

Late-onset multiple sclerosis part one: clinical features

Multiple sclerosis (MS) is a chronic autoimmune disorder that affects movement, sensation and bodily functions. It is not as rare a disease among people over the age of 50 as previously believed and may present a diagnostic challenge because of the variability in its presentation. In part one of a two-part series, **Dr Nabil Aly** discusses the clinical features of MS in older people.

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Multiple sclerosis (MS) is the most common chronic disabling disease of the central nervous system (CNS) in young adults. Late-onset MS (LOMS) with clinical onset after 50 years old is unusual and frequently misdiagnosed¹. Clinical presentation and course also seem to be different than those between 20 and 50 years old¹. It is primarily characterised by multicentric inflammation and demyelination, but the role of axonal injury and gliosis increases as the disease evolves². Since 1993, two drugs — interferon beta and glatiramer acetate — have been identified as disease-modifying treatments^{3,4,5,6,7}.

Aetiology

A chronic autoimmune disorder, MS affects movement, sensation and bodily functions. It is caused by destruction of the myelin sheath of CNS nerve fibres (brain and spinal cord), but has no demyelination of the peripheral nerves. When the myelin is destroyed, nerve messages are sent more slowly and less efficiently. Scar tissue then forms over the affected areas, disrupting nerve communication. The distinction between MS and other benign or fulminant inflammatory demyelinating disorders is based on the number of, rather than quality of, differences in chronicity and severity⁸.

Epidemiology

MS affects approximately 85,000 people in the UK and about one in 1,000 in Western countries⁹. Most have their first symptoms between the ages of 20 and 40, yet LOMS is not as rare as previously thought; studies indicate the prevalence ranges between four per cent and 9.6 per cent¹⁰. Women are almost twice as likely to get MS as men, and people of northern European heritage are more likely to be affected than other racial backgrounds; MS rates are higher in the US, Canada, and Northern Europe than in other parts of the world. In Scotland, MS was assessed in a group of 1,055 patients, representing an unselected (epidemiological) sample observed in the north-east (Grampian) region for a period ranging between one and 60 years¹¹. In seven per cent the disease began before the age of 20 years, in 12 per cent after the age of 50, and in the remainder onset was between the ages of 20 and 50 years. The male/female ratio was 1:1.8. Mean disease duration in those observed until death (216 patients) was 24.5 years with no significant difference between the sexes¹¹.

Clinical features

MS is an extremely variable disease and its symptoms are determined by the combined effects

Table 1. Clinical features of MS according to the location of the lesion

Lesion Location	Signs/ Symptoms
Cerebrum and Cerebellum	Balance problems, speech problems, co-ordination, tremors
Motor nerve tracts	Muscle weakness, spasticity, paralysis, vision problems, bladder, bowel problems
Sensory nerve tract	Altered sensation, numbness, prickling, burning sensation

of which CNS areas have been demyelinated and how much neural tissue has been destroyed (*see Table 1*). There is no typical pattern for its course, every patient has an unique set of symptoms. Most will experience more than one symptom and though there are symptoms common to many, no one ever has every one of them. Not all symptoms affect all MS patients and no two persons would have the same complaints. Symptoms may be persistent or may cease from time to time.

However, most patients have episodic patterns of attacks and remissions. Symptoms may remit completely, leaving no residual damage or only degrees of partial permanent impairment. In most patients the disease begins with acute episodes of neurologic dysfunction, followed by periods of partial or complete remission with clinical stability between relapses – the relapsing/remitting phase. This phase is usually followed by progressive clinical disability, with or without superimposed relapses and remissions^{13,14}. In a minority of patients, the disease is progressive from the beginning, although there may be superimposed relapses and remissions. Therefore, neurologic disability may result from relapses with incomplete remissions, progression of the disease, or both.

Common symptoms (*Table 2*) include:

> *Fatigue*: the most common complaint of MS patients is fatigue. It occurs in as many as 78 per cent of patients, usually in the late afternoon and often subsides in the early evening.

> *Numbness, tingling, burning sensations*: sensory complaints occur in up to 55 per cent of patients and are often the earliest symptoms of MS, with disturbances in the extremities or the trunk such as tingling, crawling sensations, feelings of swelling or

numbness. The duration of numbness depends upon its cause. If severe neurological damage to the myelin sheath takes place, then the numbness may remain.

> *Tremors*: up to 50 per cent report extremity ataxia (shaky movements or unsteady gait) or tremors.

It impairs mobility and is often associated with difficulty in balance and co-ordination.

> *Balance and co-ordination*: gait and balance disturbances are common. Balance problems without vertigo may be more constant, causing the person to sway or stagger.

> *Spasticity*: occurs with the initial attack in up to 41 per cent of patients and is present in about 62 per cent with progressive disease.

> *Bladder and bowel*: increased frequency of urination, urgency, dribbling, hesitancy and incontinence may occur. Bowel dysfunction occurs in almost two-thirds of patients.

> *Visual disturbances and loss*: blurred, double vision or diplopia, optic neuritis, involuntary rapid eye movement (nystagmus, oscillopsia), partial blindness (scotoma) and – very rarely – complete blindness may occur. Visual loss rarely involves both eyes simultaneously. It usually starts with blurred vision followed by vision loss from 20/20 to 20/30 to 20/40. Uhthoff's symptom (temporary visual loss with exercise or an increase in body temperature) is a result of a reversible conduction block in a demyelinated optic nerve and is an indication of optic neuritis. Optic neuritis can be the presenting sign of MS after the age of 50¹⁵.

> *Cognitive and emotional dysfunction*: affecting approximately 50 per cent of patients, it involves memory, reasoning, verbal fluency and speed of information processing. Emotional changes may include euphoria and/or depression.

> *Heat sensitivity*: this causes a temporary worsening of symptoms and may lead to blurred vision (Uhthoff's syndrome). Body functions normalise when the body cools off and the neuron can safely resume transmitting nerve impulse. Without its myelin coating, all CNS tissue is more sensitive to heat and prone to quit transmitting electrical signals when the body's core temperature is increased by just 0.5°C.

> *Pain*: experienced in about 50–60 per cent of MS patients; it may include facial pain (trigeminal neuralgia or tic douloureux, lightning-like acute facial pain caused by demyelination of trigeminal nerve sensory root), Lehermitte's sign (an electrical sensation when flexing the neck by lowering the head towards the chest, beginning at the base of the skull and running down the spine and into the limbs), headaches, and spasticity with muscle cramps and spasms.

> *Speech dysfunctions*: slowing of speech, slurring words, scanning speech, changes in speech rhythm

(dysarthria) and difficulty swallowing (dysphagia).

> *Weakness*: a result of the combined effects of hypotonia, ataxia and fatigue, it mainly affects the legs and quickly makes walking – or any sustained activity – extremely exhausting.

Types and stages

Although every individual will experience a different combination of MS symptoms, there are a number of distinct disease stages and/or types that have been identified and recognised (*Table 2*).

Benign MS

The mildest clinically apparent form has been labelled 'benign' MS. This concept is widely quoted by neurologists when helping patients to come to terms with their diagnosis¹⁶. The ability to predict the subsequent clinical course – based on the initial presentation and early disability – would be invaluable, adding considerably to the accuracy and quality of prognostic information provided for patients and leading to the most appropriate selection of patients for therapeutic interventions¹⁶. The lack of agreement as to what constitutes benign disease has contributed to the widely varying estimates as to its prevalence (five per cent to 40 per cent)¹⁶. In general, it affects about 20 per cent and is associated with non-visible sensory symptoms at onset. There are no motor symptoms and a totally complete recovery with no disability is usually the outcome. Some patients will find the course of disease will evolve into the progressive stages of MS within 10–15 years of its official onset.

Relapsing/remitting MS

There are sporadic attacks (exacerbations, relapses), during which new symptoms appear and/or existing ones become more severe. They can last for varying periods (days or months) and there is partial or total recovery and remission. MS may be clinically inactive (sub-clinical) for months – or years – between any number of intermittent attacks. The disease process is ongoing and damage continues with or without clinical attacks. Microscopic lesions and diffuse damage (axonal loss) silently proceed. It is the most common beginning phase, occurring in about 25 per cent of patients. However, 50 per cent of those will have progression within 10–15 years, and an additional 40 per cent within 25 years of onset as the disease evolves into the secondary progressive phase¹⁷.

Table 2. Main clinical types of MS

Benign MS

In about 20 per cent
Sensory problems at onset, but complete recovery and without any permanent disability
Some may evolve later (>10y) into progressive type

Secondary-Progressive MS (SP MS)

In about 40 per cent
Relapsing MS evolving into the progressive stage, so less complete remissions with cumulative damage
LP usually positive

Relapsing-Remitting MS

In about 25 per cent
Sporadic exacerbations/relapses with partial/total recovery or remission
50 per cent of cases will have progression within 10–15 years
LP usually negative unless recent exacerbation

Primary-Progressive MS (PP MS)

In about 12 per cent
Slow steady onset
Worsening motor deficit with increased disability
LP usually positive

LP: lumbar puncture

Secondary progressive MS (SP MS)

Individuals who initially had relapsing MS, will find over time the disease pattern changes, evolving into the progressive stage. Recovery from attacks become less and less complete, slowly deficits increase and disability grows. Clinical attacks become less pronounced and remissions tend to disappear, but more CNS tissue has now been destroyed. This cumulative damage is seen on magnetic resonance imaging (MRI) as enlarged ventricles, which is a definitive progression marker for increased atrophy of the corpus callosum, midline centres and spinal cord. Its prevalence is about 40 per cent.

Primary progressive MS (PP MS)

This form is characterised by a slow steady onset, usually beginning with walking difficulties, steadily worsening motor dysfunction and increased disability, but with a total lack of distinct inflammatory attacks. Fewer and smaller cerebral lesions, diffuse spinal cord damage and axonal loss are the hallmarks of this form of MS. Approximately 10–12 per cent of patients have primary progressive MS. They tend to be older at onset (40–60 years of age) and commonly have a progressive myelopathy. These patients usually have fewer gadolinium-enhanced lesions on cranial MRI scans and fewer inflammatory changes in

cerebro-spinal fluid than patients with secondary progressive MS¹⁸. There is continuous progression of deficits and disabilities, which may quickly level off or continue over many months and years.

Progressive relapsing MS

This subtype of progressive MS is more complex. Although its overall course mirrors PP MS in terms of disability, it differs. It includes periods of acute exacerbation (inflammatory phase) that look like relapsing MS (having gadolinium-enhancing T1 lesions) either early on or after many years have elapsed, but lost functions never return. Progressive-relapsing sub-type, seen in about three per cent of patients, is the most dreaded form of MS (known as Marburg MS). It needs protracted steroid therapy and has a high mortality rate.

Diagnoses and clinical evaluation

MS can present with classic symptoms (eg, retrobulbar neuritis, paraparesis) and a medically documented chronology of attacks. However, it often begins with a history of fluctuating vague or non-specific symptoms that family and friends dismiss or discount; resolving without treatment, the symptoms continue to return. Many of its signs could be attributed to a number of medical conditions and as there is neither a sign nor a test that proves MS, some time may elapse with a prolonged diagnostic procedural requirement before MS is confirmed or even mentioned.

Since LOMS is infrequent it presents a diagnostic challenge¹⁹. The initial symptoms may be transitory, vague and confusing. Invisible and/or subjective symptoms are often difficult to communicate to physicians, who may dismiss people as just being anxious. Various diagnostic criteria were developed in order to help the diagnosis. The Poser Criteria²⁰ (Table 3) requires clinical evidence that the neurological deficits involve at least two different areas (functional systems) of the CNS, with documented neurological signs occurring at two separate and distinct time periods while all other possible neurologic causes must have been eliminated.

The revised diagnostic criteria were developed by the International Panel in 2001 and have been proven to compare favourably to – or to be an improvement upon – prior MS diagnostic criteria²¹. The focus was on the objective demonstration of the dissemination of lesions in both time and space,

Table 3. Clinical features of MS according to the location of the lesion

Lesion Location (No MRI nor VEPs criteria)	International Panel Criteria** (IP or McDonald criteria)
A diagnosis of MS may be established with classic symptoms and a medically documented chronology of attacks:	1. Definite MS on clinical grounds: DIS: two or more lesions DIT: two or more attacks
1. Clinical evidence (neurological deficits) indicating the involvement of at least two different CNS areas (functional systems), <i>with</i>	2. Localised disease DIS: one lesion, need MRI to prove DIS, or MRI finding and positive CSF finding; or further clinical attack at a different location.
2. Documented neurological signs occurring at two separate and distinct time periods; <i>and</i>	3. Multi-focal single attack, need second attack to confirm diagnosis
3. All other possible neurological causes must have been eliminated.	4. Single attack, single lesion DIS: Need MRI prove of DIS, plus DIT: need MRI or clinical proof of second attack
	5. Primary progressive disease DIS: need MRI, Evoked potential and CSF DIT: MRI proof of DIT, or progression for over one year
*An exacerbation is defined as: -Appearance of a new clinical sign/symptom or -The clinical worsening of a previous sign/symptom that had been stable for at least the previous 30 days and -Which persisted for a minimum of 24 hours.	
** DIS=disseminated in space DIT=disseminated in time	

and MRI was integrated with clinical and other para-clinical diagnostic methods. These criteria provided the first formal incorporation of MRI in a diagnostic work-up for suspected MS. The aim is to facilitate diagnosis in patients with a variety of presentations²². Previously used terms such as 'clinically definite' and 'probable MS' are no longer recommended. The outcome of a diagnostic evaluation is either MS, 'possible MS' (for those at risk, but for whom diagnostic evaluation is equivocal) or 'not MS'²².

Investigation

MS is essentially a clinically determined diagnosis of exclusion. Conventional MRIs only image some lesions (macroscopic ones), which are non-specific as to cause. Therefore, several tests and procedures are needed to eliminate all other possible causes. Although MS remains a clinical diagnosis, MRI has become an invaluable tool in

understanding and monitoring the disease, and is commonly used to confirm the clinical diagnosis.

Evoked potential tests (EVPs)

When demyelination or sclerosis occurs, the conduction of messages along the nerve axons is slowed or interrupted. EVPs measure the time required by the brain to receive and process nerve messages. Demyelination or a lesion in the nerve pathway can cause a conduction delay and the response time will be much slower than normal. EVPs are useful because they can confirm the presence of a suspected lesion not shown on MRI and can identify the existence of an unsuspected lesion that has not produced symptom. They are not invasive, do not require a hospital stay and are positive in about 80 per cent of patients.

Magnetic resonance imaging

The MRI scanner of the brain and spinal cord may show areas of sclerosis (plaque) when they

are larger than 2mm (macroscopic lesions). Scans cannot show microscopic lesions, as they are too small for current imaging resolution, but are included in the 'lesion load' and 'atrophy totals'. These early smaller lesions are better documented by EVPs, which are equally valid in meeting the diagnostic criteria. While MRI is the only test in which some MS lesions can be seen, it cannot be regarded as conclusive because all lesions do not register on MRI scans and many other diseases can produce identical MRI images.

MRI shows the size, quantity and distribution of the macroscopic lesions and – together with supporting evidence from other diagnostic tests, history and examination – may confirm the MS diagnosis. It also provides an objective measure of lesion activity. Conventional MRIs (T1 and T2 images) are generally non-specific, have little relation to MS progression and insufficient correlation with disability. Various imaging techniques can be used but T2-weighted brain imaging remains the standard tool.

Not yet widely available, magnetisation transfer and proton MR spectroscopy are two imaging techniques that better correlate with MS activity. They place greater emphasis on the spatial and temporal distribution of lesions rather than on individual appearance^{23,24}. Furthermore, brain MRI abnormalities are frequently observed in subjects over 50 years of age. It has been suggested spinal cord MRI and cerebrospinal fluid analysis should be systematically performed in suspected LOMS for more specific diagnosis²³.

Lumbar puncture and cerebrospinal fluid analysis

The cerebrospinal fluid is tested for the presence of anti-bodies (IgG), oligo-clonal bands and fragments of myelin basic protein. Intra-thecal production of IgG can occur, but is also found in other neurological conditions. A positive finding is most common in progressive MS, while it is usually negative in relapsing MS, unless patients are having – or recently had – an exacerbation.

This test may indicate MS but is not in itself conclusive. Increased IgG synthesis rate is the first CSF abnormality in early MS and indicates activity of plasma cells. It is seen in 80–90 per cent of patients, but is also elevated in 12 per cent of normal individuals and in 30–50 per cent of CNS infections. Increased immunoglobulin G index (>0.7) is seen in 86–94 per cent of MS patients and oligoclonal bands are present in over 90 per cent of definite MS. However, the latter is seen in other inflammatory diseases and in seven per cent of normal control as well.

Other tests

These include ANA, B12, FBC and ESR on selected patients. MRI of the spinal cord is required to rule out arteriovenous malformation, tumour or disc, particularly in some older patients (age-related lesions do not occur in the spinal cord). Serology for collagen vascular disease or anti-neuronal antibodies for para-neoplastic syndromes, especially for patients with cerebellar symptoms.

Key points

- > Multiple sclerosis (MS) is a chronic autoimmune disorder affecting movement, sensation and bodily functions.
- > Late onset multiple sclerosis (LOMS) in patients over 50 is not so rare a phenomenon and the prevalence ranges between four per cent and 9.6 per cent.
- > MS is an extremely variable disease and symptoms are determined by which CNS areas have demyelinated and how much neural tissue has been destroyed.
- > The revised diagnostic criteria developed by the International Panel in 2001 integrate MRI assessment with clinical and other para-clinical methods.

Course

The course of MS is totally unpredictable. While some are only minimally affected by the disease, others experience very rapid progression to total disability. Eventually, all MS patients spend time between these extremes. The clinical course can be classified as relapsing from onset (relapsing/remitting) or progressive from onset (primary progressive). These clinical phenotypes have been based on historical and clinical observations. With or without clinical attacks, the disease process continues. The older the patients are when MS clinically begins, the less likely to have a complete initial recovery. At first, attacks are numerous, but this pace lessens very quickly and disability quickly accumulates before leveling off. Shortened lifespans are almost always due to complications rather than the primary symptoms.

Several studies have reported that LOMS patients have high frequency of progressive course, motor function involvement and poor prognosis¹. In one study among patients with LOMS, 37 per cent had a primary progressive form and 35 per cent had a secondary progressive MS¹. In another study, there was a marked increase in sphincteric and cerebellar involvement, and risk of a major depressive episode within a few years of diagnosis of LOMS, suggesting rapid neurological deterioration¹⁹. LOMS may present as major depression and, although neurological presentation at onset is similar to that of young adults, progression to disability is more rapid and a primary progressive course is more prevalent¹⁹.

Pyramidal or cerebellar involvement is observed in 60–70 per cent of the LOMS patients at presentation.

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LOMS is usually associated with a faster progression to disability compared to young adult MS patients¹⁰. Moreover, in patients over 50, MS variants and atypical forms that present a difficult diagnostic problem, may be frequently encountered¹⁰.

In the September issue of Geriatric Medicine part two of this article will outline the management of MS and discuss treatment of the disease.

Conflict of interest: none declared.