Multiple sclerosis in older people

Multiple sclerosis (MS) is the most common chronic disabling disease of the central nervous system in young adults. The late-onset MS (LOMS) variety, with clinical onset after 50 years old, is not a rare phenomenon. LOMS may present a diagnostic challenge because of the variability in its presentation. This article gives an overview of the clinical features of MS in older people, the diagnostic challenges and management lines.

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Multiple sclerosis (MS) is a chronic autoimmune disorder that affects movement, sensation and bodily functions. In older people, MS could be a continuation of the disease diagnosed at earlier age or it could be a late-onset MS (LOMS) with a clinical onset after the age of 50 years. The clinical presentation and course of LOMS seem to be different from those between 20 and 50 years old and it is frequently misdiagnosed. MS is primarily characterised by mult centric inflammation and demyelination, but the role of axonal injury and gliosis increases as the disease evolves.

Epidemiology

Although most MS patients have their first symptoms between the ages of 20 and 40 years, LOMS is not as rare as previously thought; studies indicate that prevalence ranges between 4% and 9.6%. In general, 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, and it affects approximately 85,000 people in the UK and about one in 1,000 in Western countries.

Pathogenesis

MS is a chronic autoimmune disorder caused by destruction of the myelin sheath of central nervous system (CNS) nerve fibres, in the 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.

Clinical features

There is no typical pattern for MS presentation and course; every patient has a unique set of symptoms. MS is an extremely variable disease and its symptoms are determined by the combined effects of which CNS areas have been demyelinated and how much neural tissue has been destroyed. MS is primarily characterised by mult centric inflammation and demyelination, but the role of axonal injury and gliosis increases as the disease evolves.

Clinical types

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. 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 interventions.
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Features</th>
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| Fatigue                       | • Most common complaint in MS and occurs in about 78%  
• Usually in the late afternoon and subsides in the early evening                                                                                                                                                                                                                           |
| Numbness, tingling and burning sensations | • Sensory complaints occur in about 55% of patients  
• Affect the extremities or the trunk with tingling, crawling sensations, feelings of swelling or numbness  
• Duration of numbness depends upon its cause. If severe neurological damage to the myelin sheath takes place, then the numbness may persist  
• Numbness may be due to severe neurological damage to the myelin sheath and may last for weeks to months  
• Numbness may be temporary or permanent  
| Tremor                        | • Up to 50% report extremity ataxia or tremor  
• It impairs mobility 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% of patients and is present in about 62% 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 visual loss | • Blurred, double vision or diplopia, optic neuritis, involuntary rapid eye movement (nystagmus, oscillopsia), partial blindness (scotoma) and – very rarely – complete blindness may occur  
• 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 |
| Cognitive and emotional dysfunction | • Affects approximately 50% and involves memory, reasoning, verbal fluency and speed of information processing  
• Emotional changes may include euphoria and/or depression.                                                                                                                                                                                                                       |
| Heat sensitivity              | • It causes a temporary worsening of symptoms and may lead to blurred vision (Uhthoff’s syndrome)  
• 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%  
• May include facial pain (trigeminal neuralgia or tic douloureux, lightning like acute facial pain), 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 & swallowing dysfunctions | • Slowing of speech, slurring words, scanning speech, changes in speech rhythm (dysarthria) and difficulty swallowing (dysphagia)  
• 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.                                                                                                                      |
onset is the most common beginning phase of MS, but MS may become clinically inactive (subclinical) for months — or years — between any number of intermittent attacks. However, the disease process is ongoing and damage continues with or without clinical attacks while microscopic lesions and diffuse damage (axonal loss) silently proceed.10

Diagnosis

Since LOMS is infrequent, it presents a diagnostic challenge.11 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 criteria require 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.12 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 criteria (table 1).13,14 The focus was on the objective demonstration of the dissemination of lesions in both time and space, and MRI was integrated with clinical and other para-clinical diagnostic methods.14 These criteria provided the first formal incorporation of MRI in a diagnostic work-up for suspected MS. The aim was to facilitate diagnosis in patients with a variety of presentations.14 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."14

Investigation

MS is essentially a clinically determined diagnosis of exclusion. Conventional MRI only images some lesions (macroscopic), which are nonspecific. 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. 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 evoked potential tests (EVPs), which are equally valid in meeting the diagnostic criteria. Furthermore, brain MRI abnormalities are frequently observed in subjects over 50 years of age. It has been suggested that spinal cord MRI and cerebrospinal fluid (CSF) analysis should be systematically performed in suspected LOMS for more specific diagnosis.15 The CSF is tested for the presence of antibodies (IgG), oligoclonal bands and fragments of myelin basic protein. Intrathecal production of IgG can occur, but is also found in other neurological conditions. A positive CSF 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.

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. 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 prognosis.1 In one study among patients with LOMS, 37% had a primary progressive form and 35% had a secondary progressive MS.1 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 deterioration.11 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 prevalent.11 Pyramidal or cerebellar involvement is observed in 60–70% of the LOMS patients at presentation. LOMS is usually associated with a faster progression to disability compared with young adult MS patients.3 Moreover, in patients over 50 years, MS variants and atypical forms that present a difficult diagnostic problem, may be frequently
### Box 2: Main clinical types of MS

<table>
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<th>Type</th>
<th>Main features</th>
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| **Benign MS**                       | • In about 20% of MS patients  
• Sensory problems at onset, but complete recovery without any permanent disability  
• There are no motor symptoms  
• Some may evolve later (>10 years) into progressive type |
| **Secondary-progressive MS (SP MS)**| • In about 40% of MS patients  
• Relapsing MS evolving into the progressive stage, so less complete remissions with cumulative damage  
• Lumbar puncture (LP) usually positive |
| **Relapsing-remitting MS**           | • In about 25% of MS patients  
• Sporadic exacerbations/relapses with partial/total recovery or remission  
• 50% of cases will have progression within 10–15 years  
• LP usually negative unless recent exacerbation |
| **Primary-progressive MS (PP MS)**  | • In about 12% of MS patients  
• Slow steady onset  
• Worsening motor deficit with increased disability  
• LP usually positive. |

Management

The goal of therapy in patients with LOMS is to prevent relapses and progressive worsening of the disease. Spontaneous recovery is rare when neurologic deficits have persisted for longer than six months, and there are no known therapies that promote regeneration and reverse fixed neurologic deficits. Therefore, disease modifying therapy should be considered before neurologic deficits have persisted longer than six months. Decisions in individual patients should be based both on the course of the patient's disease and on the probability of severe disabling disease. The vast majority — more than 50% — of patients have relapsing/remitting MS during the early years and secondary-progressive later. They have the best responses to treatment. Patients with progressive disease are less responsive to treatment. Disease-modifying therapy should be considered early in the course for patients with an unfavourable prognosis. The unfavourable prognostic markers related to more rapid worsening of disease can be used to select patients for treatment. Patients who have multiple cranial MRI lesions at the time of their first symptoms are much more likely to have major disability later on. Therefore, in addition to the clinical features, the findings on cranial MRI are useful in selecting patients for early treatment.

Symptomatic treatment

Corticosteroids are the mainstay of treatment for acute relapses of MS. Corticotropin was demonstrated to help recovery from relapse, but it has been largely replaced by high-dose intravenous methylprednisolone (Mдрone) because the latter has a more rapid onset of action, produces more consistent benefits, and has fewer side effects. Corticosteroids have immunomodulatory and anti-inflammatory effects that restore the blood/brain barrier, reduce oedema and possibly improve axonal conduction. Steroid therapy shortens the duration of the relapse and accelerates recovery, but whether the overall degree of recovery is improved or the long-term course altered is not known. In the optic neuritis, intravenous methylprednisolone was found to reduce by approximately 50% the risk of an attack leading to the diagnosis of MS during the two-year follow-up. This effect was
most evident in patients at highest risk for subsequent relapse — those with multicentric brain lesions on MRI. Intravenous methylprednisolone delayed, but did not stop, the development of MS after optic neuritis.

MS, whether late-onset or not, causes a large variety of symptoms and the treatments for these are equally diverse. Therapy lines include physiotherapy, vaccination and various symptomatic treatments should be considered. Most symptoms can be treated and complications avoided with good care and attention from medical professionals. Preventing complications such as pneumonia, bed sores, and injuries from falls or urinary infection requires attention to the primary problems that may cause them. Spasticity is a common problem and is treated with baclofen, dantrium or botulinum toxin injection. Chronic pain may improve once a relief of spasticity is achieved using baclofen and diazepam. Other more acute types of pain may respond to carbamazepine. Low back pain is common, secondary to increased use of the back muscles to compensate for weakened legs, and may improve on physiotherapy and/or general analgesics.

**Disease-modifying therapy**

Interferon beta is the treatment of choice for patients with relapsing/remitting MS. There are two forms of recombinant interferon beta: 1a and 1b. Interferon beta-1a is a glycosylated, recombinant mammalian cell product, with an amino-acid sequence identical to that of natural interferon beta. Interferon beta-1b is a non-glycosylated recombinant bacterial-cell product in which serine is substituted for cysteine at position.22 In clinical trials, treatment with the higher dose beta-1b and beta-1a reduced the annual relapse rate by 31% and 32% respectively, with fewer gadolinium-enhanced lesions on MRI.23-25 There was also a significant reduction in disease activity, defined as the finding of new or enlarging lesions in serial MRIs;23 and beta-1a significantly lowered the probability of progression of disability and of severe disability.24,25 Both types of interferon beta are usually well tolerated. Although interferon beta therapy is effective, a risk/benefit analysis must be done in each patient. The cost of therapy and the uncertain long-term risks may outweigh the benefits in patients with mild MS and a favourable prognosis.

Glatiramer acetate (Copaxone) is a putative auto-antigen in MS, synthesised as an immuno-chemical mimic of myelin basic protein. It represents an alternative to interferon beta therapy for patients with relapsing/remitting MS and may be most useful for patients who become resistant to interferon beta treatment owing to

**Table 1: Revised McDonald criteria for the diagnosis of MS**

<table>
<thead>
<tr>
<th>Clinical features suggesting MS (No MRI nor VEP criteria)</th>
<th>MRI &amp; other supportive diagnostic evidence</th>
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<tbody>
<tr>
<td>At least two attacks with objective clinical evidence of at least two lesions</td>
<td>No MRI lesion and negative cerebrospinal fluid (CSF) for oligoclonal bands</td>
</tr>
<tr>
<td>At least two attacks with objective clinical evidence of one lesion</td>
<td>Dissemination in space (DIS) shown on MRI or two or more MRI lesions consistent with MS Positive CSF oligoclonal bands Or await further clinical attack, suggesting a different site</td>
</tr>
<tr>
<td>One attack with objective evidence of at least two lesions</td>
<td>Dissemination in time (DIT) on MRI Or second clinical attack</td>
</tr>
<tr>
<td>One attack with objective evidence of at least two lesions</td>
<td>DIS shown on MRI or two or more lesions consistent with MS Positive CSF oligoclonal bands DIT shown on MRI or second clinical attack</td>
</tr>
<tr>
<td>Insidious neurological progressive course suggestive of MS And One year of disease progression (determined prospective or retrospectively)</td>
<td>Two out of the following: 1. Positive brain MRI (nine T2 lesions or at least four T2 lesions with positive VEP) 2. Positive spinal cord MRI result with at least two T2 lesions 3. Positive CSF oligoclonal bands</td>
</tr>
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VEP: Visual evoked potential
serum interferon beta-neutralising activity. The most common side effect is mild reactions at the injection site, which may occur in up to 90% of patients.26

Azathioprine (Imuran), a purine analogue that depresses both cell-mediated and humoral immunity should be considered in patients with relapsing/remitting MS who do not respond to therapy with interferon beta or glatiramer acetate, particularly in those with recurrent inflammatory myelitis.

Methotrexate, in low oral doses, is relatively non-toxic and effective in inhibiting both cell-mediated and humoral immunity or as a result of its anti-inflammatory effects. It provides an alternative treatment for patients with chronic progressive MS, and should be considered for those with progressive deterioration.

Cyclophosphamide, a potent cytotoxic and immunosuppressive agent, may be most appropriate for patients with rapidly progressive disease who do not respond to the less toxic methotrexate.

In the UK, the Department of Health and the manufacturers developed a "risk sharing scheme" aimed at providing conventional drugs more cost effectively. Treatment will be provided to ambulating patients with two or more disabling relapses in the past two years (about 15% of all patients with MS) and their progress monitored over 10 years.27 However, the scheme has several scientific and practical problems that might limit its ability to improve the care of patients in the long term.27 Other drugs include mitoxantrone (Onkotrone), a synthetic anthrancenedione, which is used for the treatment of worsening relapsing/remitting or progressive MS.

Combination therapy may be considered in an attempt to decrease disease activity in those with active disease, despite standard immunomodulatory therapy. The combination of mitoxantrone and interferon beta (IFNbeta) appears safe in short-term studies from a toxicity standpoint and is associated with a reduction in relapse rates, a decrease in the frequency of enhancing lesions, and a decrease in T2 lesion burden.28 Other combinations that appear safe in preliminary studies include IFNbeta-1a and methotrexate, IFNbeta-1a and azathioprine, and mitoxantrone plus methylprednisolone. The decision to use combination therapy in patients with a suboptimal response to monotherapy should be considered early and not be delayed until disability becomes advanced.28

Conclusion

MS with clinical onset after 50 years old is not as rare a phenomenon as previously thought. A confident and accurate diagnosis of MS is important, but a specific diagnostic test for the disease does not exist. The main goal of therapy is to prevent relapses and progressive worsening of the disease. Steroid therapy is the mainstay of acute relapse treatment and disease-modifying therapy should be considered early in selected patients, before neurological deficits persist. Management decisions in individual patients should be based both on the course of the patient’s disease and on the probability of severe disabling disease.

Conflict of interest: none declared

References

Multiple sclerosis


