Clinical Review

Acute management of multiple sclerosis

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Abstract

Multiple sclerosis is one of the commonest causes of disability in young adults. This review highlights some of the acute presentations of this condition, and how these may be managed in the emergency setting. The role of corticosteroids is discussed, along with the value of other drugs in symptom control during an acute relapse.

Key words

Multiple sclerosis,Relapses,Steroids,Symptom control,Disease modifying therapy

Key points

1. There is currently no available treatment that if denied a patient with multiple sclerosis acutely will make a significant difference to long-term outcome.
2. Steroid treatment (1g methylprednisolone intravenously daily for three days) can improve rate of recovery from a relapse but has a number of potential risks so should only be used if patients have a significantly disabling relapse.
3. Patients experiencing two or more relapses in a two year period should be seen by a neurologist to determine whether they would be suitable for a disease-modifying agent such as beta-interferon.
4. Many patients with MS develop general medical complications as a consequence of their disease, which not only cause problems themselves but may also dramatically exacerbate previously stable chronic symptoms.
5. Significant difference can be made with regard to symptom control (particularly spasticity and bladder dysfunction) and rehabilitation.

Introduction

Multiple sclerosis (MS) is an autoimmune disorder of the central nervous system. The precise aetiology is unknown but there is probably interplay between both genetic and environmental factors.[1] Focal areas of inflammation result in demyelination, axonal dysfunction and loss.[2] The diagnosis rests on evidence for at least two demyelinating lesions, affecting different sites within the brain or spinal cord, separated in time. Revised diagnostic criteria, incorporating evidence from magnetic imaging, propose that the second lesion may not be clinically expressed.[3]

MS takes a number of forms: relapsing-remitting (episodes of neurological dysfunction occurring over days or weeks which largely resolve spontaneously), primary and secondary progressive (initially relapsing-remitting followed by progression). 80% of patients experience relapses at disease onset, typically just under once a year. After 10 years 50% enter a secondary progressive phase (90% after 25 years) with continuous accrual of disability, with or without relapses[4]. 20% of patients have primary progressive disease, more commonly in men.

Investigations include magnetic resonance imaging (MRI) of the brain (and spinal cord), lumbar puncture and neurophysiological testing[5]. MRI demonstrates areas of high signal in the deep white matter, often in a periventricular distribution. Cerebrospinal fluid protein electrophoresis shows oligoclonal IgG bands (not matched in the serum) in over 90% of cases. Demyelination characteristically delays visual, auditory and somatosensory evoked potential latencies.

MS is one of the commonest causes of neurological disability in young adults (see Figure 1). The spectrum of disease severity is wide but approximately 50% are unable to work at 5 years and after 15 years 50% require a stick to walk 100 yards[6]. Quite apart from the personal burden of disability, the financial cost in the UK is £1.2 billion per year.

- 2.5 million people affected worldwide
- 87,000 people affected in the UK (approximately)
- Annual incidence: 7 per 100,000
- Prevalence: 120 per 100,000
- 1 in 400 lifetime risk in the UK
- Women: men 2:1
- Mean age of onset: 30 years

Figure 1. Epidemiology of multiple sclerosis

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Multiple sclerosis and the acute medical take

Patients with multiple sclerosis frequently present to hospital via the acute medical take. For some this will be the first presentation of MS and the time of diagnosis. Others will present with a relapse, with disabling symptoms, with medical complications or simply because they are unable to cope at home (see Figure 2).

- Thromboembolism
- Urinary tract infections (secondary to urinary retention or catherisation)
- Lower respiratory tract infections (aspiration or sputum clearance failure due to bulbar dysfunction, respiratory muscle weakness and immobility)
- Pressure sores
- Constipation
- Autonomic dysfunction – secondary to brainstem or cervical cord involvement
- Seizures (rare)
- Falls (musculoskeletal injury, head injury, subdural haemorrhage)
- Iatrogenic problems (drug-related)

Figure 2. Common medical problems experienced by patient with MS.

All of these problems should be managed as one would for any other patient. The only treatment modalities specific to the acute management of neurological problems in patients with multiple sclerosis are currently: corticosteroids, symptom control and early rehabilitation. Specialist advice should be sought, particularly if the patient is presenting to hospital for the first time or if there is any doubt about the diagnosis.

Corticosteroid treatment for an acute relapse multiple sclerosis

What are the benefits?

High dose corticosteroids remain the mainstay of treatment for acute relapses. Putative mechanisms of action include: resolution of oedema, alteration of blood-brain barrier permeability and immunological changes (systemically and in the central nervous system).[4] It is important to note that steroids do not affect long-term outcome, or disease course, but they do increase rate of recovery from a relapse (usually in a matter of 4 weeks).[7-8] This, and the potential risks, should be made clear to the patient.[5]

What are the risks?

The greatest concern is the potential for osteoporosis and avascular necrosis (see figure 3). No prospective studies, with account made for confounding factors such as immobility, have been performed to assess this risk. One retrospective study looked at 103 patients with MS treated with corticosteroids and reported fractures in 3% of patients annually over 7 years at-risk, increasing after 5 years but not correlating with cumulative dose.[9]

- osteoporosis
- avascular necrosis
- blood sugar abnormalities
- sepsis risk
- hypertension
- gastrointestinal irritation
- anaphylaxis
- weight-gain
- mood and sleep disturbance

Figure 3. Risks of corticosteroid treatment.

Who should receive steroids?

Trials have used strict criteria to define a relapse, referring to an episode of neurological impairment defined by a change in, for example, the Kurtzke Expanded Disability Status Score (EDSS, of 0.5 to 1.0) lasting more than 48 hours.[10] However, in routine clinical practice we rarely assess EDSS scores. The lack of long-term impact and potential side effects lead many to recommend that steroids be used only in acutely disabling relapses: a non-disabling, purely sensory event, for example, may quite reasonably be left to run its course. Efficacy should be assessed objectively as many experience a subjective sense of well-being without objective clinical benefit. Steroids, if used, should be given as early as possible as there is some evidence to suggest that delayed treatment may diminish benefit.

How are steroids given and what monitoring is undertaken?

Steroids should not be given if there is any evidence of infection. Blood glucose should be checked prior to each dose and more frequently in diabetic patients, who may need insulin during this treatment. **1 gram of intravenous methylprednisolone is given over 1 hour in 100 mls of normal saline, once daily for three days.** Late administration may cause sleep disturbance. Selected patients may have this treatment in a daycase or community setting. There is no evidence to support a subsequent reducing course of oral steroids.

There is reasonable evidence that methylprednisolone given orally at the same dose has equivalent efficacy to intravenous administration. In the UK, oral steroids are increasingly used.

Optic neuritis

Optic neuritis is common, with an annual incidence of 1-5 per 100,000, mainly seen due to idiopathic inflammatory demyelination or as a manifestation of MS.[11,12] Symptoms usually include painful subacute unilateral visual impairment (ranging from minor blurring to visual loss) progressing 2-14 days. The risk of developing multiple sclerosis following an episode of optic neuritis is up to 40% at 10 years and 60% at 40 years. The strongest predictor for the development of MS is the presence of asymptomatic white matter lesions on brain MRI. In one study 16% of patients with a normal MRI scan developed MS and 51% with 3 or more lesions, within 5 years.

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In common with other acute relapses, intravenous corticosteroid treatment increases the rate of recovery from optic neuritis but does not make any significant difference to long-term outcome[13-14]. Some offer treatment to all patients with significant visual impairment; others only advocate this for patients with pre-existing contralateral visual difficulties.

Frequent relapses and severe disease progression

If patients are experiencing frequent relapses they should be considered for a disease-modifying agent such as *interferonß-1a, interferon ß-1b, glatiramer acetate (copolymer 1), azothiaprine* or *mitoxantrone. Interferonß* is now available for use in the UK, following the Association of British Neurologists' guidelines, for patients who experience two or more relapses within two years, who are able to walk 100 metres unaided.[15] Significant disease progression may also require consideration for treatment with agents such as: *interferonß-1b, mitoxantrone, campathß-1H* or cyclophosphamide. Specialist advice should be sought in these situations.

There is no good evidence that long-term or short-term corticosteroid treatment influences disease progression.

Symptom control

Treatment largely rests on symptom control.[16-17] Coincidental or secondary complications, such as a urinary tract infection, can dramatically exacerbate previously stable chronic symptoms in multiple sclerosis, precipitating admission.

Spasticity

Spasticity is a common cause of pain and disability in MS. Some patients depend on limb rigidity to compensate for weakness, so in treatment a balance must be reached. Baclofen (starting dose 10-20mg, maximum 100mg per day in 2-4 divided doses orally) is the most widely used antispasmodic. Drowsiness is common if the dose is increased rapidly and baclofen should not be stopped abruptly as this may precipitate severe spasms. It can also be given intrathecally via a pump. Tizanidine (starting dose 2mg, maximum 36 mg daily in 2-4 divided doses orally) is an alternative. It can cause hepatotoxicity, so liver function tests should be checked monthly for the first six months. A controlled trial of cannabis is underway in the UK, for a number of symptoms but primarily spasticity. Botulinum toxin treatment is finding an increasing role in specialist centres.

Bladder dysfunction

Bladder problems in MS can be divided into failure to store urine (leading to frequency) and failure to empty (leading to hesitancy and retention).[18] Both problems may be present, making management more difficult. In practice the postmicturition urine volume is measured, by catheterisation or bladder ultrasound. If greater than 100mls, the predominant problem is failure to empty and treatment is by catheterisation (intermittent self-catheterisation or indwelling suprapubic/urethral catheter).

The commonest problem is detrusor overactivity leading to failure of adequate urine storage. Anticholinergics can inhibit this. Oxybutinin (starting dose 5mg, maximum 20mg daily in 2 divided doses) is commonly used but tolterodine (2mg twice a day), is more 'bladder-selective' with fewer systemic side effects.[19] Propiverine (an anticholinergic and calcium antagonist) is a well-tolerated alternative. Cannabis may also have a role in controlling detrusor instability.[20] Nasal vasopressin (20mcg nocte) is useful to reduce nocturia.

Sexual dysfunction

60% of men with MS experience erectile dysfunction and at least an equivalent number of women suffer sexual difficulties.[21] Sildenafil has been shown to be effective for erectile dysfunction from a variety of causes and is funded for use in MS.[22] Impotence is a complex psychosocial issue which may require multidisciplinary support for patient and partner.

Fatigue

This is the commonest symptom in MS and is seen at all stages. Treatments have been disappointing. Amantidine and pemoline have been used with minimal benefit and diaminopyridine is being trialled. Modafenil is being considered for a number of causes of fatigue.

Pain

Many factors may precipitate pain in MS. Trigeminal neuralgia is the commonest acute pain syndrome. Carbamazepine (starting dose 50-100mg, increasing to 400-500mg twice daily), gabapentin (starting dose 300mg, licensed for 1800mg but sometimes used up to 2400mg daily), amitriptylline (10-50mg nocte) and misoprostol are all useful treatments. (Surgical decompression may be warranted if MRI demonstrates a vascular loop impinging on the trigeminal nerve.) These drugs may also be helpful for other neuralgic pain and dysaesthesia.

Oscillopsia

This is the subjective experience of abnormal involuntary eye movement and may be sufficiently severe to prevent reading. Gabapentin can be very effective.

Tremor

This can be very disabling, particularly the proximal tremor of the upper limb (present at rest and accentuated by goal-directed movements) which can overflow into the trunk and head. Propranalol, primidone and benzodiazepines have not been greatly successful. Surgical intervention, such as thalamic stimulation, may prove to have a role.[23]

Rehabilitation

Evidence for the benefits of goal-orientated multidisciplinary rehabilitation is gathering for the

alleviation of symptoms, reduction of disability and improvement in quality of life.[24,25] The philosophy of rehabilitation, with its emphasis on self-management, is ideal given the limitations of pharmacological intervention and also the fluctuating and unpredictable nature of MS.

Resuscitation and intensive care

Decisions about resuscitation and provision of intensive care support are difficult and it is here that evidence-based medicine fails us. There are number of issues to bear in mind. Firstly, an additional dimension for patients with MS is the background of a largely progressive disabling disease. Some patients will have had discussions with their families, carers or doctors about their wishes should they become critically ill and this should be investigated. MS patients with concomitant disease (e.g. sepsis) can look dreadfully ill, often out of proportion to their degree of compromise. However, patients can make a good recovery from relapses. The instincts that drive us to make decisions in this setting should be tempered by these factors, by an appreciation of what good medicine can achieve and by guarding against making preformed judgements about quality of life.

MS remains a disease largely of the young in affluent societies and as such a wealth of research opportunity has arisen in this field. We are not yet able to halt this terrible disease but a great deal can be done to relieve suffering. There remains much hope for the future.

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