

MS *in focus*

Issue 14 • 2009

● Disease courses in MS



multiple sclerosis
international federation

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Multiple Sclerosis International Federation (MSIF)

MSIF's mission is to lead the global MS movement to improve the quality of life of people affected by MS and to support better understanding and treatment of MS by facilitating international cooperation between MS societies, the international research community and other stakeholders.

Our objectives are to:

- Support the development of effective national MS societies
- Communicate knowledge, experience and information about MS
- Advocate globally for the international MS community
- Stimulate and facilitate international cooperation and collaboration in research into the understanding, treatment and cure of MS

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Cover photo: Lester Lefkowitz/Corbis

Designed and produced by

Cambridge Publishers Ltd
275 Newmarket Road
Cambridge
CB5 8JE
UK
+44 (0)1223 477411
info@cpl.biz
www.cpl.biz

ISSN1478467x

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Letter from the Editor



Multiple sclerosis can be a difficult disease to diagnose as well as to treat. Unfortunately there is no single laboratory or other type of test that provides a definitive diagnosis. While in the past diagnosing MS might have taken years, requiring the individual to be seen by numerous specialists before arriving at the correct diagnosis, today, fortunately, the situation is very different.

There are a number of aspects that have evolved over the years that contribute to this progress, including accepted diagnostic criteria and better instrumentation that permits an earlier and more accurate diagnosis. MS specialists are more knowledgeable than ever before about different disease courses and the complexities of making the diagnosis. General practitioners have access to more information, which hopefully helps them make appropriate and more timely referrals to specialists.

One aspect that has not changed over the years is the fact that an accurate diagnosis of MS is still based on the medical history, a neurological examination and various tests. The diagnosis of MS continues to depend on the skill of the specialist in asking the right questions and interpreting the answers.

Progress through collaborative initiatives has helped specialists to refine the identification of disease courses, also called subtypes or patterns of progression. Understanding the disease pattern, at the time of diagnosis as well as throughout the course of the disease, helps specialists in making appropriate treatment decisions.

Yet MS remains unpredictable. Many of those with relapsing-remitting MS live in fear of developing the secondary progressive form. Furthermore, information about the different courses of MS can be useful in planning and tailoring services that meet the needs of people with MS with specific disease characteristics.

This issue of *MS in focus* provides detailed descriptions of the various types of MS and how each is diagnosed and treated – and the glossary on page 27 defines some unfamiliar terms. We hope that this information is useful for healthcare professionals as well as for people with MS.

I look forward to receiving your comments.

Michele Messmer Uccelli, Editor

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The next issue of *MS in focus* will be on complementary and alternative therapies in MS. Please send questions and letters to michele@aism.it or marked for the attention of Michele Messmer Uccelli at the Italian MS Society, Via Operai 40, Genoa, Italy 16149.

Editorial statement

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Introduction to the disease courses of MS

Fred D Lublin, Saunders Family Professor of Neurology, Corinne Goldsmith Dickinson Center for Multiple Sclerosis, Mount Sinai School of Medicine, New York, USA

One of the several intriguing mysteries of multiple sclerosis (MS) is the variability of the clinical course. Some people have rather severe forms of MS, leading to marked disability and dysfunction, while others may have a course so mild that it is not diagnosable or even noticeable, except as a surprise finding at autopsy. This variability has led some to conclude that MS might be a syndrome or spectrum of different disorders rather than a single disease.

This variability has long been recognised, but a standardisation of the terms used to describe the clinical courses of MS was not undertaken until 1995. At that time a committee of the National Multiple Sclerosis Society (USA) undertook the task of codifying the clinical courses in an attempt to unify the course descriptions. The need for this had become more acute as MS had just entered the disease treatment era and new clinical trial designs needed to utilise more similar groups of subjects. Further, there was speculation at that time, which has since been supported by more recent clinical trial results, that response

to disease-modifying agents might be different for the various sub-types of MS.

At that time, we looked to see if there were reliable ways to measure the disease course – called markers. The advent of readily available magnetic resonance imaging (MRI) has greatly aided the diagnosis of MS. This led to new diagnostic guidelines, called the McDonald's criteria, in which MRI features play an important role in the diagnostic process, allowing for easier and earlier reliable diagnosis of the illness. After discussions with imaging experts, we concluded that there were no MRI features that distinguished the clinical sub-types of MS.

Similarly, a search for a laboratory biomarker in blood or cerebrospinal fluid was unsuccessful. The absence of a validated, reproducible biomarker for the disease course still eludes us, although very interesting and promising immunologic and genetic markers are under active investigation. We were left with trying to develop a consensus on the course definitions. This was accomplished through a survey of members of the international MS clinical research community. Of the 215 persons sent the survey, 125 responded and their responses were the basis for the course definitions employed. In addition to the course definitions, definitions of benign and malignant MS were developed.

The course definitions developed are as follows:

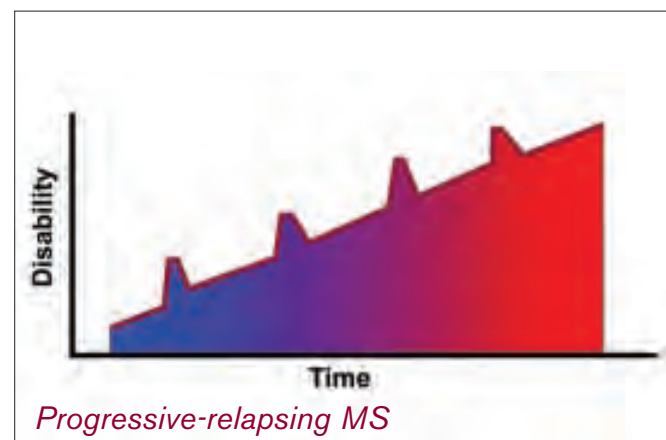
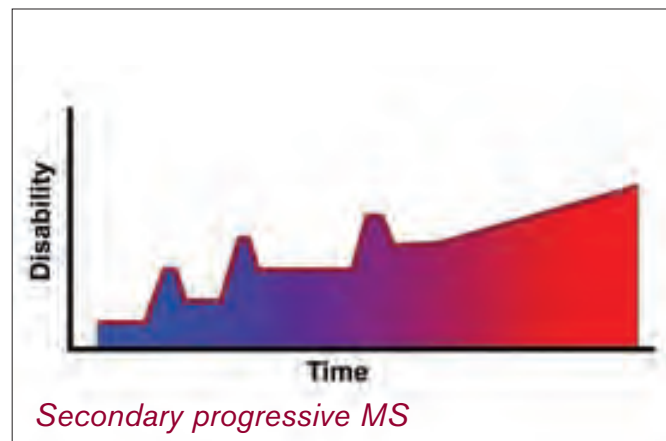
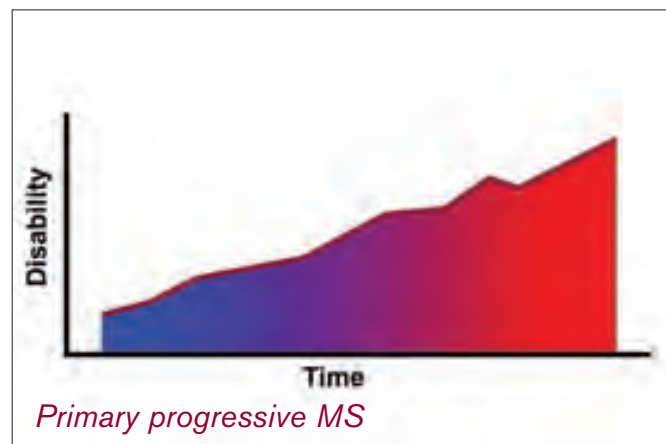
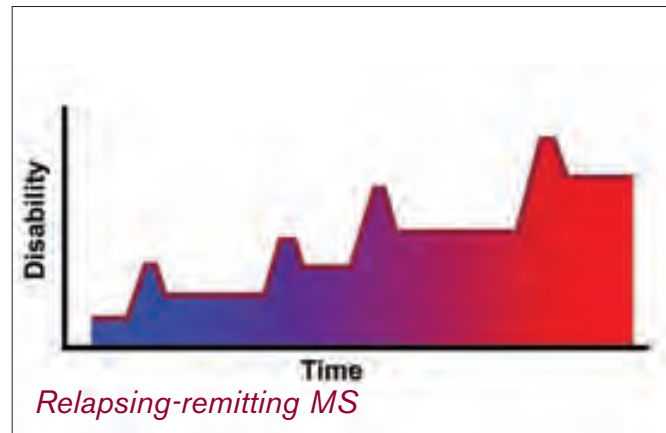
● **Relapsing-remitting (RRMS)** is characterised by clearly defined disease relapses* with full recovery or with some after effects upon recovery. Periods between disease relapses are characterised by a lack of disease progression. The defining elements of RRMS are episodes of acute worsening of neurologic function followed by a variable degree of recovery, with a stable course between attacks. The period of time between relapses is highly variable.

● **Primary progressive (PPMS)** is defined as disease progression from onset with occasional plateaus and temporary minor improvements. The essential element in PPMS is a gradual, nearly continuously worsening with minor fluctuations, but no distinct relapses.

● **Secondary progressive (SPMS)** is characterised by an initial relapsing-remitting disease course followed by progression with or without occasional relapses, minor remissions and plateaus. SPMS may be seen as a long-term outcome of RRMS, in that most people with SPMS initially had RR disease as defined here. However, once the baseline between relapses begins to progressively worsen, the person is considered to have switched from RRMS to SPMS.

● **Progressive-relapsing (PRMS)** is defined as progressive disease from onset, with clear acute relapses, with or without recovery, with periods between relapses characterised by continuing progression. Although the least common of the subtypes, recent clinical trials of progressive MS have provided ample evidence for this form of MS. The behaviour of PRMS is similar to that of SPMS.

A relapse – also called an exacerbation, attack or flare – is a period when people with MS experience new symptoms or when their old symptoms reoccur, followed by complete or partial recovery. To be a true relapse, it must last at least 24 hours and be separated from the previous one by at least 30 days. Most relapses last from a few days to several weeks or even months.



One could think about grouping these disease courses into relapsing forms and progressive forms of MS. The relapsing forms would encompass RR, SP and PR MS. This characterisation has been utilised in some clinical trials and also has been used in regulatory labelling of drugs by the US Food and Drug Administration (the regulatory body which approves drugs in the US). Progressive forms of MS would encompass PP, PR and SP MS. This has also been utilised in clinical trials. Although there are overlaps between these two combined groups, they offer certain advantages in clinical trial design, so long as it is clear which types of MS are being studied.

Since the publication of these MS subtypes, two additional disease courses have been described. The inelegantly named 'clinically isolated syndrome' (CIS) refers to the first episode of inflammatory demyelination that occurs in those who are eventually to be diagnosed as RRMS. Current diagnostic rules require the identification of two relapses separated in time and involving different areas of the central nervous system – so individuals with CIS are not diagnosable with MS. Yet clinical trials of such individuals demonstrate that, when properly chosen, this group has a high probability of conversion to MS. Less clear is what is now being referred to as the 'radiologic isolated syndrome' (RIS, also referred to recently as CIS type 5). This designation is applied to individuals who have MRI scans for reasons unrelated to MS and are found to have changes on these scans suggestive of (asymptomatic) MS. Recent reports have expanded our understanding of this group, but much more information is needed.

As mentioned above, the clinical course definitions will benefit from the development of discriminative MRI and biomarker data. Once available, we should be better able to employ these disease course definitions for making prognoses and deciding on the best treatment for each individual.

Defining the disease course

Stephen Reingold, co-author with Fred Lublin of the influential paper on MS clinical courses, reflects on its influence

The survey by the international Advisory Committee on Clinical Trials in MS resulting in this publication aimed to standardise terminology describing the course of MS, enhance communications and facilitate design and recruitment for clinical trials. This was a subjective "consensus effort" among MS clinicians worldwide because objective data to support standardised definitions were not available.

The resulting definitions have found wide use. Virtually every paper describing the course(s) of MS cites the publication. Our diagrams portraying RR, SP, PP and PR disease are reproduced in lectures, journal articles and book chapters. Clinical trial protocols use these definitions to identify target populations for study. Thus the consensus clinical course definitions have well served their original purpose.

What has *not* been achieved since the publication is development of objective measures using biological markers to replace these more subjective clinical definitions. But this may be changing. New data, particularly using advanced MRI techniques, are working towards helping to differentiate between types of MS. I expect that within the next few years we will see some, if not all, of the clinical course descriptions enhanced by more objective findings that will further the original goals of the 1996 effort.

Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: Results of an international study. *Neurology* 1996; 46(2):907-911.

Relapsing-remitting MS

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Relapsing-remitting multiple sclerosis is characterised by the occurrence of acute but brief episodes of neurological dysfunction (referred to as relapses, exacerbations, or attacks), which can be followed by complete or partial recovery. The characteristics of clinical relapses may vary widely in both type and severity, ranging from subjective sensory disturbances to a complete loss of motor functioning. About 85% of people with MS initially have RRMS. In this type of MS neurological problems from relapses may persist but, by definition, they are stable; that is, they do not worsen between the episodes of acute neurological dysfunction.

It is well known, however, that a significant proportion of people with RRMS subsequently enter a secondary progressive disease course, a phase characterised by a continuous worsening of neurological impairment with or without occasional relapses, minor remissions and plateaux (see page 13). The results of studies conducted in placebo groups of people with MS indicate that the time from RRMS onset to secondary progression is, on average, about 20 years. A minority of people with RRMS are termed as “benign” when, a long time after the onset of the disease, neurological impairment is



Today, it is impossible to predict the future course of MS.



Many people with relapsing-remitting MS have 'invisible' symptoms such as fatigue or pain.

absent or minimal. See page 15 for a description of benign MS.

Prognosis

Most studies investigating the likely course of the disease for those with RRMS indicate that an older age at onset, male gender, higher relapse rate or faster clinical deterioration during the first five years are hallmarks of an unfavourable disease evolution. Initial visual or sensory symptoms have been found to be associated with a longer time to secondary progression, while spinal cord-related symptoms (for example, urinary symptoms or lower limb dysfunction) are associated with a shorter time to secondary progression. Incomplete recovery from the initial exacerbation has also consistently been associated with a shorter time to secondary progression.

Studies conducted on *post mortem* samples or brain biopsies from people with MS have highlighted that focal, potentially reversible inflammation is the hallmark of tissue damage in RRMS; when present, a loss of axons (ie, irreversible damage) and diffuse white and grey matter pathology are less pronounced than in the more advanced and disabling stages of MS. The use of MRI has greatly increased our ability to study the evolution of all these types of damage in RRMS. It is now established that monthly MRI scans of the brain can detect the occurrence of disease activity (the presence of new lesions) in RRMS five to ten times more frequently than clinical monitoring alone, such as assessing the presence of new symptoms and signs. But the actual cost of performing monthly MRIs is impractical in most cases.

The high sensitivity of MRI makes it possible to determine the presence of the disease soon after its first clinical signs, thereby enabling an earlier diagnosis and disease-modifying treatment (DMT). In addition, MRI-derived measures of RRMS activity have become reliable markers to assess the efficacy of experimental treatments in clinical trials. It is also worth noting

that the application of more sophisticated, “non-conventional” MRI techniques to the study of RRMS has improved our knowledge about the mechanisms of this disease. We have learned from non-conventional MRI studies that irreversible loss of neurons and axons is present from the early stages of RRMS, and that grey matter is not spared. The severity of these pathological features is less pronounced in people with stable RRMS and tends to increase when RRMS shifts to the secondary progressive phase.

There is, however, an extreme variability from person to person with regard to the presence and extent of all these features, in spite of similar clinical profiles. As shown by functional MRI studies, this variability can be explained by the differing efficacy of innate compensatory mechanisms among individuals, namely the reorganisation of cortical activity, which the brain uses from the earliest stages of RRMS to try to limit the consequences of tissue damage. Disappointingly, MRI features still have limited value in giving individual prognoses to people with RRMS. Nonetheless, the results of recent studies seem to suggest that integrating clinical and MRI data may represent a valuable strategy to overcome this limitation.

Treatments

During the last 15 years, the efficacy of numerous experimental treatments has been investigated in RRMS, with the dual aim of reducing the frequency and/or severity of relapses and, possibly, the risk of subsequent secondary progression of the disease. Thanks to the use of MRI, we have been able to reduce the duration and sample size needed to run RRMS trials and this has led to the approval of several DMTs, namely beta-interferons and glatiramer acetate. These injectable drugs for people with RRMS are now widely accepted in that they are able to reduce clinical and MRI disease activity with a reasonably good risk/benefit ratio – that is, the risk of side effects is acceptable when compared to expected benefits.

Whether these DMTs work in preventing the shift from relapsing-remitting to secondary progressive MS remains debatable, but some evidence supporting their efficacy has come out of “post marketing” surveys, which are clinical trials that pharmaceutical companies conduct after approval to gather additional information about a product's safety, efficacy or optimal use. Even though the average efficacy of interferons and glatiramer acetate does not seem to be significantly different, it is well known that individuals with RRMS may be “non-responders” to one or all of these treatments. The early identification of non-responders and the development of further therapies remain, therefore, issues of outstanding importance in the therapeutic management of RRMS. There are already approved drugs in some countries, such as mitoxantrone (an immunosuppressant drug and chemotherapy agent) and natalizumab (a monoclonal antibody), which are used in more severe cases of RRMS, thanks to their average increased efficacy compared with first-line DMT. This efficacy is, however, accompanied by a greater risk/benefit ratio.

The high sensitivity of MRI makes it possible to determine the presence of the disease soon after its first clinical signs, enabling earlier diagnosis and treatment.

Future treatment options

Several trials are being or have been recently conducted to assess the efficacy of oral compounds (for example, cladribine, fingolimod, laquinimod, teriflunomide) and monoclonal antibodies (such as rituximab, alemtuzumab, daclizumab) as potential therapies for RRMS. It is likely that some of these treatments will show a significantly greater efficacy than “traditional” DMT for RRMS. If such findings are combined with an acceptable safety profile, the scenario of RRMS treatment might further and dramatically improve during the next few years.

Primary progressive MS



Marilyn/stockphoto

Increased difficulty in walking is common in people with PPMS.

Juan Ignacio Rojas, Department of Neurology, MS Center, Italian Hospital of Buenos Aires, Argentina

Most people with MS have relapsing symptoms that last days or weeks before resolving; however, one in ten do not. Instead, from the beginning, these people have a progressive and continuous accumulation of neurological symptoms, with occasional plateaus and temporary minor improvement but without typical relapses. People who show a gradual worsening of MS from the onset of the disease are considered to have primary progressive multiple sclerosis (PPMS). The cause of PPMS is still unknown. Various theories attempt to combine the available data into plausible explanations but, thus far, none has proved definitive.

Clinical characteristics

People with PPMS tend to be older than people with a relapsing-remitting form at onset of the disease (an average of 40 years old). The clinical features often suggest involvement of the spinal cord which often bears the brunt of the disease. The most common symptom is a progressive weakness of the lower limbs with spasticity (spastic paraparesis), which is seen in 80% of people with PPMS.

Another common symptom is difficulty with coordination and balance (known as ataxia) due to progressive cerebellar involvement, which is found in 15% of individuals. Other symptoms may include

changes in sensation, muscle weakness, muscle spasms, difficulty in moving, problems in speech or swallowing, visual problems, fatigue, pain and bladder and/or bowel difficulties.

Pathological, immunological and MRI findings

The lesions seen in people with PPMS show a loss of oligodendrocytes (the cells that form the myelin sheath) and a reduction in myelin repair when compared to other MS subtypes. Widespread inflammation (though less than in relapsing forms) with diffuse axonal damage in white brain matter and demyelination of cortical tissue are also found. Axonal damage is the basis of irreversible and progressive disability.

There is limited information regarding immunological findings compared with other forms of the disease. The most frequently reported is the increased intrathecal synthesis of IgG antibodies and the appearance of oligoclonal bands in the cerebrospinal fluid of approximately 90% of people with PPMS. Another immunological finding includes the observation by some researchers of auto-antibodies, part of the body's immune system, that mistakenly target proteins of the brain. Although several studies have attempted to investigate this issue, immunological patterns that differentiate PPMS have not yet been described.

Despite their increased disability that occurs over time, people with PPMS usually have fewer brain MRI abnormalities than people with other subtypes of MS, and those lesions tend to be smaller. Another characteristic of MRI findings is that those with PPMS have a lower frequency of gadolinium-enhancing lesions when compared with other MS subtypes, and fewer new lesions developing over time. However, as these findings vary from person to person, it is impossible to determine what type of MS a person has from an MRI scan alone.

Diagnosis

As PPMS does not have relapsing symptoms, it

It is impossible to determine what type of MS a person has from an MRI scan alone.

is important to listen to the person's own story of the disease and combine this with tests (MRI and oligoclonal bands) in order to determine a diagnosis of PPMS.

The story of gradually progressive neurological symptoms, including paraparesis or unsteadiness, is characteristic. To make the diagnosis of PPMS, the condition must have been present for one or more years; this protracted diagnosis can be very stressful. A neurological examination should demonstrate abnormalities related to brain or spine disease, for example, spasticity, Babinski sign (a reflex action in which the big toe moves upward and the other toes fan out when the sole is stroked – a normal reflex in infants but an indication of CNS damage in adults) or hyperreflexia (overresponsive reflexes). MRI should show lesions, especially in the brain and cervical spine. The spinal fluid normally shows oligoclonal bands; however, a small group of people have no immunological abnormalities in CSF. The McDonald criteria contain a section on diagnosing PPMS.

Treatment

To date, there is no proven or licensed disease modifying treatment to slow the course of PPMS. Two small studies of interferon beta could not demonstrate a delay in the progression of the disease. A large study with glatiramer acetate also failed to demonstrate a substantial reduction in the proportion of people who showed progression.

Other studies have evaluated different medications for the treatment of PPMS. Medications such as intravenous cyclophosphamide and methylprednisone, azathioprine, methotrexate, cladribine, rituximab, immunoglobulin and autologous stem cell transplantation have not proven effective in modifying the course of PPMS, although

some of these treatments continue to be investigated. Future treatment options, including the monoclonal antibodies natalizumab and alemtuzumab, have received much attention; however, as their mode of action appears to be mediated through a decrease in cerebral inflammation, their role in PPMS may be limited. Finally, strategies to promote remyelination or to repair or replace damaged axons are under investigation.

Because there is no proven disease-modifying treatment for PPMS, it is highly relevant to consider symptomatic treatment in order to improve quality of life. Treatment often includes rehabilitation and symptomatic therapies.

Prognosis

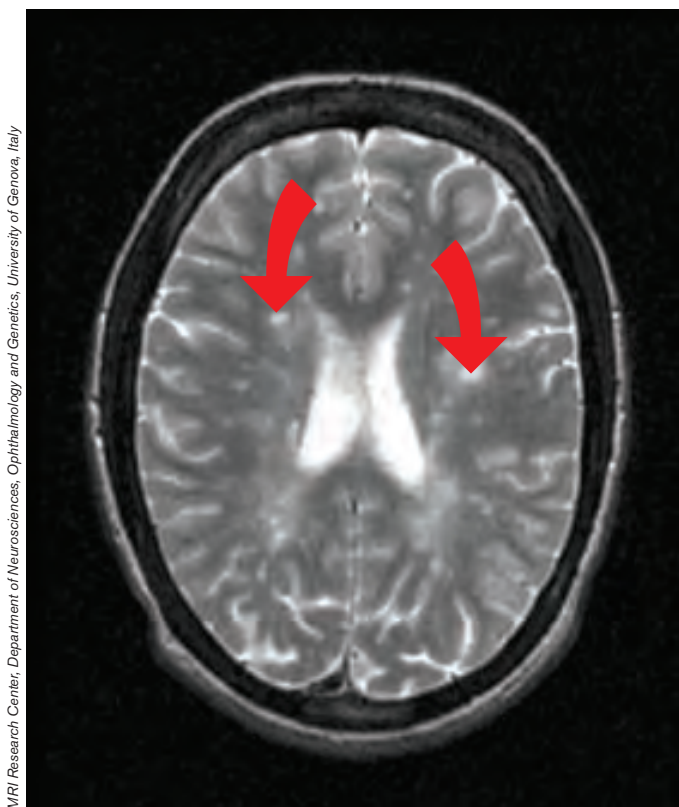
In general, the prognosis in PPMS differs from that of the relapsing form of the disease. In PPMS, people usually start experiencing symptoms at 40 to 45 years (a more advanced age than in the

Despite an increased interest in PPMS in recent years, the pathophysiology of this disorder is still poorly understood.

relapsing MS form) and are able to walk years after diagnosis, although they tend to worsen over time. This worsening ability to walk is a common disabling symptom in nearly all people with PPMS.

Conclusions

People with PPMS represent about ten per cent of all those with MS. Despite an increased interest in PPMS in recent years, the pathophysiology of this disorder is still poorly understood. Research priorities include a better understanding of the mechanism of the disease and its natural history, as well as a search for new therapeutic approaches that may delay progression. Above all, it is important to be aware of symptom management strategies so that the quality of life of people with PPMS may be improved.



T1 weighted MRI scan showing multiple areas of gadolinium (Gd) enhancement, indicating a breakdown of the blood brain barrier, a sign of disease activity.



MRI of the cervical spinal cord showing multiple hyperintense areas (demyelinating lesions) utilising a technique called short inversion time inversion recovery fast spin echo.

Secondary progressive MS

Helen Tremlett, Faculty of Medicine (Neurology), Brain Research Centre, University of British Columbia, Vancouver, Canada

Around 85% of people with MS will start off with a relapsing-remitting disease course. After some years, a portion of people with RRMS find that their disease is progressing gradually, even though they are no longer experiencing relapses (or at least have very few relapses). This is then called secondary progressive or SPMS).

SPMS seems to mark a turning point. The disease becomes less 'inflammatory', with fewer acute relapses. Instead, gradual and irreversible disease progression can occur.

There are no reliable laboratory markers or specific tests to differentiate RRMS from SPMS, so the conversion to SPMS is determined by neurologists based on clinical findings. It has been reported that after five years of having MS, nearly 10% of those with RRMS had reached SP stage. This increased to almost 25% at ten years and 75% at 30 years.

Prognosis

On average, the RR phase lasts around two decades before SPMS begins. However, as indicated above, some people reach the progressive phase much more quickly than others, and some never reach it at all. Based on research, it appears that people who are younger at the onset of MS take longer to reach SP stage. Yet these

people still tend to reach SPMS at a younger age than those who are older at the onset of MS. Men typically reach SPMS around five years earlier than women (from the onset of MS); from the perspective of age, men reach SPMS at around 47 years of age, with women averaging 50 years. Once secondary progression has been reached, it becomes more difficult to make general statements about the prognosis. We do know that people who take longer to reach the SP phase also progress more slowly once in that phase.



Italian MS Society

A healthy lifestyle is recommended for any MS disease course.

Treatment

Disease-modifying drugs

We do not know if any drug can actually delay the onset of secondary progressive MS. This is, in part, because most clinical trials only last two to three years, while secondary progression can take decades to develop. Once secondary progression is reached, it seems to mark a change in the effectiveness of drug therapy.

Most of the currently licensed drugs for MS, the so-called disease modifying drugs, such as beta-interferon or glatiramer acetate, are not very effective in SPMS. If a person is still experiencing relapses these drugs can help reduce the risk of a future relapse, but they do not appear to have a long-term impact on disease progression, although this is under debate. The possible beneficial effect on reducing the number and intensity of relapses has to be balanced with the fact that during the SP phase, people tend to experience fewer and fewer relapses anyway. Thus the risk of treatment (that is, risk of side effects) might be greater than any expected benefits.

Other drugs, such as mitoxantrone (a drug also used to treat some types of cancer), might be suitable for some people with aggressive SPMS, but again, serious risks, such as cardiac side effects and leukemia, need to be considered.

Newer drugs, such as natalizumab, are not approved for use in SPMS and we do not know whether they are effective or not in SPMS. There are a number of other drugs currently in clinical trials designed to prevent disease progression in SPMS. These include an oral cannabis extract (dronabinol, in the UK); cyclophosphamide (France) and lamotrigine (UK). For more details and updates, see <http://www.nationalmssociety.org/research/clinical-trials/index.aspx>.

Symptomatic treatments

There are a number of effective drugs to manage the symptoms of MS, such as spasticity, bladder issues or pain. These drugs can be just as effective in SPMS as in RRMS. They do not affect disease progression, but they can alleviate troublesome symptoms and enhance quality of life.

On average, the RR phase lasts around two decades before SPMS begins. Some people reach the progressive phase much more quickly, and some never reach it at all.

Short courses of oral or intravenous corticosteroids are also available to accelerate recovery from a relapse if one does occur, but they do not affect the long-term outcome or overall disease progression.

Many non-pharmacological approaches can be helpful in SPMS, including the common sense approach of maintaining a healthy lifestyle, a balanced diet and regular exercise. *[For more information on alternative therapies, see: http://www.msif.org/en/about_ms/alternative.html]*

“It’s just a name”



Italian MS Society

People with MS can live in fear of the word ‘progression’. Being told they have SPMS can be just as big a shock as the initial diagnosis of MS was. They can feel they have a completely new disease, and it’s no longer treatable. It can feel like the end of the world for some.

But in reality, this is not the case. As a nurse, I reassure them that SPMS is just a name for one pattern of the disease – it doesn’t change the fact that their symptoms will still be treated and it doesn’t signal a sudden onset of disabling symptoms. They’ve still got the same disease, but perhaps very slowly changing.

Of course people need to know what type of MS they have, but we need to tell them in a way that’s not just clinical but takes account of their fears and concerns.

Nicki Ward-Abel, MS Nurse, UK

Extremes of MS: benign and aggressive forms

Lisa Costelloe, Department of Neurology, Beaumont Hospital, Dublin, Ireland



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Some people live with MS for many years without accumulating disability.

Whilst the majority of people with MS initially have the relapsing-remitting variant of the disease (see page 7) and go on to enter the secondary progressive phase (see page 13), a small proportion will have a milder-than-usual course, so-called benign MS, and another minority will have a more aggressive course from the outset.

Benign MS

Some people live with MS for many years without accumulating disability. This group has so-called benign MS, the reported frequency of which varies between 5% and 40% in studies. It is the mildest form of MS that is clinically apparent. People with benign MS have a minimal amount of physical disability after ten years or more of the disease.

Clinical predictors of a benign course vary but several studies have found that female gender, younger age at onset, and less disability early in the disease course, are more predictive of a benign course in the long term.

Abnormalities on conventional MRI do not necessarily correlate with disability and people with

benign MS may have a large number of lesions on MRI despite relatively minimal clinical features.

Early identification of benign MS would be important in deciding who should or should not take lifelong disease-modifying treatments. However, benign MS cannot be diagnosed at the onset of the disease but only becomes clear over time. Moreover, long-term follow-up has found that many people with benign MS do go on to develop progressive disease, and therefore labelling someone as having benign MS too early in the disease course may be misleading.

Malignant MS

This MS variant, previously referred to as Marburg's MS, was first described by Otto Marburg in 1906 and it is, thankfully, very rare. This is an aggressive form of MS that is characterised by rapid accumulation of disability and death within a few months to a year of the onset of symptoms. This type of MS is poorly responsive to standard MS treatment, although there are some reports of a response to mitoxantrone in individual cases.

Devic's disease, also known as Devic's syndrome or neuromyelitis optica (NMO), is a rare disorder that resembles MS in several ways.

As in MS, the body's immune system attacks the myelin surrounding nerve cells. Symptoms are similar to those seen in MS, although mainly associated with transverse myelitis and optic neuritis. Currently, there is no cure for Devic's disease, but symptoms can be treated and corticosteroids can be given.

Clinically isolated syndrome

Pierre Duquette and Joëlle Proulx-Therrien, Multiple Sclerosis Clinic, Centre hospitalier de l'Université de Montréal, Canada

A clinically isolated syndrome (CIS) can be defined as the heralding manifestation of MS.

The clinical diagnosis of MS requires identifying two relapses, separated in time and involving different areas of the central nervous system (CNS). With the advent of MRI of the brain and spinal cord, it is now possible to identify people at risk of developing MS as they show a CIS. Multiple studies have now made it possible to better define the risk of “converting” from a CIS to MS. There is evidence that initiating a disease-modifying treatment (DMT) at the CIS stage delays both conversion to MS and onset of the progressive phase.

Natural history

The clinical presentation of initial symptoms is highly variable. However, typically people with a CIS are young Caucasian adults (average age of onset being 30 years). In 46% of CIS cases, the lesion sits in the spinal cord, more frequently presenting with sensory than with motor signs. The optic nerve is the second most frequent site, as 21% of people with CIS have an acute optic neuritis. Multifocal symptoms (involving more than one site in the CNS) are encountered in 23% of cases. Others will have a lesion in the brainstem, or in the cerebral hemispheres. After a few weeks, these symptoms remit partially or completely.

The natural long-term history of people with CIS is now better known, through the observation of groups with CIS followed over periods of up to 20 years. Some demographic or early clinical variables are strong predictors of an individual's risk profile. Female gender, early age at onset, sensory symptoms only, and a complete recovery usually carry a good prognosis. Optic neuritis, as published recently by the Optic Neuritis Study Group, is associated with an overall 50% risk of developing MS 15 years after onset. On the other hand, cerebellar or multifocal symptoms and poor recovery are usually associated with a poor prognosis.



Optic neuritis can cause blurry vision, temporary blindness, and pain behind the eye.

Diagnosis

Since a CIS is a possible prelude to MS, it is of utmost importance to rule out other conditions. This is done through history, clinical examination, and blood testing (to exclude systemic and other autoimmune conditions). The two main tests are MRI of the brain and spinal cord, and examination of the cerebrospinal fluid (CSF). MRI will show inflammatory lesions with features compatible with demyelination in up to 90% of CIS cases. These lesions validate the clinical suspicion of MS and have an impact on the risk of conversion to RRMS and, subsequently, to SPMS. One study of 107 people concluded that 80% of people with CIS with an abnormal MRI, and 20% with a normal MRI, will develop clinically confirmed MS after an average of 20 years. A higher number of lesions carries a higher risk of converting to MS and of an earlier phase of secondary progression.

CSF testing is commonly used to support a clinically defined MS (CDMS) diagnosis, mainly through the detection of oligoclonal bands (OBs). These bands are not specific to MS, but occur in over 95 per cent of people with CDMS. They are found in two thirds of those with CIS. In a trial of 52 people with CIS, their detection was associated with a sensitivity of 91 per cent and a specificity of 94 per cent for the risk of converting to CDMS. (Sensitivity measures the proportion of people correctly identified as having the condition and specificity the proportion correctly identified as not having it). About 70 per cent of people with CIS with more than two OBs will eventually evolve to MS, independently from the presence of MRI lesions. In some countries, lumbar punctures are done less commonly in establishing a diagnosis of CDMS and rarely for CIS.

Treatment

Steroids, usually high doses of IV methylprednisolone, are used to treat acute exacerbations that cause new symptoms or worsen existing symptoms.

Identifying those who have high risk CIS and initiating early disease-modifying therapy is of major importance.

Multiple clinical trials with interferon beta preparations have established their effectiveness in reducing the frequency of relapses and delaying the progression of the disease. Interferon beta has anti-inflammatory properties and is able to improve the integrity of the blood-brain barrier. The placebo arm of these trials (the subjects in a study who are not on the active treatment) also established that the longer the treatment is delayed, the higher the risk of disability progression. Three clinical trials have shown that interferon beta can reduce the risk of a second episode by 50% over two years. In fact, 40% of untreated people with CIS will evolve to CDMS within two years. If therapy is initiated two years after the CIS, the risk for CDMS is higher when compared to patients who received early treatment (49% for those with delayed treatment versus 36% for those treated early, after five years). Identifying those who have high risk CIS and initiating early disease-modifying therapy is then of major importance.

Similar results, in people with CIS and MS, have been achieved with glatiramer acetate, a synthetic form of a myelin protein which induces a suppressive response against lymphocytes reactive to CNS antigens.

Natalizumab, a humanised monoclonal antibody which prevents the infiltration of activated lymphocytes through the blood-brain barrier into the CNS, has not been tried in people with CIS.

In conclusion, CIS is now recognised as an initial manifestation of MS. People with CIS who have inflammatory lesions on MRI of the brain or spinal cord, coupled with OB in the CSF, are at a high risk of early conversion to clinically definite MS, possibly also to an earlier phase of secondary progression. Treating these people with an interferon beta or with glatiramer acetate delays these events.

Your questions answered

The Editor, Michele Messmer Uccelli, answers your questions about MS disease courses.

Q. I am a 36-year-old male from Poland and was diagnosed with MS in 1999. I only learned recently that my MS is secondary progressive. Why didn't my doctors in Poland tell me anything about this then? I experience no relapses or improvements at all. In this type of MS, will my symptoms just continue to get worse? Are there any medical trials for this? How do I cope with this and a young, dependent family?

A. Secondary progressive MS is called "secondary" because it follows an initially relapsing-remitting course. If your physician says that you are currently in the secondary progressive phase of the disease, it probably means that you passed through a RR phase without knowing it, perhaps as a teenager or very young adult.

The speed of progression in secondary MS and the particular symptoms that occur, vary significantly from one person to another. This means that some people with SPMS will experience more disability than others. Your national MS society can provide information about how to manage your disease, and about medications that are currently being tested or are in use for progressive MS. They can also tell you what support may be available for your family.

Q. I was diagnosed with CIS and started on interferon beta and haven't had a second attack for two years. Do I have to take interferon for ever?

A. The purpose of interferon for CIS is to prevent conversion to clinically definite MS, so continuing to take interferon decreases this chance. We do not know yet from research how long people with CIS will need to continue treatment.

World MS Day 2009

MS societies in 67 countries held events and activities to mark the first ever World MS Day on 27 May 2009.

Big names from film, sport and music helped promote the global movement and MSIF launched a short film, available in ten languages. Watch it online at www.worldmsday.org

Mountaineer Lori Schneider, who herself has MS, planted a flag on Mount Everest.

Lori said, "It was an amazing feeling to go step by step up Mount Everest with the World MS Day flag in my pack.

"Each step was hard. It gave me a whole new feeling for people with MS who may have a hard time walking across a room. I encourage them not to give up hope and to keep following their dreams!"



Disease courses of MS: survey results

1746 people completed the survey on disease courses of MS – the biggest response for any MSIF online survey to date.

Respondents ranged from people newly diagnosed with MS to those who have been living with MS for 40 years or more (the longest was 54 years). The average length of time since diagnosis was 10.5 years. A small number were awaiting diagnosis.

MS 'types'

Three-fifths (60.6%) of respondents had relapsing-remitting MS. One-fifth (21.6%) had secondary progressive MS, and a tenth (10.7%) primary progressive. Just 3.6% had clinically isolated syndrome.

"My neurologist says I still have RRMS but I wonder if I now have SPMS, as I don't have dramatic attacks, I'm just getting slowly worse."

"It seems that the professionals are more focussed on the label than the patient."

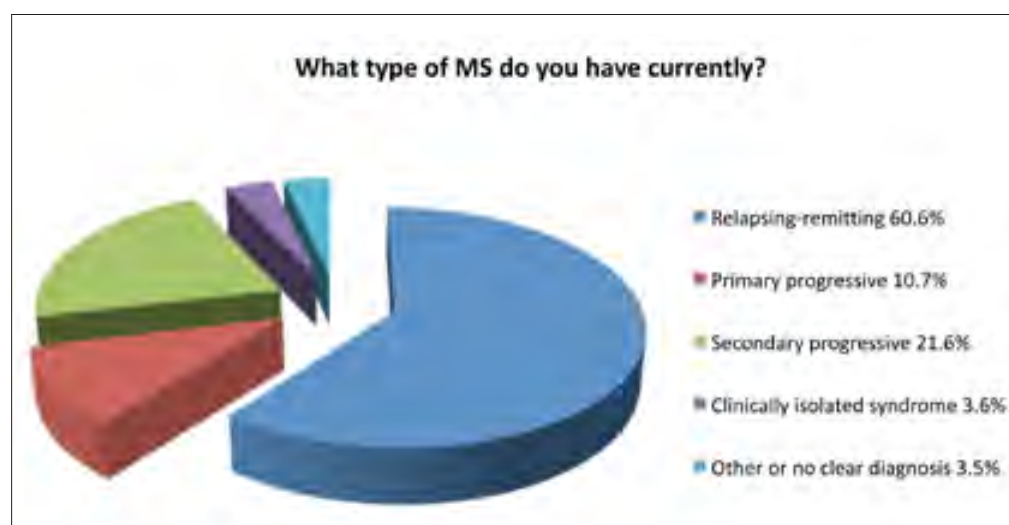
Among those with the less common forms of MS, there is a strong feeling that they get less attention and support than the RR majority.

"Most information/treatment/studies are on relapsing-remitting – people with PPMS are the 'poor relations'"

Finding information

Over four-fifths of respondents found it "fairly easy" or "very easy" to find information about their disease course. Many noted that finding information is much easier now than in the past, thanks to the internet and the growth of MS societies and local groups.

People use a range of different information sources, with most respondents using more than one. MS societies are the most used source, closely followed by health professionals. The internet is





"I'm living in Vietnam, where MS cases are very rare... I'm lucky I can use English to search for information about this disease, while many others in this country cannot."

"More info is not better, it just adds to the confusion. I want the doctors to spend more time with me at

widely used, though some respondents mentioned downsides of online research: information overload and difficulty in judging the quality of information found.

Respondents' confidence in their physicians varied widely, with some having a very high opinion of their family doctors or neurologists, while others find them uninformed or uninterested.

"There are so many websites and support groups available now. This wasn't the case when I first had MS."

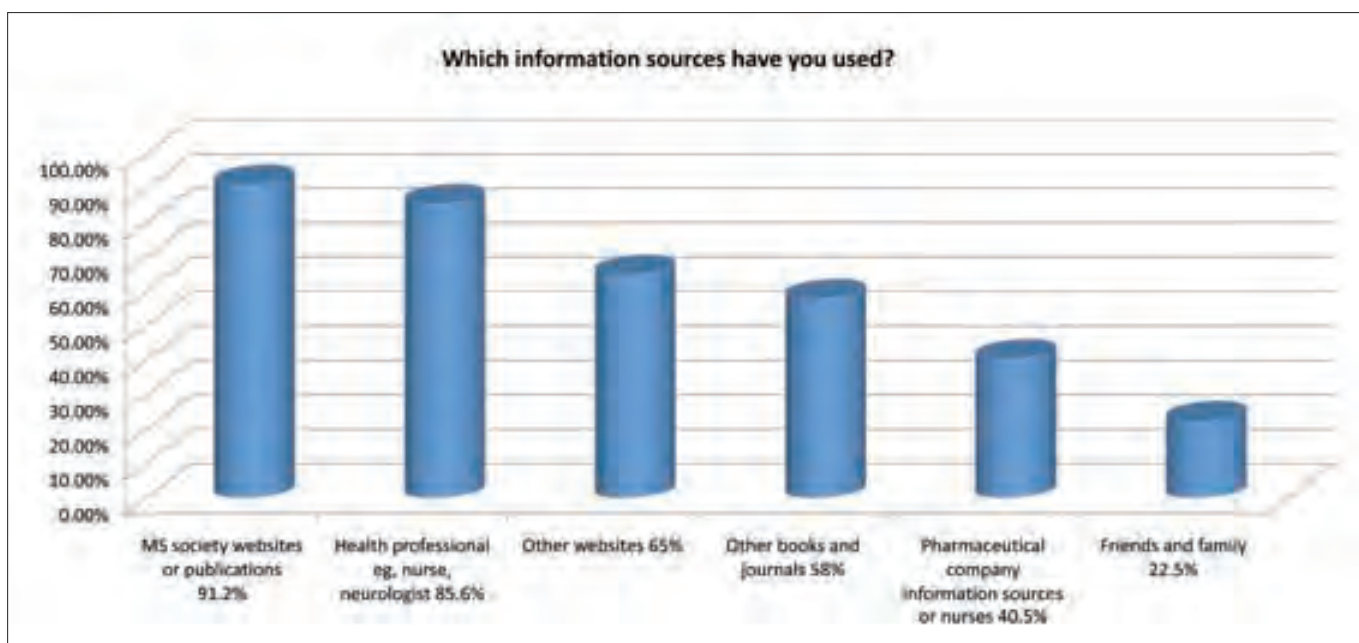
"There is so much info – it can get somewhat overwhelming."

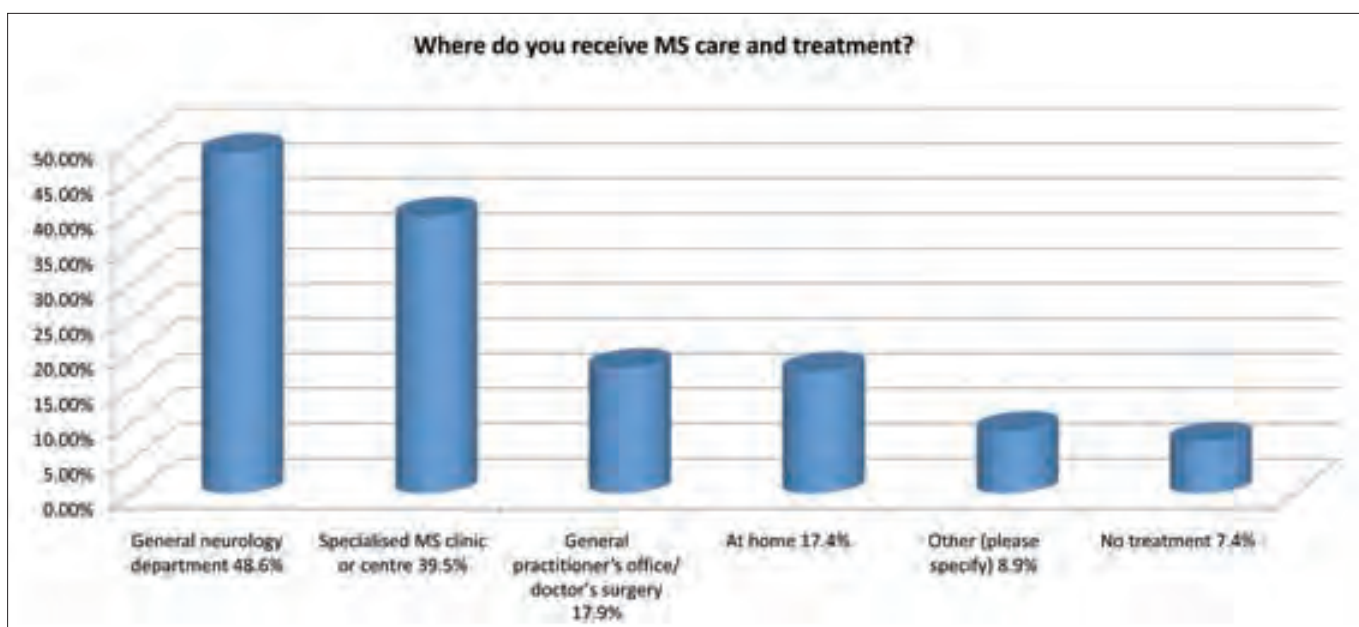
appointments – not tell me where to look things up."

Access to treatment

While the majority of respondents receive treatment from a neurologist or general practitioner, a substantial minority use alternative therapies, either exclusively or alongside conventional treatments. Over 7% were not receiving treatment, citing a variety of reasons, including affordability/lack of insurance cover, failure of their doctors to inform them about available treatments, and mistrust of the treatments available.

Those with PPSS were vocal in their frustration that there are no treatments available.





"I don't visit any medical practitioner as I feel there is nothing they can really do."

While over half felt well informed about treatment options available to them, over a third would like to know more, particularly about complementary therapies and new drugs currently undergoing trial.

There were striking divisions in people's confidence in the information provided by their doctors, with several commenting that they had to research treatments themselves and request them from their family doctor.

Some respondents expressed a concern that the information available about drug treatments is one-sided, with little independent information to balance

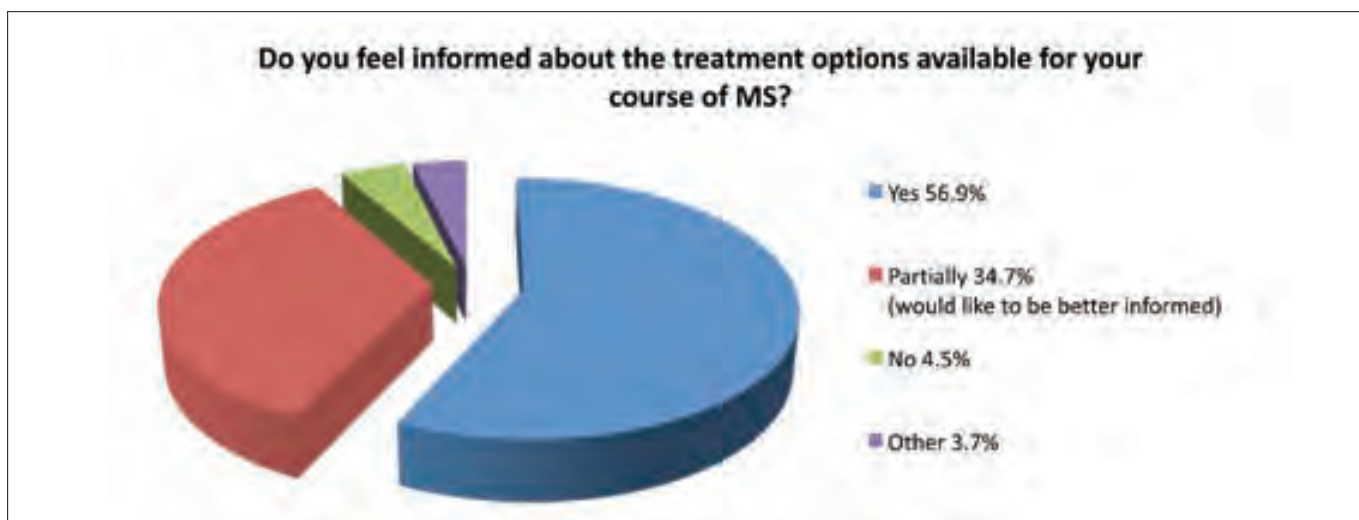
the promotional material provided by the drug companies.

"I've had to research treatments then ask if I can have them."

"Not enough info on alternative treatments, especially for secondary progressive."

"I am avoiding intramuscular injections due to the cost, side effects, and seemingly fishy monopoly of the drug companies."

"I believe there needs to be more availability and information of the interlacing of medicine and alternative medicine. "



Support for the newly diagnosed

When first diagnosed with MS, people need information, support and time to learn about their disease and how to live well with it. Two national MS societies describe special programmes they offer to the newly diagnosed.

'Expert talks' in Austria

Sandra Lakitsch, MS Society of Vienna

Being diagnosed with MS means uncertainty, fear and confusion for most people. At this critical stage, people need expert information on personal, social and psychological questions, tailored to their individual needs. The medical routine at many healthcare institutions does not always leave time for this.

To help and support people newly diagnosed with MS, the MS Society of Vienna (Multiple Sklerose Gesellschaft Wien) launched a programme of 'expert talks' in 2007.

Ursula Hensel, managing director, explains: "Newly diagnosed people have different needs than those who have lived with the disease for several years. For this reason we run our expert talks about four times a year. Each time, we welcome newly diagnosed people and their relatives, who get the chance to ask all their questions directly to a neurologist, a psychologist or psychotherapist, and a social worker.

"As the group is small – ten people at the most – there is no time pressure and the atmosphere is relaxed and informal. People get all their questions

answered and are encouraged to address their individual issues. Some express their thoughts and feelings freely."

As well as the discussion, a psychologist explains common psychological problems that are often caused by the diagnosis.

This informal forum also serves as a platform to meet people who are in a similar situation.

"After the initial shock of my diagnosis had passed, I had so many questions I needed answers to," said one recent participant. "The biggest benefit, apart from the truly informative opening medical lecture, was realising that I was not alone. I saw that there are other people with the same disease and similar problems – and institutions that provide support and can point me in the right direction if my road ever gets bumpy, or if I feel anxious and depressed. It came as such a relief at just the right time."

Ursula Hensel says, "We are very happy with the success of the expert talks initiative and plan to make it even better. We will introduce a follow-up meeting one year after the initial session, to offer another opportunity to ask questions that might have come up in the meantime."

'Learn About MS' in Australia

Andrea Salmon, Education Programme Coordinator, MS Australia – ACT/NSW/VIC

Margo, 23, was diagnosed with MS after many months of investigations. The next day, she contacted MS Australia and registered to attend an education programme. Brian was diagnosed 25 years ago.

He contacted MS Australia recently about a physiotherapy assessment and to learn more about MS. Grace, 32, wanted her husband to understand her fatigue and other symptoms better.

All three recently attended a Learn About MS session, run by MS Australia.

These sessions are run regularly in the Australian Capital Territory, New South Wales and Victoria. Their purpose is to help people with MS and their families and friends to live well with MS by providing up to date information, enabling informed choices, and promoting self-management skills.

While the programme is targeted at the newly diagnosed, it also attracts people who have been diagnosed for some time and have decided they want to find out more about their condition.

Learn About MS is offered as a full day session, held at a weekend in order to be accessible to people in the workforce. Family members and friends are welcome to attend along with those with MS.

Topics covered include:

- a medical and research update

- strategies for symptom management
- a presentation from an 'MS Ambassador' (a person with MS sharing their story)
- tips and strategies for staying active with MS

Participants also learn about MS Australia services in each state and connect with other people living with MS. Feedback from participants consistently identifies the enormous value of realising that they are not alone as they face the challenges of MS.

Offering education programs in a way that is appealing and in a variety of formats is a constant challenge in this era of rapidly advancing technology. Components of the Learn About MS programme are also offered via teleconference and plans are in place for webcasts to be made available too.

Accessibility, fatigue and cost of travel are all factors that may restrict people's ability to attend. Language and cultural issues may be another barrier to participation, and some people find the experience of a face-to-face group too challenging.

Yet those who attend appreciate the chance to hear accurate information about their condition presented in a supportive and positive manner.



Italian MS Society

Meeting others newly diagnosed with MS is a great source of strength: young people with MS in Italy.



Nicki Ward Abel

Interview: James West

Public relations consultant James West from Birmingham, UK, is 33 and has lived with MS for ten years. He talks to MS Nurse Nicki Ward-Abel about his experience.

Q: Tell us about your diagnosis – what were the first symptoms you noticed?

The first thing was a loss of sensation – when I stepped on a metal strip in my bathroom doorway, I could feel it with my right foot but not the left.

A: I played a lot of football and after playing my legs would spasm. After that I got a lot of tightness in my stomach. I thought I had appendicitis and went to hospital. They sent me to a neurologist, who diagnosed MS.

It was very hard to come to terms with aged 23. It might have been easier if it had been a disease with a more understood prognosis. But the neurologist basically said: "There's nothing we can do."

Q: In the first five years, how did it affect you?

A: Apart from odd symptoms that came and went, I felt absolutely fine. I had optic neuritis, my eyes were blurry sometimes. But I could still walk and even run and play football. I'd have a relapse every nine

months, regular as clockwork. They were treated with steroids and after each one I would recover almost 99%.

Q: And has it changed since then?

A: In my late 20s, I began to get more symptoms. I went from walking perfectly to limping a little to dragging my left foot. Then that transferred to my right leg and I get stiffness in my legs. I am still having relapses but in between I have started to progress, albeit slowly.

My neurologist hasn't said I have SPMS in concrete terms, but I feel like that's where I am now. But I'm still having relapses, so it's a grey area.

Q: What disease-modifying treatments have you had, and how have you found them?

A: I decided to go for Avonex initially because it was a once-a-week injection, which fits with my lifestyle. I had that for nearly three years and was tolerating it well. I still had relapses every nine months but they weren't as bad and I recovered quicker.

Then I had a new neurologist, who suggested I go onto Rebif, as I was experiencing disabling relapses despite being on Avonex. This meant an injection three times a week. Initially it seemed to be working well but within three months I was getting really nasty flu-like symptoms and I became very depressed and irritable. On my honeymoon I felt so aggressive and unpredictable, I decided to come off it and the change was almost immediate.

I had three months with no disease-modifying drugs and went back to being myself. But after the initial high, I realised I was feeling seriously ill and the outlook wasn't good. My legs were very stiff, I had problems transferring from leg to leg. I was having really bad bladder problems, the fatigue was bad, and I felt I would need a wheelchair really soon. I also had another relapse at this time.

I was offered a drug called Mitoxantrone – it's a chemotherapy drug, used to treat breast cancer, and is really toxic. Potential side effects include leukaemia, heart failure and infertility. The long term

effects aren't really known, but in the short term it can stop MS progressing. I thought it over for some months with my wife and my family and decided to go for it.

Q: How did you make the decision?

A: I weighed it up and in the end, it wasn't a hard decision. I'd like to keep mobile for as long as I can because I enjoy life and there's more I want to do. If I die of heart failure, I die of heart failure; it's worth it to try to prolong my mobility for a few years.

Q: And have you done well on the treatment?

A: The first time I took it my white blood cell count dropped and I was in hospital for ten days.

But now I feel healthy. It hasn't greatly affected my disability – I walk with a stick and I still have bladder problems – but it has plateau'd. And it's completely reversed my fatigue. I feel confident doing anything now. I've put in a request to increase my hours at work, which I had reduced because of the MS. It has really given my energy a boost and I'd like to keep taking it as long as possible.

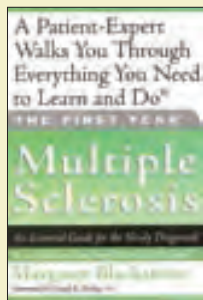
I'd like to keep mobile for as long as I can because I enjoy life and there's more I want to do.

Q: What aspects of living with MS do you find hardest to manage?

A: My walking is bad for a man my age, although it has improved since I've had the chemotherapy. And managing stiffness in my legs is one of the hardest things on a day-to-day level because there's nothing I have found that takes that away. And my bladder continues to be a problem.

But perhaps the hardest thing is psychological: knowing that you live with a condition that could in the long term make you very ill, which is at the moment incurable and for which treatments are quite limited when you get into SP stage. Having MS can feel like an indefinite prison sentence and it's really difficult to come to terms with that.

Reviews



The First Year: Multiple Sclerosis
By Margaret Blackstone. Published by Marlowe and Company, 2007.
ISBN -13 978-1-56924-261-2, ISBN -10 1-56924-261-5

Being diagnosed with MS is often traumatic, and seldom well handled by the medical profession, whether general practitioner or neurologist. This book aims to reassure and inform the newly diagnosed. The author, who has MS herself, is an experienced medical writer, and writes with an easy informal style.

The book is structured on a week-by-week basis, and gives what the author believes is the key information for that part of the patient experience. Whilst this implicitly assumes the book is acquired at time of diagnosis, a decent index means this is not insurmountable. Most of the basic information is here and very firmly targeted at a non-expert audience. Note that the book is written with a US reader in mind. Details of medical insurance structures and references to the legal protections that people with MS enjoy are specifically American.

The book will appeal to those who like anecdotes, which it uses widely to illustrate the points being made. It sits somewhere between the 'self-help' genre and a more medically-orientated patient guide. Whilst there is much useful information, there are a couple of weaknesses with the book.

First, it could usefully incorporate more data and diagrams. There are no stylised illustrations, for example, of neurons or the role that myelin plays in the nerve fibre – and no tables reporting on or comparing the (clinically evidenced) efficacy of the various disease modifying treatments.

Second, it feels a bit partial. For example, there is no reference to cannabis, which many people with MS use to manage symptoms, and which most newly diagnosed people will hear about. A simple pros and cons section would have been useful without necessarily advocating law-breaking.

Finally, it can be irritatingly platitudinous at times. Take this from the Preface, "...the point is to let MS change you and in the process to make sure you let it change you for the better, which it will if you try and if you let it." The next edition should exorcise this type of drivel.

Reviewed by Ian Douglas, Treasurer, UK MS Society
Reviewers write in a personal capacity



ms.about.com

ms.about.com is part of the New York Times company's portal, about.com.

The plain language used throughout the site makes it easy to understand for non-professionals. The clear descriptions of MS, its symptoms and related matters put the reader in the picture quickly and effectively. A glossary of terms is provided but rarely required.

This site can greatly help newly-diagnosed people with MS who need straightforward, uncomplicated answers to their questions on medical and sensitive issues. Health professionals may be interested in a more scientific approach to the same issues.

The information is presented by Julie Stachowiak, PhD, who herself has MS. This gains the reader's trust and makes the site feel like talking to a peer.

Most content is related to MS diagnostics, therapy, symptoms (including often overlooked ones), alternative treatment, and issues for families and friends. The site is easy to navigate, and information easy to find. You can view most topics as text only with one click. There are short videos about the effects of MS and about diet.

All articles are accessible for free. However, visually impaired people may want to read the text in larger type – a facility not offered on this site.

You will find the website interactive. As well as offering information to read, it encourages visitors to leave comments and discuss some issues.

Information sources like this sometimes offer non-conventional therapies for MS, and care is needed in their use. The links to such treatments are few here and the site warns if they are not approved for use.

English is not my first language, yet I found the website content easy to follow and enjoyable to read.

Reviewed by Pavel Zlobin, Vice President, All-Russian MS Society

Glossary

Antibodies – molecules made by the immune system, which stick to antigens and signal that they must be destroyed.

Antigens – molecules that trigger an immune response.

Ataxia – uncoordinated movements, caused by damage to nerves, not by muscle weakness.

Atrophy – shrinkage of tissue. In MS, damage to the brain causes it to shrink or atrophy. Muscles also atrophy, due to lack of use.

Axons are the long extensions of nerve cells that transmit nerve signals.

Biomarkers – measurable characteristics that indicate normal biologic processes, processes that cause disease, or pharmacologic responses to therapy.

Central nervous system (CNS) – the collective name for the brain and spinal cord.

Cerebrospinal fluid (CSF) – the fluid that surrounds CNS and fills the cavities inside. A sample of CSF is often used in helping to confirm a diagnosis of MS.

Cognition – any mental process involved in gaining knowledge and comprehension, including perception, attention, learning, memory, thought, concept formation, reading, problem solving.

Corticosteroids – hormones produced by the adrenal gland in times of stress. They are effective in reducing inflammation. Synthetic versions of corticosteroids are used to treat relapses in MS.

Demyelination – the destruction, loss or removal of the myelin sheath from a nerve fibre (axon).

Glatiramer acetate – an artificial protein resembling a natural myelin protein used for reducing the number and severity of relapses.

Grey matter – the areas in the brain and spinal cord where nerves do not have a myelin sheath. These areas are darker in colour.

Immunoglobulin G (IgG) antibodies –

Immunoglobulins are the proteins that form antibodies. They are being researched as a treatment for MS.

Immunosuppression – reducing the activity of the immune system.

Interferon beta – Interferons are a group of molecules in the immune system. Interferon beta reduces inflammation. It has been licensed to treat people with RRMS and some people with SPMS (if they continue to have relapses).

Lesions – patches in the CNS where inflammation has resulted in the loss of myelin. Some lesions repair themselves and disappear; others become permanent areas of visible scarring.

Lumbar puncture – a procedure used to collect a sample of CSF. This fluid is analysed to aid MS diagnosis.

Magnetic resonance imaging (MRI) – using radio waves and magnetic fields to produce a 3D image of soft tissues in the body. MRI can be used to detect the presence of lesions in a person with MS.

McDonald criteria – criteria used to diagnose MS in people who present with symptoms suggestive of the disease. The McDonald criteria use MRI evidence.

Monoclonal antibody – a highly specific, laboratory-produced antibody that can locate and bind to specific targets wherever they are in the body.

Myelin – made by oligodendrocytes. These cells wrap themselves around nerve axons to form a protective myelin sheath, which increases the speed at which nerve signals travel. In MS, myelin is vulnerable to attack from the immune system.

Oligoclonal bands (OBs) – bands of immunoglobulin. If present in CSF they indicate the presence of disease. Oligoclonal bands are an important indicator in the diagnosis of MS, although a small percentage of people with MS do not have OBs in the CSF.

Oligodendrocytes – cells in the brain and spinal cord that form myelin.

Remyelination – the replacement of lost or damaged myelin. In MS, the body's failure to repair myelin is the cause of increasing levels of disability. Finding ways to encourage remyelination is therefore a major goal for MS research.

MS *in focus*



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MSIF is a charity and company limited by guarantee, registered in England and Wales. Company No: 5088553. Registered Charity No: 1105321.

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- Issue 6 Intimacy and sexuality
- Issue 7 Rehabilitation
- Issue 8 Genetics and hereditary aspects of MS
- Issue 9 Caregiving and MS
- Issue 10 Pain and MS
- Issue 11 Stem cells and regeneration in MS
- Issue 13 Tremor and ataxia in MS

With many thanks

MSIF would like to thank Merck Serono for their generous unrestricted grant, which makes the production of **MS in focus** possible.



Merck Serono, a division of Merck KGaA, are specialists in innovative prescription pharmaceuticals with products available in over 150 countries worldwide. We have been active in the fight against MS for over a decade. Through pharmacogenomics, we

are active in research towards understanding the genetic basis of MS. Merck Serono has a long-term commitment to people with MS through constant research and discovery efforts as we look for new therapies and hopefully, one day, a cure.