

IMPROVING THE CARE OF PATIENTS WITH PROGRESSIVE MULTIPLE SCLEROSIS: AN EVIDENCE-BASED APPROACH

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INTRODUCTION

Many readers will have had patients admitted under their care or referred to their clinic with a label of 'known MS'. Multiple sclerosis (MS) is indeed the most common physically disabling neurological disease in young adults in the UK. Since the availability of neurologists is less than half that recommended,^{1, 2} much of the care of people with chronic disability due to MS falls to physicians from other specialities. This paper is written for physicians rather than neurologists and aims to provide practical, evidence-based guidance on improving care in MS.

NATURAL HISTORY AND EPIDEMIOLOGY

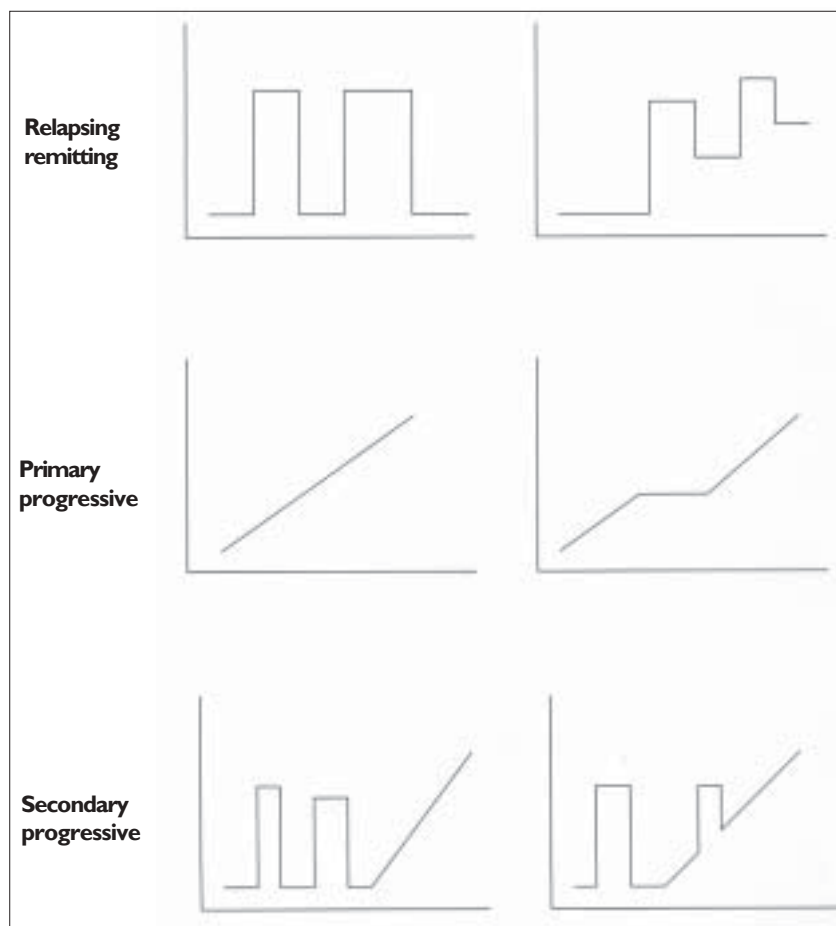
It has been estimated that 80,000 people suffer from MS in the UK.³ The prevalence varies with latitude, rising with increasing latitude in Europe.⁴ Swingler *et al.* estimated the prevalence rate for Scotland to be 158 in

1992 compared to 116 for England and Wales.⁵

The classification of MS is best formulated on the basis of the presence or absence of two factors – relapses and progression of the disease. Relapses may be defined as episodes of new neurological abnormality or the reappearance of previously observed abnormalities for at least 48 hours, preceded by a stable or improving neurological state and ideally accompanied by changes in objective signs. A fluctuation in symptom intensity does not constitute a relapse.

Patients with relapsing/remitting MS are clinically stable between relapses, although they may accrue disability due to incomplete recovery (Figure 1). Progression refers to a steady deterioration with or without superimposed relapses. The majority of individuals diagnosed with MS

FIGURE 1
Evolution of disability over time for different MS disease states.



have the relapsing/remitting form and only 15% are progressive from onset, i.e. primary progressive.⁶

Conversion to a progressive course occurs in 50% of relapsing/remitting patients within about ten years.^{6,7} Thereafter, studies of natural history and data from placebo groups in trials of progressive MS show that 30–50% of patients with progressive MS may be expected to show a deterioration of one point in the EDSS within two to three years.⁸ However, prospective studies also show that a significant proportion of progressive patients become stable, albeit with disability, within a few years.⁹

Multiple sclerosis disability is often graded in trials using the Expanded Disability Status Scale (EDSS). This is a ten point scale ranging from 0 (i.e. normal neurological examination) to 10 (i.e. death from MS) (Table 1). At lower values, scoring is based on neurological examination of a series of functional systems. For example, EDSS 3 is one functional system grade 3, or three to four functional system grade 2, with other functional system scores 0 to 1. At higher values mobility is critical, i.e. EDSS 6.5 is

TABLE 1
Expanded Disability Status Scale (EDSS).

0	Normal neurological examination
1.0	No disability, minimal signs in one FS
2.0	Minimal disability in one FS
3.0	Moderate disability in one FS or mild disability in three or four FS, though fully ambulatory
4.0	Fully ambulatory without aid; self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 or combinations of lesser grades exceeding limits of previous steps; able to walk 500 m without aid or rest
5.0	Ambulatory without aid or rest for about 200 m, disability severe enough to impair full daily activities (e.g. to work a full day without special provisions)
5.5	Ambulatory without aid or rest for about 100 m, disability severe enough to preclude full daily activities
6.0	Intermittent or unilateral constant assistance (stick, crutch, brace) required to walk about 100 m with or without resting
6.5	Constant bilateral assistance (sticks, crutches, braces, frame) required to walk about 20 m without resting
7.0	Unable to walk beyond about 5 m even with aid, essentially restricted to wheelchair. Wheels self and transfers alone; up and about in wheelchair some 12 hours a day
8.0	Essentially restricted to chair or perambulated in wheelchair but out of bed most of the day; retains many self-care functions, generally has effective use of arms
9.0	Helpless, bed confined patient; can communicate and eat
10.0	Death due to MS

bilateral assistance required to walk 20 metres without resting.¹⁰ Although the EDSS has been criticised,¹¹ it has been used in the eligibility criteria of all the treatment trials and subsequent treatment guidelines.

CLINICAL MANAGEMENT

From the perspective of appropriately managing a person with MS admitted because of increased disability, it is crucial to decide whether disability has risen because of a superimposed relapse, progression, poor symptom control (e.g. pain or spasms) or due to other intercurrent illness.

Relapses

Relapses may be treated with steroids given as high dose pulses. Various doses of intravenous methylprednisolone have been used in double blind placebo controlled randomised trials.^{12,13} Oral methylprednisolone at high dose (500 mgs for five days) may also be useful.¹⁴ While steroids appear to shorten the recovery time of the treated relapse, there is no conclusive evidence that they alter the eventual degree of recovery or the long-term prognosis.

Progression

The drug treatment of progressive MS is more problematic. Three trials of β interferon in secondary progressive MS are completed, two of which have been published.

The first large double blind placebo controlled randomised study of β interferon 1 b or placebo recruited 718 patients who scored EDSS 3–6.5 at entry and who had either experienced two or more relapses, or a one point or more increase in EDSS, in the previous two years. Confirmed progression was defined as a one point increase in EDSS sustained for at least three months, or a 0.5 increase if the baseline EDSS was 6 or 6.5. Interim analysis indicated that sustained progression was delayed in the β interferon treated group, for nine to 12 months in a study period of two to three years.¹⁵

The second large randomised controlled trial involved 618 patients receiving placebo or interferon β 1 a (22 or 44 micrograms) over three years. The primary outcome measure of time to confirmed progression of disability was not significantly affected by treatment. However, there was an effect on relapse rate and several exacerbation-related outcomes.¹⁶ There have been pilot studies of primary progressive MS and β interferon.

Other immunosuppressive drugs have been trialled for benefit on progression in secondary progressive MS. Some benefit was reported for mitoxantrone,¹⁷ and limited information is available on cladribine¹⁸ and methotrexate.¹⁹ Due to the conflicting or limited evidence at present, use of all disease modifying drugs in secondary progressive MS should be restricted to use by specialists in MS.

Symptom Control

Much remediable disability in progressive MS is not caused by relapses or progression but by poor symptom control and management. It is useful to consider the health consequences of MS at three levels. First, there are the direct consequences of demyelination, such as spasticity, weakness, tremor, paraesthesiae, etc. (Table 2). Next, secondary disorders arise from these primary conditions, like contractures and pressure sores due to spasticity and weakness (Table 3). Third, there are psychological, social and vocational consequences of these primary and secondary causes of disability and ill-health.

TABLE 2
Primary disorders, due to demyelination.

<ul style="list-style-type: none"> • Decreased vision • Weakness • Spasticity • Bladder problems • Ataxia • Sensory disturbance • Impaired cognition • Fatigue • Paroxysmal, e.g. dystonic spasms • Impotence

TABLE 3
Secondary disorders, arising from primary disorders.

<ul style="list-style-type: none"> • Contractures • Urinary tract infection • Pressure sores • Constipation • Muscle atrophy • Osteoporosis • Fatigue • Depression • Pain • Sexual difficulties • Obesity
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Symptom control and better recognition of secondary disorders are two important and poorly managed areas in the treatment of secondary progressive MS. Primary symptoms can often be treated either pharmacologically or physically. It may theoretically be possible to avoid many of the secondary disorders by careful management of primary symptoms and high-quality nursing care or physiotherapy. However, some secondary disorders may require specific treatments, e.g. osteoporosis, pain or urinary tract infections.

PRINCIPLES OF SYMPTOM MANAGEMENT

Graduated approach

Broad principles can be illustrated within a given area of symptom management. Spasticity provides an excellent example. Initial interventions are safe, non-invasive and can be applied to all MS patients with the problem. Avoidance of nociceptive stimuli and a regular home-administered stretching programme are cornerstones of treatment. A proportion of patients need oral antispasticity agents, such as baclofen (15–120 mgs total daily),²⁰ dantrolene (50–400 mgs total daily)²¹ or tizanidine (12–36 mgs total daily).²² Some of these patients may also benefit from specialist input with the use of intramuscular botulinum toxin injections²³ or intrathecal phenol administration for more focal spasticity relief.²⁴ A smaller proportion will benefit from intrathecal baclofen pumps and, even more rarely, destructive operative procedures such as rhizotomy would be considered. In general, interventions are employed systematically with greater potential risk and cost only considered if earlier levels of input have failed.

Pharmacological and physical therapies

Ataxia is a profoundly disabling MS symptom which may be treated by both pharmacological and physical therapies. The best studied agent in the treatment of tremor is isoniazid, and it has been used effectively in several trials.^{25–27} Doses employed were about 1,000 mgs daily with 100 mgs of pyridoxine. Physical therapies should serve as ancillary treatment: they range from weighted wrist bands, available through any occupational therapy department, to expensive feeding aids, which damp down tremor while permitting slower purposeful movements.

Underlying physiology and anatomy

An appreciation of underlying physiology and anatomy assists in the development of sound management plans for MS symptoms. Bladder dysfunction is very common among people disabled with progressive MS. Anticholinergics, such as oxybutinin and tolterodine, are frequently prescribed, but it is important to remember that the bladder is an organ of voiding as well as storage. Anticholinergics may be useful for the treatment of frequency, urgency and incontinence, but if bladder post-micturition residual volumes are consistently high (e.g. above 100 mls) then a mechanism to improve bladder emptying is also required. Options include inexpensive bladder stimulators that can be applied to the suprapubic area for voiding,²⁸ and intermittent self-catheterisation.

Accurate diagnosis

Accurate diagnostic skills are required when MS symptoms may be primary or secondary, or a mixture of both, to ensure the most appropriate treatment. Weakness may be primary due to demyelination and/or secondary due to deconditioning. Pain may be primary neuropathic pain, or secondary as a result of spasticity, poor posture

or inadequate pressure relief. Distinction is important because treatments differ – neuropathic pain is best treated with anticonvulsants or tricyclic antidepressants, while painful spasms respond to antispasticity agents.

Fatigue is a prime example of a multi-factorial MS symptom. Fatigue may be a primary MS symptom, and is common in clinic- and population-based studies of people with MS.²⁹ Fatigue may also be a secondary disorder related to sleep disturbance from pain or nocturia, to high energy expenditure from spasticity, or to deconditioning from weakness and restricted lifestyle. Sedating medication may exacerbate fatigue. A sense of perpetual tiredness, it must always be remembered, may be a manifestation of depression.

The treatment of fatigue relies upon treating the causative factors. Cases of fatigue as a primary symptom may be treated with amantadine (100 mgs b.d.), for which large double blind placebo controlled randomised trials provide supportive evidence.^{30, 31} Smaller studies have explored the use of diaminopyridines.³²

Future directions

Best management of progressive MS relies greatly on skilled prescribing of symptomatic treatments. Critical reviews of available evidence are required linked to additional well designed studies to supplement gaps in current knowledge. Such research may offer new treatments and clarify the role of well publicised (and less orthodox) agents such as cannabis.

REHABILITATION IN MS

Many patients with progressive MS have a range of primary and secondary disorders leading to considerable disability and handicap. Successful management requires a variety of skills in addition to the careful medical assessment and prescribing described above. When doctors work with other disciplines to achieve optimisation of function and independence for their patients, they are providing rehabilitation.

Randomised trials of in- and out-patient rehabilitation have been conducted using waiting list controls. In-patient rehabilitation for an average of 20 days in progressive MS leads to significantly lessened disability and handicap by seven weeks.³³ Extended out-patient programmes on a once weekly basis for a year reduced fatigue and other symptoms.³⁴

Scarcity of neurologists and rehabilitation specialists may preclude local referral to neurological rehabilitation services. In the absence of such well organised services, whether in- or out-patient, how may an individual doctor help an individual patient with complex problems? The benefits of a comprehensive assessment and coordination of referrals cannot be overemphasised. Patients may often benefit from input from other specialists such as urology,

orthopaedics and psychiatry.

Physiotherapy, occupational therapy, speech and language therapy assessment for communication and swallowing and social work will be available in every hospital. Wheelchair assessment, special seating, orthoptics and driving assessment can be accessed widely. Commissioners of care should be informed when health needs cannot be met by existing services. Finally, the doctor has an important role in providing information and support to patients and carers.

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