Case Report

Assessment and Treatment Strategies for a Multiple Sclerosis Relapse

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Abstract

Relapses are the hallmark features of relapsing-remitting multiple sclerosis (RRMS). True relapses may be challenging to accurately diagnose. A clinician must rely on a combination of history, exam findings, laboratory studies, and neuroimaging to decide whether or not to treat for a presumed relapse. Although many consider MRI as the gold standard diagnostic test, it may not be rapidly accessible and still could miss lesions. In light of this diagnostic complexity, future directions including development and validation of a scale to assess MS relapse probability and severity would be useful to multiple sclerosis specialists and practicing neurologists. Given the complex pathophysiology of MS, more research is needed to ascertain the validity of promising biomarkers for predicting relapse.

INTRODUCTION

Relapses are the defining features of relapsing-remitting multiple sclerosis (MS). Approximately 85% to 90% of patients with MS will experience one or more relapses, also called flares or exacerbations, at some point in the course of their disease [1]. The standard definition of an MS relapse as stated in the revised McDonald Criteria is a "patient-reported or objectively observed event typical of an acute inflammatory demyelinating event in the central nervous system, current or historical, with the duration of at least 24 hours in the absence of fever or infection" [2].

Common symptoms of an MS relapse

MS relapses can manifest as a wide array of symptoms. Among the most frequent are sensory symptoms, such as numbness and tingling (54.3%), and visual symptoms (21.5%) [3]. Other features include imbalance from cerebellar involvement, extremity weakness, and bladder and bowel dysfunction from spinal cord involvement of the pyramidal tracts. MS relapses associated with pyramidal signs, cerebellar involvement, or sphincter dysfunction tend to be more severe and require prompt identification and treatment. In contrast, patients with sensory, visual, and brainstem symptoms may have a more complete recovery and not necessarily require immediate treatment. Cerebellar relapses are more common in patients who are male, older, and have progressive disease, whereas women tend to exhibit more sensory or visual symptoms [4]. In general, relapse severity increases and recovery decreases with age and with more advanced disease [4].

MS relapse assessment options

The physical exam is the most important tool for assessing MS relapse. This involves assessing vital signs, which may reveal alterations in temperature, blood pressure, and heart rate. A thorough neurological exam should include assessment of vision, strength, sensation, gait, and coordination. Vision testing consists of examining visual acuity, color vision, eye movements, and visual fields. Abnormal or new findings on vision testing may indicate a new episode of optic neuritis. In addition, optical coherence tomography (OCT) and visual evoked potentials (VEPs) are adjunctive studies that are increasingly being utilized to provide objective evidence of a patient's complaint. The neurological exam may also uncover brainstem findings including double vision, altered facial sensation, and speech changes. Abnormalities in a patient's strength and sensory exams could point to transverse myelitis. Difficulties with gait, coordination, and tremor are often referable to the cerebellum. The neurological examination should always be compared to previously documented exams since new findings may indicate a new relapse or progression of symptoms.

Magnetic resonance imaging (MRI) has also been an essential tool in diagnosing and monitoring MS disease activity and progression over time. When a patient's subjective complaint, such as numbness, can be correlated with new objective findings on an MRI study, this argues for a true relapse. There are unique utilities with different sequences of MRI. For example, T2 FLAIR sequences generally measure the total disease burden based on the accumulated number and size of brain lesions.

Meanwhile, gadolinium-enhancing T1 lesions are indicative of breakdown of the blood-brain barrier and signal recent disease activity. Therefore, finding a new lesion, especially a gadolinium-enhancing lesion that corresponds to a patient's new symptoms, lends support to the diagnosis of a true relapse. However, determining a relapse should not exclusively rely on MRI findings, as new lesions may not be apparent immediately on imaging. Also, the imaging study may not encompass the pertinent area of the nervous system affected (e.g., lesion evidence on MRI orbit but not MRI brain). Sometimes it is necessary to scan the entire spinal axis if transverse myelitis is suspected. However, since this can be time-intensive and cost-prohibitive, a practitioner needs to carefully choose the most appropriate imaging location and modality based on localizing information gathered during the history and examination.

Determining the validity of a relapse

The combination of patient symptoms, objective physical exam findings, and neuroimaging results help determine whether a patient is truly having an MS relapse. A key consideration is the need to rule out fever, metabolic disturbances, infection, or other altered physiological processes to differentiate a true relapse from a "pseudo-relapse." True relapses are associated with new or worsening symptoms that persist at least 1-3 days, and the recovery phase may span weeks or even months. In contrast, pseudo-relapses are acutely worsening symptoms that are typically associated with an increase in body temperature due to infection, heat exposure, or exercise. Symptoms caused by a pseudo-relapse often resolve once an individual's physiological status returns to his or her baseline, such as when one's body temperature normalizes after exercise or with resolution of fever.

Pseudo-relapses can occur in the setting of a worsening medical illness, such as poor glycemic control in severe diabetes mellitus and poorly controlled thyroid disease. An underlying, infection, such as a urinary tract or upper respiratory infection is frequently associated with neurological symptoms linked to a previous MS attack. Thus, it is important to obtain screening laboratory testing including complete blood count, serum electrolytes, and urinalysis.

It is essential to differentiate a relapse from medical comorbidities and infectious symptoms and treat the underlying illness first. However, in clinical practice the distinction between a true relapse and a pseudo-relapse may not be clear. For instance, a true relapse may be the inciting cause of an infection (e.g., a urinary tract infection secondary to an exacerbation causing bladder retention) or can occur concomitantly with an infection. Another important aspect defining an MS relapse is the patients' understanding of what relapses are and their perception of relapse symptoms, which can differ considerably from clinicians' perceptions. Some patients may not readily report relapses, whereas others may report frequent "relapses," particularly if they perceive fluctuations in baseline residual symptoms as relapses. It is also important to take into account the role that anxiety and emotional status may have in how someone reports symptoms. In addition, patients have different thresholds for symptom tolerance and degree of disability that they find acceptable.

Furthermore, as a patient enters more advanced phases of disease, worsening symptoms and accruing disability may indicate progressive disease rather than signify relapse. A diagnosis of secondary progressive MS requires a history of at least one clinical relapse followed by at least 6 to 12 months of continuous disability progression independent of clinical relapses. However, no clear clinical criteria exist to determine when a patient transitions from relapsing-remitting multiple sclerosis to secondary progressive multiple sclerosis [5].

Assessment of the severity of an MS relapse

There is currently no validated tool or consensus guideline on how to assess the severity of an MS relapse. Determination of severity is an important factor in deciding whether or not to treat a patient's relapse. As relapse severity correlates with disease disability, a patient with a severe relapse should be treated more promptly.

In clinical trial settings, scales such as the Kurtzke Expanded Disability Status Scale (EDSS) [6] and Multiple Sclerosis Functional Composite (MSFC) [7] are used to document neurological status and track changes over time. However, these tools are not commonly utilized in routine practice to assess for a possible MS relapse. Some groups have attempted to create tools to characterize relapses. Freedman and colleagues developed a system that characterizes relapse severity as mild, moderate, and severe depending on the symptoms, number and type of body system involvement, effect on Activities of Daily Living (ADLs), whether treatment or hospitalization is required, and the time to recovery [8]. However, these guidelines are more helpful in the retrospective evaluation of a relapse. Ross et al. produced a patient questionnaire called the Assessing Relapse in Multiple Sclerosis (ARMS) Questionnaire to assess relapse in multiple sclerosis [9]. It is a relatively easy to use and practical system, which asks the patient to rate symptoms using a 1-10 scale that could be further categorized as mild, moderate, and severe. If formally validated, this questionnaire could provide an effective method for clinicians to evaluate the patient's perceptions of relapse symptoms and quickly identify issues to focus on during history taking, examination, and testing.

Biomarkers for an MS relapse

Over the past two decades, research has been geared toward identifying biomarkers that can help with the diagnosis, prognosis, and individualized treatment of multiple sclerosis. However, there are no definitive biomarkers for identifying when a relapse will occur. Gene expression studies have identified promising targets that can help to predict relapses. A previous report found 266 genes differentially expressed in peripheral blood mononuclear cells (PBMCs), distinguishing MS patients in relapse versus remission [10]. Otaegui et al. analyzed microRNA (miRNA) expression patterns in PBMCs from MS patients in relapse, remission, and in healthy individuals. Importantly, the study showed that miR-18b and miR-599 are increased during relapse, while miR-193a increased in remission [11]. A study by Fenoglio et al. compared miRNA expression from PBMCs between MS patients and healthy subjects. Intriguingly, increased expression of miR-21, miR-146a, and miR-146b occurred during the relapse phase in RRMS patients as compared with controls

[12].

Cytokine production in MS is also an important area of interest, although with less concrete results. Simpson et al. identified cytokine expression profiles in stimulated PBMCs to predict relapse risk in RRMS patients using a prospective cohort study design. Their analysis showed that, on mutual adjustment, increased levels of IFN-γ correlate with increased risk of relapse, while increased levels of TNF-α reduce the risk of relapse [13]. These findings differ by immunomodulatory therapy, season, serum vitamin D, and genotype. Furthermore, the study is limited by the lack of MRI data, which is the gold standard used to validate active disease. Another study sought to determine the relationship between IL-10 and MRI activity between RRMS patients and healthy controls. The results showed decreased IL-10 serum levels prior to relapse, while elevated levels occurred the month during which MRI disease activity resolved [14].

Factors involved in regulating inflammation and maintaining the structural integrity of the blood-brain barrier to measure disease activity are growing in popularity. Studies have found that matrix metalloproteinases (MMPs), specifically MMP-2 and MMP-9, increased in the cerebrospinal fluid (CSF) and/or serum during relapse and correlated with MRI disease activity [15-17]. A study by Norgren et al. evaluated the levels of neurofilament light (NF-L) in CSF from MS patients. The study found that NF-L levels increased during active relapse and correlated with MS activity [18].

Another area of growing interest is how oxidative stress plays a role in MS pathogenesis. Our group recently showed that MS treatment dimethyl fumarate enhances Nrf2-mediated antioxidant response gene transcription through activation of ERK1/2 MAPK signaling pathway thus leading to neuroprotection in neural progenitor cells and neurons [19]. Different biomarkers have been elucidated that can potentially predict the occurrence of relapses. Sbardella et al. compared CSF levels of isoprostanes (IsoP), a potential marker for oxidative stress, between patients with a first clinical attack suggestive of MS and healthy controls. Their results showed that the risk of experiencing a relapse correlated with higher levels of IsoP [20]. Another report by Fiorini et al. found that vitamin D-binding protein (DBP) is more oxidized in both relapsing and remitting patients compared to healthy individuals [21]. Furthermore, apolipoprotein A-IV also showed increased oxidation during the relapse phase compared to both remitting and healthy patients [21].

Because obtaining CSF samples is not clinically practical due to lumbar puncture procedure, there is a preference to identify serum biomarkers for an easier approach for both healthcare provider and patient. Overall, though potentially promising, these results need further confirmation. For the moment, they are still far from being exploitable in routine clinical practice.

MS relapse treatments

The severity of a patient's relapse influences how quickly and aggressively it should be treated. For severe relapses, the patient may need to be hospitalized, evaluated in an emergency department, or treated in an outpatient infusion center. In contrast, less severe relapses may be treated with an outpatient course of oral prednisone. IV methylprednisolone is the preferred first-line treatment for MS acute relapse based on a double-blind study showing that a significantly higher percentage of patients receiving high dose IV methylprednisolone had an accelerated recovery from MS relapse compared to patients receiving placebo [22]. It is usually dosed 1000 mg daily for 3-7 days.

Dexamethasone and prednisone are other frequently utilized corticosteroids that may be given orally or by IV. Studies suggest that as long as an equivalent dose of the corticosteroid is given, there are no significant differences in terms of clinical, radiographic, or pharmacological outcomes of the particular treatment [23]. Some clinicians choose to follow this treatment with an oral steroid taper based on the Optic Neuritis Treatment Trial, which found that the group of patients who did not receive an oral steroid taper had an increased risk for a later rebound in symptoms [24].

For patients previously resistant to steroids or those with persistent symptoms after steroid treatment, second-line therapies including plasmapheresis, intravenous immunoglobulin (IVIG), and adrenocorticotropic hormone (ACTH) can be considered. Plasmapheresis is often utilized for severe symptoms refractory to corticosteroids, including weakness, inability to walk, and impaired vision or speech. The updated evidence-based guidelines from the American Academy of Neurology describe plasma exchange as "probably effective" for the management of corticosteroid-resistant acute relapses of relapsing-remitting multiple sclerosis [25]. Plasma exchange typically requires prolonged inpatient hospitalization and specialized personnel and equipment which may not be practical or accessible to the patient. IVIG is not currently approved for acute relapse in MS. Still, many clinicians use this as an off-label alternative if a patient does not respond to steroids or plasmapheresis. IVIG is typically considered a second- or third-line treatment for MS exacerbation, except for postpartum women for whom it is often considered the preferred treatment.

Placebo-controlled studies suggest that adrenocorticotropic hormone (ACTH) can accelerate recovery in MS relapses. ACTH activates melanocortin receptors (MCRs), including MC2Rs on the adrenal gland, which promote the synthesis and release of corticosteroids [26]. In 1978, the U.S. Food and Drug Administration approved the use of a slow-release gel formulation of ACTH for the treatment of acute exacerbations of MS. It can be administered as an intramuscular or subcutaneous injection at 80-120 units for 14-21 days [27]. Studies suggest that the effectiveness of ACTH is similar to corticosteroids. However, the ACTH gel is significantly more expensive than steroids.

All treatments have side effects, and it is important to consider these and counsel the patient accordingly. IV or oral corticosteroids may lead to GI distress, mood fluctuations, and insomnia. Steroids may also cause hyperglycemia, thus it is imperative to monitor blood glucose levels in patients with comorbid diabetes mellitus. Long-term complications of corticosteroid use include osteoporosis, cataracts, and metabolic syndrome. Plasma exchange has a number of potential adverse effects as well, including anemia, thrombocytopenia, hypotension, and bleeding. It often requires placement of an invasive large caliber catheter. Common side effects of IVIG include headache, rash, allergic reaction, hypercoagulability, and renal dysfunction

including acute renal failure. Given the potential for adverse events, treatment for an MS relapse requires consideration and discussion with the patient about the potential risks and side effects of treatment, thus therapy should be selected using an individualized approach.

Pregnancy and MS relapse

Managing MS relapses in pregnancy presents different challenges. Fortunately, pregnancy is often protective against relapses in the MS patient. A meta-analysis of 13 studies with 1221 pregnancies published in 2011 concluded that pregnancy is associated with a significant decrease in MS disease activity, while the postpartum period is associated with an increase in MS activity [28]. Thus, the decision of when to resume disease-modifying treatment should be made soon after delivery. It is important to closely monitor patients during pregnancy and assess any new symptoms to provide treatment as early as possible. MRI studies should be avoided, especially contrast MRI, particularly during the first trimester. In regards to treatment, corticosteroids are used with caution during the first trimester and are not typically followed by a taper. During the second or third trimester, IV methylprednisolone may be used.

After treating the acute relapse

Studies indicate that MS relapses correlate with disability [1]. Thus, it is important to consider whether an acute relapse represents treatment failure. Frequent exacerbations, especially ones involving new, enhancing lesions in the brain or spinal cord, should lead to discussion about transitioning to an alternative, potentially more effective disease-modifying treatment. Rio score is a method to assess the efficacy of a disease-modifying medication by taking into account the number of active T2 lesions, presence of relapses, and increases in EDSS score over the course of a year [29]. It is important to evaluate treatment compliance prior to concluding whether a relapse represents a treatment failure. This can be challenging, as patients may not be forthcoming about noncompliance or not be able to accurately assess their compliance. When patients are doing well in the relapsing-remitting phase, they may be more lenient with missing doses. If sub-optimal compliance is strongly suspected, switching to another treatment may not yet be indicated. However, if the patient's poor compliance is related to poor tolerability of their treatment, this should prompt discussion about whether a different agent should be taken to improve compliance.

Frequent relapses, especially ones with any unusual or aggressive features should also prompt scrutiny of the diagnosis of relapsing-remitting multiple sclerosis. Alternative demyelinating syndromes and MS mimics such as neuromyelitis optica, sarcoidosis, lupus, Susac syndrome, or central nervous system vasculitis should be taken into consideration.

SUMMARY

True MS relapses need to be distinguished from pseudo-relapses that are caused by infection, fever, or metabolic dysfunction. The ARMS questionnaire is helpful in assessing the degree of impairment that the symptom causes. Assessing the validity and severity of a relapse is important given the implications for whether or not to treat a relapse, especially since

corticosteroids are not benign. Plasma exchange is "probably effective," therefore its use is limited to symptoms that are severe and refractory to corticosteroids. Moreover the preferred treatment for postpartum women who experience a relapse is IVIG. For pregnant women in the first trimester, corticosteroids are used carefully without a taper. Although MRI is the gold standard, it is often impractical to obtain on time or could potentially miss lesions. Research is needed to look for cytokines, gene expression markers, metalloproteinases, oxidative stress-related proteins and other biomarkers for predicting relapse in MS. If such research is successful, we might be able to prevent a relapse with more effective treatment.

AUTHOR DISCLOSURES

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