



Multiple Sclerosis Flare-ups Diagnostic and Management Approach in Emergency Department, Review Article

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ABSTRACT

Multiple sclerosis is a chronic inflammatory autoimmune condition that causes axonal demyelination and neural dysfunction. It is the most prevalent non-traumatic disabling condition in young adults, with a prevalence of over 2 million cases worldwide. Patients are classified into different subtypes based on their clinical course. The majority of cases have the Relapsing-remitting form that is characterized by acute exacerbation also known as flare-ups. Which could have an immense toll on patients' physical and emotional health. acute multiple sclerosis flare-ups and their management. PubMed database was used for articles selection, papers were then obtained and reviewed. Multiple sclerosis flare-ups can vary dramatically in their presentation and severity from one patient to other. Establishing a diagnosis of an acute flare-up is mainly clinical but could be supported by MRI findings of a gadolinium-enhancing lesion. Pseudo-relapses are a group of numerous conditions that can lead to acute worsening of the patient symptoms mimicking a true relapse, therefore physicians should take active measures to confirm the absence of such conditions. Treatment should be offered for patients with disabling symptoms or if impaired daily function. First-line therapies are glucocorticoids or ACTH injection gels as both have similar efficacy and relatively safe profile, as for irresponsive cases a trial of either plasma exchange or immunoadsorption could be tried.

Keywords: Multiple sclerosis, Flare-ups, Exacerbations, Management

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INTRODUCTION

Multiple sclerosis is a chronic and depleting autoimmune condition, affecting the central nervous system through axonal demyelination and neural dysfunction (Ghasemi *et al.*, 2017; Alshammari *et al.*, 2019; Narkevich *et al.*, 2021). It is the most prevalent non-traumatic disabling condition in young adults (Dobson & Giovannoni, 2019), with more than 2 million patients around the globe (He *et al.*, 2011). despite that its exact etiology remains enigmatic, but current evidence suggests that MS is multifactorial encompassing both genetic and environmental factors (Ghasemi *et al.*, 2017). Patients are classified into different subtypes based on their clinical course. this includes primary progressive, secondary progressive, and Relapsing-

remitting forms, with the latter being the most common subtype experienced in 80% of the cases (He *et al.*, 2011). This form is characterized by acute exacerbation also known as flare-ups, spaced in between periods of complete or partial remission (Kamel, 2019).

In this paper, we will look into the acute exacerbations in multiple sclerosis and its management

MATERIALS AND METHODS

PubMed database was used for articles selection, and the following keys used in the mesh (((multiple sclerosis) AND (exacerbation)) OR (flare-up)) in regards to the inclusion criteria, the articles were selected based on the inclusion of one of the following topics; multiple sclerosis, exacerbation or flare-ups. Exclusion criteria were all other articles that did not have one of these topics as their primary endpoint.

*Review**Definition of a flare-up*

Multiple sclerosis flare-ups, exacerbation, and relapse are all synonyms used to denote an episode of inflammatory demyelination of the central nervous system, reflected clinically by either the onset of new symptoms or transient worsening of existing complaints. It can develop abruptly or in a subacute fashion over hours to days, followed by complete or partial remission. But for an episode to qualify as a relapse its duration needs to be more than 24 hours, in addition, the time interval between it and the last attacks must be at least 30 days, lastly, it can not be associated with fever nor infections (Tillery *et al.*, 2017; Thompson *et al.*, 2018; Kamel, 2019). Another essential term is a clinically isolated syndrome (CIS) which refers to the first-ever clinical MS episode experienced in a previously healthy individual (Miller *et al.*, 2012).

Clinical presentation

Flare-ups are very heterogeneous and vary dramatically from one patient to the other. But the typical complaints are usually neurological and fall under the following domains, cognitive, motor, sensory, vision, in addition to fatigue (Galea *et al.*, 2015). One of the most frequent initial complaints is optic neuritis. It usually involves one eye and leads to slow and progressive visual loss lasting for more than 2 weeks, abnormal color perception in particular red and green. In addition to pain with the use of extraocular muscles (Ford, 2020). Another possible eye manifestation is internuclear ophthalmoplegia (INO) leading to diplopia due to impaired control of conjugate eye movements, which is considered to be pathognomonic for MS if bilateral. Less common presentations include cerebellar ocular disorders causing gaze-evoked nystagmus, hypermetria, and absence of vestibulo-ocular reflex inhibition. Fundoscopy may show edematous optic disc, with or without central scotoma or a reduction of visual acuity (Nerrant & Tilikete, 2017; Ford, 2020).

In the case of brainstem affection than different cranial nerves may get involved, such as isolated 6th nerve palsy causing diplopia, 7th nerve affection leading to unilateral facial weakness or numbness, vertigo due to 8th nerve, lastly dysarthria and dysphagia (Ghasemi *et al.*, 2017; Ford, 2020).

Myelitis is one prevalent complication, which can give rise to a plethora of sensory and motor symptoms with the former being more common. These complaints vary based on the level of affection, for example, cervical myelitis manifests as a feeling of an electrical shock down the spine with forwarding bending of the neck known as the Lhermitte sign. While thoracic patients may exhibit chest pain and tightness that is circumferential. Moreover, it even may present as Brown-Séquard syndrome. Other symptoms include sexual or bladder dysfunction. A neurological examination will help to localize the level of lesion, as such patients may demonstrate abnormal or even absent perception of sensory stimuli like vibration and touch. In addition to motor signs including hypertonia, hyperreflexia, and weakness (Ford, 2020).

Cognitive impairments are a common occurrence especially in patients with severe disease, namely amnesia, inattention, impaired critical thinking, sluggish information processing, and difficulty when alternating between tasks (Hunter, 2016).

Evaluation and diagnosis

Establishing the diagnosis of an acute flare-up is mainly clinical. Through a combination of the patient's subjective complaints and objective findings on physical examination. With or without neuroimaging and other paraclinical tests. In addition, ruling out a pseudo-relapse can be done.

Therefore, every patient should undergo a thorough history-taking session to establish the patient's baseline status, nature of the new complaints and their duration, also time span since the last relapse. This is usually followed by a full neurologic and ophthalmic examination to assess the patient's condition and to look for any of the typical signs mentioned earlier.

Neuroimaging in particular MRI (brain and or spinal cord) can aid in making the diagnosis of MS flare. As research has shown that the presence of a gadolinium-enhancing lesion on T1 is suggestive of a recent breakdown in the blood-brain barrier, which could indicate recent disease activity. But making a diagnosis solely based on MRI findings is not recommended due to high false positives rates. Therefore, correlating between the lesion's anatomical site and clinical symptoms of the patient is deemed essential (Mills *et al.*, 2017; Pakpoor *et al.*, 2017; Wang *et al.*, 2018).

Pseudo-relapse is a term used to describe temporary worsening of MS symptoms, due to a change in a patient's physiological status rather than an autoimmune sequel. Those pseudo-relapse triggers include exercise, infections, and fever, as elevation in body temperature may negatively impact axonal nerve transmission. And once these events are treated patient's condition returns to baseline. Henceforth physicians should actively seek to rule out such triggers, through the use of the appropriate test, for example, CBC, electrolytes, urine analysis, and lumbar puncture (Mills *et al.*, 2017; Wang *et al.*, 2018; Ford, 2020).

Management

The majority of flare-ups are self-limiting in nature and will usually subside over a few weeks to months. Therefore, mild cases with isolated symptoms that don't impair daily life can be managed conservatively with simple means such as analgesia and bed rest. On the other hand, severe cases with disabling symptoms interfere with daily activities, for example, visual impairment, motor weakness, cognitive symptoms, and vertigo. Such patients are a candidate for medical intervention. But an essential point to keep in mind is that those treatment modalities are only effective in limiting the duration and severity of episodes, and don't affect the progression of the disease nor do they minimize the chances of relapse. Therefore, following acute management these patients should be offered to start on disease-modifying agents put those won't be discussed here in this paper (Goldenberg, 2012; Dsouza, 2021).

Glucocorticoid

High-dose glucocorticoids are considered to be agents of choice for the management of acute flare-ups requiring therapy. But a necessary precaution before their administration is confirming the absence of any infection, this is due to their immunosuppressive properties which may further worsen the patient's condition if the underlying infection was present.

They could be administered either intravenously (methylprednisolone) or orally (prednisone). Numerous data have shown that both routes have similar outcomes even in cases of optic neuritis, which was previously thought to be

irresponsive to oral therapy (Burton *et al.*, 1996; Kalincik, 2015; Nazareth *et al.*, 2019). Henceforth, oral glucocorticoids are usually more preferable options for patients due to being easier, cheaper, and less invasive (Liu *et al.*, 2017; Narkevich *et al.*, 2021). Doses can range from 500mg (up to 1 gram) for intravenous and 625 mg (up to 1250 mg) for oral, with the duration of the therapy falling between 3 to 5 days. Nevertheless, there are no established guidelines to guide exact dosing (Berkovich, 2013).

Adverse effects for glucocorticoids are numerous and can include immunosuppression, fluctuating mood, GI complaints, psychiatric symptoms such as euphoria/mania/depression, decrease bone density thus increased risk of fractures, also hyperglycemia may happen. Few measures can be taken to mitigate those complications such as the use of the smallest effective dose and for the shortest course possible, prescription of proton pump inhibitor, close blood glucose level monitoring in patients with comorbid diabetes, and proper patients' education (Morrow *et al.*, 2015; Hunter, 2016; Wang *et al.*, 2018).

Even though there are no standardized tools for assessment of clinical response to therapy, the physician could base their assessment on the extent of symptom resolution and the degree of return to baseline status. This is especially important in patients who exhibit no or insignificant improvement during treatment, as these patients are less likely to get better down the line. And should be a candidate to undergo a trial of different therapy as we will discuss below (Berkovich, 2013).

Adrenocorticotrophic hormone (ACTH)

ACTH is considered to be 2nd line therapy for patients who do not respond to a trial of glucocorticoid therapy, or when they can not be used due to intolerance or in case of specific contraindication. Multiple types of research have demonstrated that there is no significant difference in their efficacy if compared to glucocorticoids, but their main drawback is the high price tag (Berkovich, 2013). They can be found in a gel form known as Repository Corticotropin Injection (RCI) which can be injected either intramuscular or subcutaneously, with the latter being more favorable due to a lesser degree of pain while eliciting a similar response (Simsarian *et al.*, 2011). The commonly used dose can vary but, 80 units daily, is administered usually for at least 1 week. Lastly, unlike glucocorticoids which may lead to serious adverse effects, RCI has an excellent safety profile with the most frequently encountered side effect simply being acne (Costello *et al.*, 2019).

Plasma exchange

Plasma exchange is regarded as rescue therapy in severe cases irresponsive to glucocorticoids and/or ACTH, in particular patients who continue to deteriorate throughout treatment (Cortese *et al.*, 2011). Such patients usually require several sessions (typically 5 to 10) performed daily or every other day (Berkovich, 2013). Side effects are infrequent and mostly well tolerated, with more serious ones, fortunately, being rare for instance DVT, allergic reactions, hypotension, arrhythmias, anemia, and coagulation imbalance (Correia *et al.*, 2018; Lipphardt *et al.*, 2020).

Immunoadsorption

Immunoadsorption is a newer method of plasma apheresis, but unlike plasma exchange, this technique is more selective as it only removes circulating antibodies sparing other proteins. Due to this difference, it is considered to be a safer option than an exchange, but its main disadvantages are cost and lack of widespread availability. As for its efficacy gathered data have demonstrated similar outcomes to plasma exchange (Mauch *et al.*, 2011; Lipphardt *et al.*, 2020), with some studies concluding that it outperformed the latter (Dorst *et al.*, 2019; Metleva *et al.*, 2021). But most of these pieces of evidence are yet to be taken for guarantee until future large-scale RCT are to be conducted.

CONCLUSION

Multiple sclerosis flare-ups can vary dramatically in their presentation and severity from one patient to other. Establishing a diagnosis of an acute flare-up is mainly clinical but could be supported by MRI findings of a gadolinium-enhancing lesion. Pseudo-relapses are a group of numerous conditions that can lead to acute worsening of the patient symptoms mimicking a true relapse, therefore physicians should take active measures to confirm the absence of such conditions. Treatment should be offered for patients with disabling symptoms or if impaired daily function. First-line therapies are glucocorticoids or ACTH injection gels as both have similar efficacy and relatively safe profile, as for irresponsive cases a trial of either plasma exchange or Immunoadsorption could be tried.

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