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CLINICAL REVIEW

Relapse in multiple sclerosis

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Multiple sclerosis is an autoimmune inflammatory disorder of the central nervous system. The global prevalence of the condition varies widely, with the most recent meta-analysis finding an increase in 3 cases per 100 000 per degree of latitude.[1] The disease is more common in females, with a female to male incident ratio of 2.4.[2]

This review discusses the recognition and management of relapses in multiple sclerosis, and focuses on facts that are applicable to the generalist, not specialist.

How is multiple sclerosis classified?

The clinical course of multiple sclerosis may vary.[3] It is relapsing-remitting from onset in 85% of cases, characterised by episodes of neurological deficit (relapses) that recover (that is, remit), to varying degrees; if relapses are severe and frequent the term "rapidly evolving severe multiple sclerosis" is sometimes used. In the other 15% of cases, a gradual progression occurs from onset (primary progressive multiple sclerosis). Relapsing-remitting multiple sclerosis converts to secondary progressive multiple sclerosis after 15 years in 50% of cases.[4] This conversion is gradual,[5] with a decline in the number of relapses[6 7] and a steady deterioration in neurological function between relapses.

Relapses were traditionally associated with relapsing-remitting multiple sclerosis and secondary progressive multiple sclerosis.[8] It has become increasingly recognised that various permutations of relapses and progression occur within and between patients, whatever their disease course. Hence a new classification system was developed by consensus in 2013, which is yet to permeate real life clinical practice fully. This system subclassifies secondary progressive multiple sclerosis and primary progressive multiple sclerosis, based on activity (active versus non-active) and progression (with progression versus without progression). Activity is determined by relapses or activity on magnetic resonance imaging, while progression is determined by sustained accumulation of disability.[5]

Why is managing relapses important?

In recent years there has been a remarkable expansion in the number of immunotherapies available for relapsing-remitting multiple sclerosis, with a range of efficacies (fig 1⇓). Increasing efficacy is, however, accompanied by an increased risk of adverse events. Availability of potent treatments to suppress disease activity has led to two major effects. Firstly, there is a renewed importance of monitoring the occurrence of relapses after starting first line treatment in case there is a need for treatment escalation. Secondly, a zero tolerance approach to relapses has become possible, leading to the concept of "no evidence of disease activity" (NEDA).[9 10] This has been adopted as an outcome measure in clinical trials of multiple sclerosis,[11 12] for the purpose of which NEDA is defined by the triad of no evidence of relapse occurrence, no sustained progression of disability, and no appearance of new lesions on magnetic resonance imaging. Neurologists are currently divided on their opinion regarding NEDA, and therefore the degree of tolerance to ongoing inflammatory activity varies between centres and countries.

Since the eligibility criteria for immunotherapy rely on enumeration of relapses and their severity, the precise recognition and documentation of relapses has gained additional importance. In countries where such escalation is recommended by national guidelines, a diagnosis of a relapse needs to be followed by prompt communication of its occurrence to the neurologist to enable a timely decision to be made regarding initiation or escalation of immunotherapy.

A delay in treatment escalation may impact negatively on long term outcome. However, evidence is conflicting. Some early versus delayed treatment studies of established relapsing-remitting multiple sclerosis suggest a lasting impact on accumulation of disability (for example, interferon beta and laquinimod),[13 14] but not others.[15] These studies were either observational or extension trials, retrospectively looking for an

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The bottom line

- Relapse of multiple sclerosis is a patient reported, or objectively observed, event typical of an acute inflammatory demyelinating event in the central nervous system, current or historical, with a duration of at least 24 hours
- The differential diagnosis of a relapse includes alternative neurological diagnoses, pseudo-relapses, short lived paroxysmal symptoms, day to day fluctuations, and functional symptoms
- Clinically significant or severe relapses may benefit from treatment with corticosteroid for five days
- Documentation and timely communication of the relapse to the patient's multiple sclerosis specialist service, such as through the multiple sclerosis specialist nurse, is important, to enable timely decisions on immunotherapy initiation or escalation
- Non-adherence with immunotherapy is under-recognised by both patients and doctors

Sources and selection criteria

We carried out an electronic search through PubMed, Ovid, and CINAHL using the search terms "multiple sclerosis" and "relapse". We also searched personal reference archives and had discussions with colleagues. One author (CH) used information from three highly standardised patient education programmes developed at the Hamburg centre.

early versus delayed start of treatment effect. A randomised trial comparing immediate versus delayed start of treatment in relapsing-remitting multiple sclerosis with long term disability as the planned primary outcome has not been performed.

How common are relapses?

The true prevalence of relapses can be difficult to record since patients present variably to community services, general practices, and tertiary services, or do not contact health services at all. Indeed a recent survey of patients with multiple sclerosis showed that 28% of respondents failed to report their most recent attack and 46% had failed to report an attack in the past.[16] In England, with a prevalence for multiple sclerosis of 203 per 100 000 population,[2] a relapsing-remitting multiple sclerosis subtype prevalence of 47%,[17] an average patient population of 6487 per practice,[18] and a relapse rate of between 0.3 and 1.0,[19] the average general practice would expect to see between two and six relapses a year.

It is a recognised feature that the frequency of relapses decreases with time from diagnosis and age, and relapse-free periods are not uncommon.[7] Annualised relapse rates in placebo groups of randomised controlled trials have been decreasing with time[20]; this is most likely the result of changes in trial populations in response to the increasing availability of treatments, rather than to a reflection of a changing clinical course of the disease.[21]

What factors affect the frequency of relapses?

Several factors have been hypothesised to trigger relapses or to influence the frequency of relapses, and their modifiable or predictive nature makes them attractive candidates for intervention. Substantial evidence to support an association with relapses has been shown only for systemic infections, self reported stress, and the postpartum period.[22] Reasonable experimental evidence shows that the association is causal in the case of systemic infections.[23] It might be worth taking steps to prevent recurrent infections if they trigger relapses. Although self reported stress may be a prodrome of relapses,[24] external threat increases the risk of relapse, suggesting a causal association.[25] Physical trauma,[26] vaccinations,[27] and epidural analgesia[28] are not associated with relapses. No controlled studies have examined the effect of surgical operations. There is only limited evidence that omega 6 fatty acid, exposure to sunlight, and vitamin D reduce the relapse rate.[22]

How is a relapse diagnosed?

Diagnosis of a relapse is predominantly clinical. Since any part of the central nervous system may be affected, the neurological deficits are protean, and may involve one or multiple sites (monofocal or multifocal, respectively). Common symptoms include loss of visual acuity (optic neuritis), sensory alterations, weakness, imbalance (ataxia), fatigue, and cognitive difficulty. According to the 2010 revisions to the McDonald Criteria of the International Panel on Diagnosis of Multiple Sclerosis,[29] a relapse "is defined as a patient-reported or objectively observed event typical of an acute inflammatory demyelinating event in the CNS [central nervous system], current or historical, with duration of at least 24 hours, in the absence of fever or infection." A relapse typically develops over hours or days until a plateau is reached, which may last days or weeks, followed by complete or incomplete recovery at varying rates. Since relapses may be multifocal and may have a fluctuating or staggered onset and course, it may be difficult to differentiate between a single complex relapse and multiple relapses close to each other. Therefore a stable or improving period of 30 days should separate the onset of subsequent events for them to be distinguished as separate relapses.[30 31]

In the largest study of relapse phenotype to date, most relapses were monofocal (74%) and the commonest relapse phenotype was sensory (48%), followed by weakness (34%) and problems with visual acuity (20%).[32] Recurring relapses are more likely to be of the same phenotype,[32 33] but multiple relapses in the same limb are uncommon,[34] indicating that within individuals, relapses may have a predilection for neuroanatomical area types but not for precise location.

What are the differential diagnoses?

Since the diagnosis of relapses is predominantly clinical, it is important to be aware of situations which may lead to under-diagnosis or over-diagnosis of relapses (box 1). In addition, several differential diagnoses need to be considered.

Alternative diagnoses

A diagnosis of multiple sclerosis does not render a patient immune from a second neurological condition. This can include common (for example, compressive spondyloradiculopathy, carpal tunnel syndrome) or uncommon (for example, cauda equina syndrome, cerebral sinus thrombosis) diagnoses.

Box 1 Symptoms or situations leading to under-diagnosis or over-diagnosis of relapses

Non-physical relapses

Characterised by purely subjective symptoms such as increased fatigue, or cognitive impairment, with no physical component

Minor relapses

Where it is difficult to measure symptoms objectively such as sensory disturbances, or clinically undetectable visual or other symptoms

Infection related relapse

May be dismissed owing to the occurrence of infection, or misdiagnosed as pseudo-relapses. It is a well known observation that systemic infections are associated with an increased likelihood of relapses during the "at risk period," which extends from one week before to five weeks after the onset of the infection; infection associated relapses account for one third of all relapses.[w12-w17] It has been shown that infection related relapses are accompanied by true inflammatory activity, with gadolinium enhancement[w14]

Relapses masquerading as progression and vice versa

Multiple overlapping relapses with poor recovery may masquerade as progression; conversely progression may masquerade as multiple reported relapses, especially with poor historians or cognitive problems. Multiple collateral histories are important if relapses are unusually high in number with disproportionately little accumulation of disability, or if a diagnosis of secondary progression is being considered early after onset of multiple sclerosis (conversion to secondary progression only occurs in 25% at six years after onset)[w18]

Relapses consisting of a cluster of paroxysmal symptoms

Although single paroxysmal episodes do not constitute a relapse, multiple episodes occurring within a self limited period with a duration longer than 24 hours constitute a relapse[w19]

Paroxysmal symptoms

Patients with multiple sclerosis are prone to paroxysmal symptoms, such as trigeminal neuralgia, Lhermitte's phenomenon, and tonic spasms. These are usually intermittent and are not relapses if present for less than 24 hours.[30]

Pseudo-relapses

A pseudo-relapse is an exacerbation of previous symptoms occurring in the context of elevation of body temperature (heat, exercise, or fever) or systemic inflammatory activity (infection or another ongoing systemic illness), which cause conduction block in abnormal axons.[3] Hence unlike relapses, pseudo-relapses are always exacerbations of previous symptoms, are typically transient, and their onset and resolution roughly coincide with the triggering situation.

Day to day fluctuations

Day to day fluctuations in chronic symptoms are common in multiple sclerosis[35] and may be misinterpreted as relapses. This is usually indicated by their stereotypical nature, and a disproportionate frequency of reported relapses, higher than expected when considering the patient's disability progression.

Functional relapses

Medically unexplained symptoms are common, especially in general practice, where they can constitute two thirds of all reported symptoms[36] and account for the predominant confident diagnosis in 4% of consultations.[37] Their occurrence in the context of multiple sclerosis can be challenging. Non-organic "relapses" are well documented, and functional overlay during genuine relapses may inflate severity.[38-41] It is important to recognise the unconscious needs underlying this presentation.

Where are relapses best managed?

Uncommonly there is a need for hospital admission, owing to the severity of relapse (such as severe paralysis, swallowing or breathing difficulty, urinary retention), the need for intensive physiotherapy, or doubts about diagnosis. Most relapses can be managed without hospital admission, with support from community based multiple sclerosis nurses and neurorehabilitation services or multiple sclerosis relapse clinics, or both. Communication of relapse occurrence to the multiple sclerosis specialist team is essential, and therefore documentation of relapse is important (box 2). Severity of relapses may importantly affect decisions about immunotherapy in some healthcare systems and are important to document. NHS England has produced some guidelines to help in the assessment of severity (fig 2⇓).[31] These are not validated and each case should be treated on its own merits, within the context of the individual patient.

How are relapses treated?

Use of high dose short term corticosteroids is the accepted treatment for relapses.[42] Before corticosteroid is administered, a rapid infection screen (symptoms, temperature, urine dipstick) is recommended, since infections commonly associate with relapses (box 1). Active symptomatic infections need treatment before corticosteroids are given. Relapses accompanied by an asymptomatic dipstick positive urinary tract infection can be safely, simultaneously, and rapidly treated with corticosteroids and trimethoprim until the results of microbiological culture and sensitivity analysis become available.[43]

Three systematic reviews, the largest of which was a meta-analysis of 12 randomised controlled trials in 1714 people, showed that corticosteroid treatment shortened the duration of relapses but did not seem to affect long term outcome.[44-46] Improvement was seen in trials allowing randomisation up to eight weeks after the onset of relapse.[45] There is considerable diversity among neurologists and national guidelines regarding dose, duration, and choice of corticosteroid agent.[47] The National Institute for Health and Care Excellence (NICE) recommends oral treatment with 500 mg methylprednisolone daily for five days.[42] If patients are in hospital, or if oral corticosteroids are not effective, intravenous treatment with 1 g methylprednisolone daily for 3-5 days is recommended.[42] Oral treatment is as effective as the intravenous route.[48] The clinical effectiveness of corticosteroid administered in home or outpatient settings is similar.[49]

The decision to treat is best taken in conjunction with the patient in a process of shared decision making,[50] based on the provision of adequate information and an assessment of the impact of the relapse on the patient. In a randomised controlled trial, patients educated about the evidence on corticosteroid use during relapse decided to treat fewer relapses, opted for more oral than intravenous corticosteroids, had higher levels of perceived

Box 2 Important characteristics of a relapse to document

- Date of onset
- Duration
- Functional system affected
- Severity (mild, moderate, or severe)
- Any treatment given for the relapse
- Extent of recovery
- Length of immunotherapy and adherence

autonomy, and had less contact with their clinicians.[51] Patients were able to self administer oral treatments with no substantial risks; however, NICE guidelines advise against giving patients a supply of corticosteroids to self administer for future relapses.[42] Clinical study data supporting a second ultra high (2 g/day) corticosteroid treatment after failure of a first course are missing, and this practice is still based on animal data.[52] In tertiary settings, plasmapheresis is used for severe corticosteroid resistant relapses, based on one small randomised controlled trial.[53] Two well conducted randomised controlled trials of 76 and 19 patients showed that intravenous immunoglobulins as add-on treatment with methylprednisolone did not confer additional benefit.[54 55] It has been suggested that intravenous immunoglobulins may be a therapeutic option if steroids are contraindicated, based on one small study of 17 patients.[56]

Advising on recovery and prognosis after relapse

It is important to manage expectations during a relapse, especially early after a diagnosis of multiple sclerosis.

Recovery from individual relapse

Significant recovery usually occurs within the first two or three months,[57 58] but relapses may continue to improve for up to 12 months.[57] Residual disability is seen in one third to half of all relapses[59-62] and is more likely if the relapse is severe, multifocal, initially slow to recover, and in people 30 years or older.[60 62] One study indicates that a lack of recovery from a relapse predicts incomplete remission of future relapses.[63]

Impact of relapses on long term disability

Whether relapses affect long term disability is a contentious issue. Modern evaluation of long term follow-up patient cohort studies suggests that overall relapse rate does not impact on long term disability (several studies, recently reviewed),[64] and although relapses in the first two years seem to be important,[6 65] the effect of individual relapses is overshadowed by the onset of progressive disease beyond this initial period.[66] Hence, currently it is generally accepted that the greatest determinant of irreversible neurological disability is entry into the progressive phase.

Rehabilitation

A recent systematic review has tackled rehabilitation interventions in relapses.[67] Three studies were identified; two used a before and after design, whereas one small study (n=40) applied a randomised design. All studies used multidisciplinary interventions and showed strong improvements. The specificity of the effect through control of the amount of attention is, however, unclear. Owing to this and other methodological problems, the added value of a comprehensive rehabilitation intervention needs further investigation.

The role of the multiple sclerosis specialist nurse

Although their role varies between countries and regions,[68] multiple sclerosis nurses have become integral to the care of the patients in relapse. Perhaps, most importantly, the nurses provide a vital link between general practices, community health services, social support, and neurology specialist care. When relapse occurs these nurses are typically the patient's first port of call through, for instance, a dedicated telephone helpline. Increasingly they provide a rapid (for example, within 48 hours), responsive, reliable service, which may be inclusive of modern methods of communication such as text messaging or video and voice over internet (VoIP). Multiple sclerosis nurses can help general practitioners in the diagnosis of a relapse, particularly when meticulous history taking may be needed. They can screen for infection, prescribe steroids if needed, and provide support during the relapse, including the identification of specific needs and referral to the appropriate allied health professionals. In most centres, multiple sclerosis nurses follow up patients at six weeks post-relapse to assess recovery, provide relapse education, deal with any issues with adherence or side effects from immunotherapies, and communicate with the patient's neurologist.

Although high quality research into the cost effectiveness of multiple sclerosis nurses is lacking, and it is now hard to justify the ethics of controlled studies since they have become so essential, there is evidence supporting their role. Multiple sclerosis nurses facilitate a timely response to relapses; in one study[69] patients reported their relapse symptoms to a nurse sooner (within 10 days of onset) compared with a mean time of 51 days when reporting the same symptoms to a general practitioner; 85% of patients were treated for their relapse within 10 days of first reporting symptoms; and a threefold increase in treatment capacity occurred. In a more recent study, a noticeable reduction in hospital bed utilisation by patients with multiple sclerosis was seen.[70]

Relapse occurrence: implications for immunotherapy

Relapses may be a reflection of non-adherence or may signal the need for initiation of immunotherapy or its escalation, if there has been a suboptimal response to immunotherapy.

Adherence

Treatment adherence may be assessed and managed at community level, by the general practitioner or multiple sclerosis specialist nurse. Non-adherence to drugs may be an underlying reason for relapse and is under-recognised by doctors.[71] Its management may avoid unnecessary referral to neurology and treatment changes. Non-adherence may manifest as discontinuation or incomplete persistence.

Discontinuation—In the literature, mean discontinuation rates of first line injectable treatments range from 10% to 50%,[72-74] with major reasons including adverse events and perceived lack of efficacy. Common adverse events include flu-like symptoms with interferon beta, injection site reactions with glatiramer acetate, and flushing or gastrointestinal symptoms with dimethyl fumarate. Discontinuation usually necessitates switching to another agent.

Incomplete persistence, or "treatment breaks"—These are also prevalent. Two studies using electronic means of monitoring injections found that 9% to 20% of patients were administering less than 80% of injections, with a mean adherence of 66%.[75 76] In addition, patients underestimated their adherence.[75] Collateral history taking and electronic or manual (for example, diary) monitoring may help in the diagnosis of incomplete persistence. Causes of incomplete persistence are numerous. If forgetfulness is the main culprit, simple measures may include reminder alarms, pill boxes, smartphone apps (recently reviewed),[77] and the help of relatives. If side effects are the main reason, prophylactic drugs (for example, non-steroidal anti-inflammatory agents before injection), practical measures such as administering weekly injections on a Saturday, or switching to an alternative injection method may be enough. Adequate patient education,[78] software based telephone contact,[79] nursing support,[80] and treatment of depression[81] may help.

Immunotherapy initiation or escalation

Review of immunotherapy falls within the remit of specialist neurology services; hence discussion or referral, or both is recommended. Occurrence of a relapse in a treatment naive patient may render them eligible for first line immunotherapy (fig 1 and box 3).

For patients recently established on first line treatment, most neurologists would wait at least six months or a year before offering treatment escalation, unless a rapidly evolving severe clinical course becomes apparent. It is important to be aware of the potential for overzealous escalation of treatment at low levels of disability in the context of over-interpretation of relapses.

Only two phase III treatment escalation trials have been performed: natalizumab add-on to interferon beta[82] (findings did not enter clinical practice owing to high risk of progressive multifocal leucoencephalopathy) and alemtuzumab in patients non-responsive to interferon beta or glatiramer acetate.[83] Several small other treatment escalation studies exist.[84] Hence guidelines and decisions on escalation to other treatments are mainly based on data from comparator studies that have not been powered to detect superiority (for example, DEFINE),[85] post hoc subgroup analysis comparing treatment naive with non-naive patients in placebo controlled trials (for example, FREEDOMS,[86] TRANSFORMS),[87] and less appropriately from comparing relative risk reductions across different placebo controlled studies. Clearly, large well designed treatment escalation or comparator studies are needed. This lack of evidence is partly responsible for variation in choice of second line treatment, but other factors include neurologist and patient preference, local practice, regional or national guidelines, availability, and disease severity.

The decision to start or escalate immunotherapy, and the choice of agent, is best made using shared decision making, tailored to individual patients, which takes into account patient factors (autonomy and preference) and physician factors (medical evidence and expertise).[88] Patients with multiple sclerosis are able to process evidence and scientific uncertainty without additional emotional burden, and they can be educated in very basic statistics such as calculations of absolute risk reduction as presented in figure 1.[89]

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Box 3 Immunotherapy for relapsing-remitting multiple sclerosis

First line treatment

- Interferon beta[w20]
- Glatiramer acetate[w20]
- Teriflunomide[w21]
- Dimethyl fumarate[w22]
- Alemtuzumab[w23]

First line, rapidly evolving severe relapsing remitting multiple sclerosis

- Natalizumab[w20]

Second line treatment

- Fingolimod[w20]
- Natalizumab[w20]

Questions for future research

What is the value of treating to a target of "no evidence of disease activity"?

What is the relative benefit of immunotherapies when compared head to head?

What is the benefit of starting immunotherapy early in delayed start drug trials?

What is the benefit of treatment escalation using specific immunotherapies?

Which multiple sclerosis specialist nursing roles are cost effective during management of relapses?

Which forms of rehabilitation are cost effective after a multiple sclerosis relapse?

Would better information provision and shared decision making pathways increase patient participation and psychological wellbeing?

Additional educational resources

Resources for healthcare professionals

NICE guidelines for management of multiple sclerosis in primary and secondary care (www.nice.org.uk/guidance/cg186)

NHS England commissioning policy for immunotherapies (www.england.nhs.uk/wp-content/uploads/2013/10/d04-p-b.pdf)

Resources for multiple sclerosis specialist nurses (www.msnursepro.org/)

Resources for patients

Multiple sclerosis societies (www.mssociety.org.uk/, www.mstrust.org.uk/, and www.nationalmssociety.org/)

Patient decision aids (http://sdm.rightcare.nhs.uk/pda/multiple-sclerosis/ and www.msdecisions.org.uk/)

Patient symptom tracker (www.symtrac.com/)

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Figures

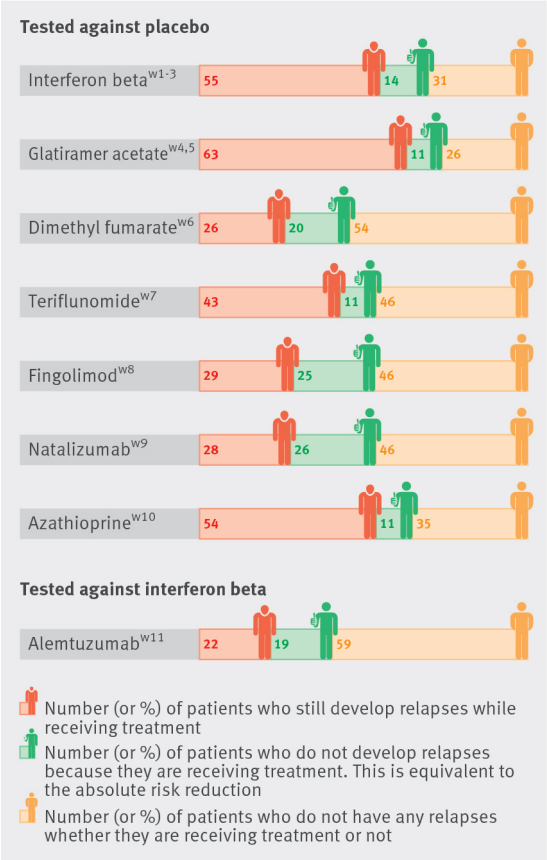

Fig 1 Three possible outcomes in patients with multiple sclerosis within two years of trial duration. For patient education purposes, the absolute risk reduction (ARR) is recommended versus the relative risk reduction (RRR), since the ARR more closely reflects real treatment effects. The RRR is the ARR expressed as a percentage of relapsing patients in the control group. Therefore the RRR always appears larger than the ARR. Each bar represents the outcome of 100 patients, and numbers are therefore equivalent to percentages

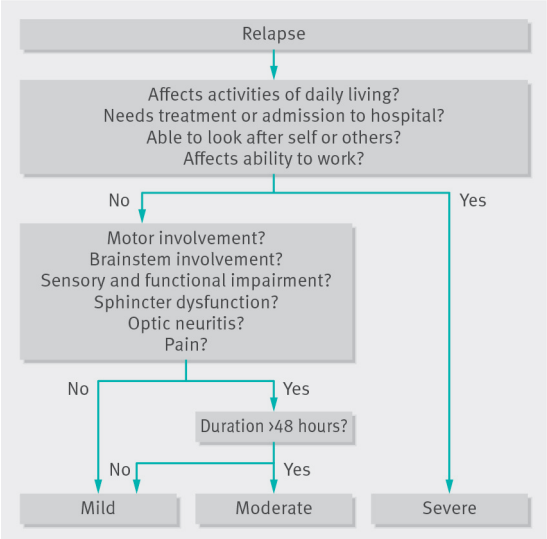

Fig 2 Assessing severity of relapses. “Severe” and “disabling” are used interchangeably, as are “moderate” and “clinically significant”