Management and prognosis of multiple sclerosis

Introduction

Multiple sclerosis is a common disease of the CNS. The first of these articles (Hassan-Smith and Douglas, 2011) examined its epidemiology and diagnosis. This article explores the management and prognosis of multiple sclerosis, including the rapidly evolving field of disease-modifying therapeutics. However, equally important is the management of problems related to chronic multiple sclerosis and knowledge of which symptomatic treatments may be helpful. Finally, the prognosis is discussed; vital when counselling newly diagnosed patients.

Treatment

Treatment can be categorized as acute relapse management often with steroid treatment, disease-modifying treatments to alter the long-term course or outcome of disease and symptomatic treatments to treat or ameliorate the wide spectrum of multiple sclerosis-related complications.

Management of an acute relapse

A key issue is to establish that the neurological event is a genuine relapse, in contrast to a 'pseudorelapse', typically associated with sepsis such as a urinary tract infection. Typical clinical presentations of relapses are outlined in *Table 1* and how to take a quick relapse history in *Table 2*. It is important to perform a series of simple assessments and tests: temperature measurement, urine dipstick and a more extensive septic screen where appropriate. If there is no evidence of infection and the patient is significantly disabled (a categorization which will vary according to the patient and the relapse), then give intravenous methylprednisolone 1 g once daily for 3 days. Alternatives include methylprednisolone 500 mg orally once daily for 5 days. Steroid therapy is often supplemented with gastrointestinal cover for 2 weeks (with ranitidine or a proton pump inhibitor). Corticosteroids do not change the long-term clinical outcome, but often expedite symptom resolution.

Management of the initial demyelinating event in a patient with a likely clinically isolated syndrome is identical to those in patients with established relapsing-remitting multiple sclerosis and prompt referral to neurology services is recommended.

Disease-modifying treatment

Development of disease-modifying therapies – which aim to alter the natural course of multiple sclerosis – has radically altered management. Specific guidelines vary by country and have been revised several times over the past decade. The injected beta-interferons (Rebif, Betaferon and Avonex)

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Table 2. How to take a relapse history

When was multiple sclerosis diagnosed, is the patient cared for by a local neurology team; who is the patient's multiple sclerosis nurse
Current treatment
'Normal' baseline of multiple sclerosis symptoms, e.g. use of walking aid, catheterization
Previous number and/or pattern of relapses
Current specific symptoms representing defined change in baseline
Onset and duration of symptoms – should be sustained longer than 24 hours
Establish that any previous relapse was greater than 30 days before onset of current episode
Identify any symptoms suggestive of intercurrent infection, e.g. urinary tract infection

Table 1. Typical clinical presentation of acute multiple sclerosis relapse

Transverse or partial myelitis	Manifestation of acutely evolving inflammatory demyelinating lesion in spinal cord
	'Symptoms in one leg, signs in both' – signs usually asymmetric and incomplete, and involve only a part of the long ascending and descending tracts
	Clinically, characterized by rapid onset over hours or days of symmetrical or asymmetric paraparesis, ascending paraesthesiae, truncal sensory level, sphincteric dysfunction and bilateral Babinski signs
	Magnetic resonance imaging: focal high signal changes on T2-weighted images at the appropriate level and/or contrast enhancement
Optic neuritis	Initial manifestation of multiple sclerosis in ~25% of patients
	Classically, partial or total unilateral visual loss developing over the course of days with preceding or concomitant retrobulbar pain
	Clinically, a scotoma affecting central vision and colour desaturation using Ishihara charts are usually evident
	Rarely, both optic nerves involved although this should alert the assessor to consider multiple sclerosis mimics, e.g. neuromyelitis optica
	Fundoscopy can reveal papillitis with evidence of disc swelling, although is often normal in appearance. A relative afferent papillary defect can result, and there are usually abnormalities of the visual evoked potentials
Cerebellar ataxia	Caused by lesions of the cerebellum or its connections in cerebellar peduncles, pons or red nucleus
	Can be severely disabling; early physiotherapy essential
Brainstem syndromes	Resulting from disruption of the lower brainstem nuclei or supranuclear connections, e.g. ataxia, internuclear ophthalmoplegia, facial pain, numbness, bulbar symptoms, e.g. dysarthria or dysphagia
Sensory syndromes	Regional sensory loss may not be accompanied by other cord symptoms, and so may be dismissed
	The useless hand (Oppenheim) results from a high cervical cord lesion in the dorsal columns; recovery can take up to 9 months

and glatiramer acetate (Copaxone) are 'first-line' disease-modifying therapies introduced in the 1990s. They reduce relapse rate by about one-third (IFNB Multiple Sclerosis Study Group, 1993; PRISMS Study Group, 1998) and have broadly similar efficacies. A previous history of significant depression is a relative contraindication to using interferons, and glatiramer acetate is often used in these cases.

According to the current Association of British Neurologists (2009) guidelines, patients eligible for first-line disease-modifying therapies should be over the age of 18 years, ambulant and have active disease. The latter is demonstrated by:

1. Two clinically significant relapses within the last 2 years
2. Patients within 12 months of a clinically significant clinically isolated syndrome when magnetic resonance imaging evidence predicts a high likelihood of recurrent episodes (i.e. development of clinically definite multiple sclerosis
3. Patients with a single major relapse in the preceding 2 years, but with magnetic resonance imaging evidence of continuing disease activity
4. Individuals aged less than 18 years with relapsing-remitting multiple sclerosis.

Natalizumab (Tysabri), a monoclonal antibody to the vascular adhesion molecule α4β1 integrin VLA-4, has been introduced as a second-line disease-modifying therapy, given as a monthly intravenous infusion. It reduces relapse rate by 68% (O'Connor, 2004), more significant than first-line disease-modifying therapies. This is reserved for 'aggressive' relapsing-remitting multiple sclerosis, defined by Association of British Neurologists (2009) guidelines as:

1. Two or more disabling relapses in 1 year
2. One or more gadolinium-enhancing lesions on magnetic resonance imaging
3. A significant increase in T2 lesion load compared with a previous magnetic resonance imaging.

Other infused monoclonals, such as alemtuzumab and rituximab, are in phase III clinical trials and also show significant efficacy. A major limitation of many multiple sclerosis trials relates to the uncertain correlation between brain magnetic resonance imaging parameters (e.g. the number or volume of T2 high signal or contrast enhancing lesions) or even annual relapse rates, and underlying disease progression and accumulation of disability. The need to demonstrate clear clinical benefits is particularly important with newer multiple sclerosis drugs, which appear to have greater therapeutic potency, but an increased risk of serious side effects. The use of natalizumab for example has been associated with the development of progressive multifocal leukoencephalopathy in approximately 1:1000 patients.

Further therapeutic developments are imminent, with recent studies (Khatri et al, 2011; Nicholas et al, 2011) finding significant efficacy of several new oral disease-modifying therapies (approaching that of infused biologicals in some cases), with convenient administration. Oral fingolimod has European approval as a disease-modifying therapy in patients with highly active relapsing-remitting multiple sclerosis despite treatment with beta interferon, or those with rapidly evolving severe relapsing-remitting multiple sclerosis. The advantages of oral therapy must be balanced against the relative lack of information on long-term safety.

Symptomatic treatment

Despite advances in disease-modifying therapies, many patients experience significant ongoing symptoms, which generally become the dominant issue in progressive disease in particular. Effective management of multiple sclerosis symptoms can have a major impact in improving the quality of life for patients, although a strong evidence base is lacking for many therapies.

As with most chronic diseases, a multidisciplinary approach is at the heart of effective management. The multiple sclerosis specialist nurse in particular plays a critical role by providing information, holistic support and advice about the condition from time of diagnosis and throughout the disease course. Neurorehabilitation specialists also direct patient care, especially during the progressive phase, and can minimize the impact of disability by effectively coordinating the activity of the multidisciplinary team.

Spasticity

This results from loss of descending inhibition and subsequent increase in muscle tone. Minimizing provoking factors, physiotherapy and various pharmacological agents can help, e.g. baclofen, clonazepam for nocturnal spasms, and tizanidine. Botulinum toxin can be helpful in localized problems, e.g. adductor spasms. Sativex – a nasal cannabinoid spray – has a UK license as add-on treatment for multiple sclerosis-related spasticity when people have inadequate response to other symptomatic treatments or their side effects are intolerable.

Fatigue

Fatigue can be a prominent symptom for multiple sclerosis sufferers and comprehensive assessment is needed to identify secondary causes of disrupted sleep (e.g. nocturnal frequency or pain). Fatigue management courses are often helpful, in addition to trials of medication such as amantadine, selective serotonin-reuptake inhibitors, e.g. fluoxetine, or, less commonly, modafanil.

Bladder, bowel and sexual dysfunction

If patients report urgency and/or incontinence, they must be screened for any evidence of infection and treated accordingly. If symptoms continue, residual bladder volume should be assessed using a portable ultrasound scanner. If this is significant, then intermittent self-catheterization should be started in addition to antimuscarinic drugs such as solifenacin. If the volume is insignificant antimuscarinics alone should be used. Another important treatment for detrusor hyperreflexia is intravesical botulinum toxin. Mild constipation is a common complaint and iso-osmotic laxatives such as Movicol are most effective. Specific neurological impairment and psychosexual factors can lead to sexual dysfunction. Sildenafil can be helpful to both sexes and prostaglandin E1 administered urethrally is another option.

Neuropathic or paroxysmal pain

Carbamazepine can be effective, in addition to gabapentin, pregabalin and tricyclic antidepressants, e.g. nortriptyline.

Tremor

This can be particularly disabling and mechanical damping (e.g. diving weights, Lycra splinting) along with drugs such as propanolol and benzodiazepines are used with varying efficacy. Severe, treatment-resistant cases may also be considered for deep brain stimulation.

Prognosis

Although a diagnosis of multiple sclerosis may impact on overall life expectancy (potentially reducing this by up to 10 years), it is expected that patients will live for

40 years or more following diagnosis. The long-term nature of the condition is particularly important, as long-term outcomes determine the true socioeconomic impact. The heterogeneity of natural history studies and long-term follow-up trial data make accurate prognostication difficult. Despite this, the following sub-groups illustrate important aspects of prognosis which are useful when counselling patients. One must always emphasize that each patient's pattern of disease is unique and these figures are merely a guide.

Risk of conversion to clinically definite multiple sclerosis

Three major trials have generated outcome data in treatment-naive multiple sclerosis patients: Optic Neuritis Treatment Trial (Beck et al, 1993), Controlled High-risk Subjects Avonex MS Prevention Study (Jacobs et al, 2000) and Early Treatment of MS study (Comi et al, 2001). The probability of a second episode, i.e. conversion to clinically definite multiple sclerosis, in the relatively short follow-up periods were 16.7%, 38% and 45% respectively, although the placebo outcomes of these studies are not directly comparable because of discrepant selection criteria. However, given the chronic nature of multiple sclerosis, longer-term follow-up is recommended as a longitudinal study found that conversion to clinically definite multiple sclerosis occurred in 63% of cases over a 20-year period, increasing to 82% in patients with abnormal magnetic resonance imaging scans at baseline (Fisniku et al, 2008). Factors thought to affect prognosis are summarized in *Table 3*.

Time to disability, e.g. use of walking aid

Disability in multiple sclerosis is quantified using the expanded disability severity score and can monitor changes over time. Scores range from 0, indicating no signs or symptoms at assessment, to 10 which indicates death, increasing in increments of 0.5 as functional ability is compromised. Need for a walking aid is an important step in the patient's multiple sclerosis history, indicating significant decompensation in his/her neurological function, and is given a score of 6.

In a natural history study from the London, Ontario multiple sclerosis patient cohort, the Kaplan–Meier estimate of median time to needing a walking aid from disease onset was 18 years, although this was likely related to the number of relapses in the earliest phase of disease (Ebers et al, 2010). One relapse in the first 2 years from disease onset produced a median time to walking aid of 20 years, whereas three or more relapses in this initial period resulted in a median time of 10 years. Long-term follow up of trial patients receiving disease-modifying therapies has been published (Freedman, 2011) and there may be some effect of disease-modifying therapy, e.g. IFNB-1b, on delaying time to walking aid.

Table 3. Prognostic factors in patients with multiple sclerosis

Good prognosis	Poor prognosis
Optic neuritis	'Multifocal' clinically isolated syndrome
Isolated sensory symptoms	Efferent (motor/cerebellar) systems affected
Long interval to second relapse	High relapse rate in first 5 years
No evidence of disability after 5 years	Substantial disability after 5 years
Normal magnetic resonance imaging of the brain	Abnormal magnetic resonance imaging with heavy lesion load
Younger age at onset	Older age at onset
Female gender	Male gender

KEY POINTS

- Patients presenting with an acute relapse must have intercurrent infection excluded before giving high-dose methylprednisolone.
- New treatments are changing management and modifying the disease course of multiple sclerosis; effective symptomatic treatment is important at all stages of disease.
- Patients with an abnormal magnetic resonance imaging scan presenting with a clinically isolated syndrome have increased risk of converting to clinically definite multiple sclerosis over 20 years.

Conclusions

Disease-modifying therapies have a direct clinical impact upon the lives of patients with multiple sclerosis, by reducing the number of relapses, but it is unclear whether or not they slow the accumulation of permanent disability over time. While a number of prognostic features help us in counselling patients, comprehensive, longitudinal data will be critical in understanding the long-term effects on patient outcomes. BJHM

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