patients who died of MS). The median EDSS at follow-up in those with more than 10 lesions at presentation was 6. These data confirm and extend the previous observations made on the same cohort after 10 years [O’Riordan et al. 1998, Sailer et al. 1999]. Few other studies have been of sufficiently long follow-up to allow an evaluation of the relationship between MRI findings at presentation and the development of disability in CIS patients [Optic Neuritis Study Group 1997, Ghezzi et al. 1999]. These studies only included patients with optic neuritis and the follow-up periods were short so that the patients generally had only developed mild disability.
After 5 years, 10% of the patients studied by the Optic Neuritis Study Group who had converted to MS had developed an EDSS > 3 [Optic Neuritis Study Group 1997]. By comparison, in the study by Ghezzi et al. 19% had developed this level of disability after a mean of 6.2 years [Ghezzi et al. 1999]. Only in the study by the Optic Neuritis Study Group did the number of T2 lesions at baseline relate to subsequent neurological disability (7% with normal brain imaging developed an EDSS > 3, compared with 24% with three or more lesions) [Optic Neuritis Study Group 1997].

A new observation in this study is that the T2 lesion volume after five years and the change in T2 lesion volume during the first 5 years both correlated more strongly with EDSS at 14 years than did either the T2 lesion load at baseline or subsequent T2 lesion loads measured at year 10 or change measured from years 5 – 10 and 10 - 14. Previous natural history studies have highlighted the potential importance of a number of clinical features within the first 5 years in relation to long-term disability. Thus, relapse frequency and inter-relapse interval in the first two years [Weinshenker et al. 1989], incomplete recovery from relapses in the first 5 years, and the level of disability after five years [Kurtzke et al. 1977b, Weinshenker et al. 1989, Miller et al. 1992a] have been associated with subsequent disability up to 25 years later. Taken together, the present MRI and previous natural history clinical studies suggest that both pathological and clinical measures of disease activity in the early years after the onset with a CIS are of particular importance in the long-term prognosis for disability in MS.

What are the mechanisms by which an early increase in T2 lesion load may be associated with subsequent disability? A higher T2 load reflects a greater extent of
inflammation and demyelination, which in turn may result in secondary axonal degeneration due to inflammation-mediated axonal injury [Ferguson et al. 1997, Trapp et al. 1998] or the loss of trophic support of myelin. A recent report, using contrast-enhanced MRI as a surrogate marker of inflammation and atrophy as a surrogate marker of tissue and axonal loss, showed that progressive brain atrophy was linked to earlier inflammation [Coles et al. 1999]. However, other studies have not confirmed this finding [Saindane et al. 2000]. The mechanisms of later progression of disability may also be partly independent of focal lesion evolution seen on MRI – the weakening correlation between lesion volume and EDSS change in the 5 – 10 year and 10 – 14 year follow-up periods would be compatible with more complex mechanisms developing as the disease evolves. Although the mechanisms relating early T2 change to future disability are unclear, the findings do indicate the importance of studying the disease in its early years in order to learn more about pathogenic mechanisms and prognostic features; serial application of multiple MR techniques which investigate not only lesions, but also the normal-appearing tissues and which include measurement of tissue loss (atrophy) should be illuminating.

Technical aspects

This study provides serial MRI data over a uniquely long period. Recruitment of patients was started following the recognition that high-signal lesions identical to those seen in established MS could be detected in the brains of patients with CIS using MRI [Ormerod et al. 1987]. Furthermore, the population was almost entirely untreated with disease-modifying drugs (given to only three patients towards the later stages of the study). Treatments such as interferon beta and glatiramer acetate, which are now being increasingly prescribed for the treatment of early relapsing-remitting
MS, reduce the T2 lesion volumes [Paty & Li 1993, IFNB MS Study Group 1995, Jacobs et al. 1996, PRISMS 1998, European Study Group 1998, Ge et al. 2000], meaning that it is unlikely that similar data on the long-term natural history of T2 lesion development in the early stages of MS will be obtainable in the future.

The long duration has inevitably led to a number of methodological problems. Improvements in technology throughout the study period resulted in changes in the sensitivity of MRI. However, both the use of thinner slices and the increase in field strength would have increased the detection of T2 lesions [Filippi et al. 1995b, Filippi et al. 1997, Molyneux et al. 1998]. It should be noted that compared to current standards, the early imaging in this present study was of low resolution – the presence of four T2 lesions in a patient presenting with CIS, using highly sensitive modern imaging, may not have as poor a prognosis as are suggested from this present study. These findings reinforce the need for further prospective MRI studies of CIS patients such as those in Part 2 of this thesis.
Table 7.1  Demographics of the original London MRI follow-up studies

<table>
<thead>
<tr>
<th>Mean follow-up from baseline MRI (years)</th>
<th>Baseline &amp; 1.3</th>
<th>5.3</th>
<th>9.7</th>
<th>14.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients clinically assessed</td>
<td>109</td>
<td>89</td>
<td>81</td>
<td>71</td>
</tr>
<tr>
<td>Abnormal baseline MRI</td>
<td>69 (63%)</td>
<td>57 (64%)</td>
<td>54 (67%)</td>
<td>50 (70%)</td>
</tr>
<tr>
<td>Female / Male</td>
<td>68 / 41</td>
<td>53 / 36</td>
<td>53 / 28</td>
<td>49 / 22</td>
</tr>
<tr>
<td>Optic Neuritis</td>
<td>53 (49%)</td>
<td>44 (49%)</td>
<td>42 (52%)</td>
<td>36 (51%)</td>
</tr>
<tr>
<td>Brainstem syndrome</td>
<td>23 (21%)</td>
<td>17 (19%)</td>
<td>16 (20%)</td>
<td>14 (20%)</td>
</tr>
<tr>
<td>Spinal cord syndrome</td>
<td>33 (30%)</td>
<td>28 (31%)</td>
<td>23 (28%)</td>
<td>21 (30%)</td>
</tr>
<tr>
<td>Patients excluded (not CIS)</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Died (non-MS related)</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CD MS</td>
<td>20%</td>
<td>43%</td>
<td>59%</td>
<td>68%</td>
</tr>
<tr>
<td>Baseline MRI abnormal</td>
<td>22/69 (32%)</td>
<td>37/57 (65%)</td>
<td>45/54 (83%)</td>
<td>44/50 (88%)</td>
</tr>
<tr>
<td>Baseline MRI normal</td>
<td>0/40 (0%)</td>
<td>1/32 (3%)</td>
<td>3/27 (11%)</td>
<td>4/21 (19%)</td>
</tr>
<tr>
<td>MRI examination</td>
<td>109</td>
<td>89</td>
<td>64</td>
<td>55</td>
</tr>
<tr>
<td>Electronic data</td>
<td>70</td>
<td>66</td>
<td>57</td>
<td>55</td>
</tr>
<tr>
<td>(for lesion volume measurement)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2 lesion volume (cm³)</td>
<td>Median</td>
<td>0.46</td>
<td>2.06</td>
<td>3.84</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0 – 55.0</td>
<td>0 – 114.3</td>
<td>0 – 88.6</td>
</tr>
<tr>
<td>Median EDSS (all patients)</td>
<td>0</td>
<td>1.5</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>
Table 7.2  Number / volume of T2 lesions on brain MRI at presentation with a CIS and clinical outcome after 14 years

(n = 71)

<table>
<thead>
<tr>
<th>Asymptomatic lesions at baseline</th>
<th>0</th>
<th>1 – 3</th>
<th>4 – 10</th>
<th>&gt;10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median T2 lesion volume (cm³)</td>
<td>0</td>
<td>0.6</td>
<td>0.9</td>
<td>5.6</td>
</tr>
<tr>
<td>Number of patients</td>
<td>21</td>
<td>18</td>
<td>15</td>
<td>17</td>
</tr>
</tbody>
</table>

Clinical outcome after 14 years

<table>
<thead>
<tr>
<th></th>
<th>CIS</th>
<th>CP MS</th>
<th>CD MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDSS &gt; 3</td>
<td>16 (76%)</td>
<td>1 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>EDSS ≥ 6</td>
<td>1 (5%)</td>
<td>1 (6%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>EDSS = 10</td>
<td>4 (20%)</td>
<td>16 (89%)</td>
<td>13 (87%)</td>
</tr>
<tr>
<td>EDSS as a result of CD MS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDSS</td>
<td>0</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>EDSS</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>EDSS</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Median (range) EDSS</td>
<td>1.75 (1 – 2.0)</td>
<td>2 (0 – 8)</td>
<td>4 (0 – 10)</td>
</tr>
</tbody>
</table>

* EDSS as a result of CD MS

# Where available
Table 7.3  Relationship between T2 lesion volume and EDSS at time-points throughout the study and EDSS after 14 years

<table>
<thead>
<tr>
<th>T2 lesion volume</th>
<th>n</th>
<th>r</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (0)</td>
<td>63</td>
<td>0.48</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>0 – 5 years</td>
<td>59</td>
<td>0.61</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>5-years</td>
<td>59</td>
<td>0.60</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>5 – 10 years</td>
<td>52</td>
<td>0.29</td>
<td>0.037</td>
</tr>
<tr>
<td>10 years</td>
<td>52</td>
<td>0.48</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>10 – 14 years</td>
<td>45</td>
<td>0.45</td>
<td>0.002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EDSS</th>
<th>n</th>
<th>r</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-years</td>
<td>65</td>
<td>0.79</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>10-years</td>
<td>71</td>
<td>0.89</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Table 7.4  T2 lesion volumes (cm$^3$) at each time-point grouped according to clinical phenotypes after 14 years

<table>
<thead>
<tr>
<th>Year</th>
<th>Baseline Median, range</th>
<th>5 years Median, range</th>
<th>10 years Median, range</th>
<th>14 years Median, range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died (EDSS 10)</td>
<td>9.9 (1.2 - 10.5) (n = 3)</td>
<td>44.8 (22 - 76) (n = 3)</td>
<td>88.6 (n = 1)</td>
<td>- (n = 0)</td>
</tr>
<tr>
<td>SP MS</td>
<td>2.5 (0.2 - 55) (n = 12)</td>
<td>16.8 (1.3 - 114) (n = 11)</td>
<td>21.3 (1.1 - 46) (n = 7)</td>
<td>28.1 (0.5 - 70) (n = 9)</td>
</tr>
<tr>
<td>RRMS (EDSS &gt;3)</td>
<td>2.4 (0.5 - 6.1) (n = 5)</td>
<td>5.7 (3.3 - 21.7) (n = 5)</td>
<td>15.6 (6.3 - 39) (n = 5)</td>
<td>21.6 (16.6 - 52) (n = 5)</td>
</tr>
<tr>
<td>RRMS (EDSS ≤ 3)</td>
<td>0.6 (0 - 13.7) (n = 22)</td>
<td>2 (0 - 36.6) (n = 22)</td>
<td>5.9 (0.6 - 37) (n = 21)</td>
<td>8.0 (1 - 37.9) (n = 22)</td>
</tr>
<tr>
<td>CPMS</td>
<td>1.0 (0 - 2.6) (n = 5)</td>
<td>3.5 (1.4 - 10.9) (n = 5)</td>
<td>3.8 (2.0 - 16.3) (n = 5)</td>
<td>5.0 (4.2 - 15.1) (n = 5)</td>
</tr>
<tr>
<td>CIS</td>
<td>0 (0 - 0.4) (n = 16)</td>
<td>0 (0 - 0.6) (n = 13)</td>
<td>0 (0 - 0.6) (n = 13)</td>
<td>0 (0 - 5.5) (n = 13)</td>
</tr>
</tbody>
</table>

SP MS = secondary progressive MS, RR MS = relapsing-remitting MS n = number of patients in each group | CPMS = clinically probable multiple sclerosis

CIS = clinically isolated syndrome
### Table 7.5
Correlation between change in T2 lesion volume and EDSS

(all available patients)

<table>
<thead>
<tr>
<th></th>
<th>0 – 5 years</th>
<th>5 – 10 years</th>
<th>10 – 14 years</th>
<th>0 – 14 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>66</td>
<td>57</td>
<td>45</td>
<td>50</td>
</tr>
<tr>
<td>Change in EDSS ((\Delta) EDSS)</td>
<td>Median</td>
<td>1.5</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0 – 8.5</td>
<td>-1 – 5</td>
<td>-1.5 – 6</td>
</tr>
<tr>
<td>Change in T2 lesion</td>
<td>Median</td>
<td>1.11</td>
<td>0.85</td>
<td>0.83</td>
</tr>
<tr>
<td>volume ((\Delta) T2), (\text{cm}^3)</td>
<td>Range</td>
<td>-0.4 – 65.9</td>
<td>-0.34 – 67.0</td>
<td>-4.0 – 13.6</td>
</tr>
<tr>
<td>Correlation</td>
<td>SRCC ((r))</td>
<td>0.58</td>
<td>0.41</td>
<td>0.35</td>
</tr>
<tr>
<td>((\Delta) T2 – (\Delta) EDSS)</td>
<td>p-value</td>
<td>&lt; 0.001</td>
<td>0.002</td>
<td>0.02</td>
</tr>
</tbody>
</table>

SRCC = Spearman rank correlation coefficient
PART 4

SUMMARY AND CONCLUSIONS
CHAPTER 8

Summary and Conclusions

MRI has become established as an essential tool in the study of MS. In addition to its role in assisting in establishing the diagnosis, by demonstrating typical appearances in a patient with a suggestive history or examination, it is also able to detect sub-clinical disease activity, enabling its use in monitoring disease in therapeutic trials.

This thesis focused on patients with CIS; many of whom are at the earliest clinical stage of MS. The relationship between CIS and MS has been explored in many studies and although the reported risk of MS has varied widely, there is overwhelming evidence that it is greatest in CIS patients with cerebral T2 lesions at presentation. However, the majority of MRI studies of CIS patients have used techniques, which by today's standards were of low resolution. In addition follow-up has been of relatively short duration meaning that little is known about how these early findings relate to the later development of disability.

In Part 2, a prospective study of CIS patients was presented which documented the MRI findings using modern techniques, at presentation and over the subsequent year. High-resolution T2-weighted imaging was found to increase the proportion of CIS patients with abnormal brain imaging at presentation (69%) compared to earlier studies performed in the NMR Unit at the Institute of Neurology (61%), but the use of fFLAIR did not increase detection further. A high frequency of asymptomatic disease was also noted in the spinal cord – demonstrated in 36% of cases. In two cases, T2 lesions in the spinal cord were the only evidence of disseminated disease.
New MRI activity (T2 and contrast-enhancing lesions), indicating dissemination of disease in time, was found to occur more frequently than clinical attacks, in keeping with the observation in established MS that MRI is a sensitive measure of disease activity despite clinical stability. The combination of T2 lesions in the brain and cord increased the risk of developing new T2 lesions (86%) and clinical MS (43%) after one year, compared to T2 brain lesions alone (70% and 26% respectively). Contrast-enhancing lesions were seen in 31% of patients at baseline and their presence was the most predictive parameter from a single MRI examination for the development of new T2 lesions over one year (91%) and for the development of clinical MS within a year (52%). However, the introduction of a second brain MRI, performed three months after the first, provided better prognostic data for the development of early MS - a combination of T2 lesions at presentation and new T2 lesions at 3-month follow-up gave a positive predictive value of 55%, a sensitivity of 83% and a specificity of 76% for the development of clinically definite or probable MS after one year. Such a combination is desirable for optimal patient selection for treatment trials or for therapeutic intervention aimed at preventing the development of MS. The presence or absence of new T2 lesions at 3-month follow-up in patients with an abnormal MRI at presentation with CIS substantially influenced the risk of developing MS after 1 year (55% and 5% respectively) – this again emphasises that serial MRI in CIS may optimise selection of patients for trials or therapies. More prolonged follow-up is necessary to consolidate the findings.

T2 lesions are relatively non-specific, representing a number of pathological processes that occur in both MS and in other diseases. There is considerable evidence from both pathological and radiological studies in established MS that abnormalities
also occur in the NAWM. As this makes up the bulk of brain volume even small abnormalities in the NAWM may have a significant impact on disability. Quantitative MRI techniques, such as $^1$H-MR spectroscopy and MTI enable the study of both lesions and NAWM in vivo. These are proving to be valuable tools in helping with understanding of pathogenesis early in MS; direct pathological information can usually only be acquired at post-mortem in patients with chronic disease or from brain biopsy specimens taken from patients whose presentation was atypical. Using these techniques in CIS patients, evidence was found only of focal tissue damage in lesions and not the widespread changes in the NAWM that have been reported in established MS. These findings would suggest that the changes found in established MS are not due to a pre-existing inherent defect of white matter, rather being due to the accumulation of damage, possibly as a consequence of recurrent inflammatory episodes. Mild atrophy was found in both the brain and spinal cord. In view of the finding of a normal NAA concentration in NAWM and the small amount of atrophy detected, it likely that the latter is either the result of focal axonal loss in lesions or due to other pathological mechanisms such as demyelination or gliosis.

In Part 3, the long-term predictive value of MRI in CIS patients was explored. After a mean of 14.1 years prospective follow-up, the presence of T2 lesions at presentation was confirmed to significantly increase the risk of CD MS (88%) compared to patients with a normal MRI at presentation (19%). The time to the second MS-defining clinical episode was also significantly shorter in the former group (mean 2 years versus 7.5 years). Disability in the patients developing CD MS was generally mild (median EDSS 3.25), although 15 (32%) had an EDSS > 6, 3 of whom had died as a result of the disease. Baseline MRI appearance was predictive of long-tem
disability; patients with four or more lesions at baseline accounted for 75% of those with an EDSS > 3 after 14 years (including all 3 patients who died as a result of MS). Early T2 lesion volume increase (in this study over 5 years) was a better predictor of long-term disability than either T2 lesion volume at presentation or T2 volume measurement changes at later times. This suggests that the early pathological course has an important influence on outcome. Future research should concentrate on understanding the mechanisms that underlie this relationship.

In conclusion, early serial MRI findings in CIS patients identify those at greatest risk of developing MS and disability. A 3-month follow-up MRI was the best predictor of early clinical MS and lesion volume increase in the first 5 years correlated strongly with long-term disability. Early serial imaging characteristics in CIS patients may prove useful in developing revised criteria for an earlier diagnosis of MS. With the emergence of disease-modifying therapies and the increasing desire to introduce treatments before permanent tissue damage has become widespread, early MRI findings are important for selection of patients for therapeutic trials or therapies, as well as for prognostic counselling. They also suggest a potential for therapies that suppress MRI lesion formation to have long-term benefits if given early in the course of MS. However, in view of the current uncertainty as to the pathological mechanisms underlying the observed MRI-clinical relationship, long-term follow-up studies of cohorts on an appropriate disease-modifying treatment will be needed to clarify this issue.
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