Review Article

Evolving Landscape of Multiple Sclerosis in India: Challenges in the Management

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Abstract

Multiple sclerosis (MS) is a chronic neurological disease which often leads to disability. The complex etiology and progressive nature pose challenges in the management of patients with MS, particularly in developing countries like India. Lack of data on prevalence further complicates estimation of the magnitude of MS in India. There are various other challenges associated with management of patients with MS due to which the therapy is utilized by only a small segment of population in India. This article encapsulates the gaps and challenges in the management of patients with MS and presents suggestions and recommendations of the members of advisory boards held to discuss these challenges. The advisory board members suggested that an early diagnosis of MS and an early initiation of treatment are essential to achieve better results for tackling MS-related challenges. In addition, awareness and education about MS among people, regular training to physicians, emphasis on the use of revised 2010 McDonald criteria, and utilization of advanced diagnostic modalities in magnetic resonance imaging would help to achieve desirable as well as effective therapeutic outcomes. Further, access to an easy-to-use therapy delivery system could also be beneficial in attaining an adequate treatment adherence and related health benefits.

Keywords: Adherence, challenges, diagnosis, multiple sclerosis, referral, treatment

Introduction

Multiple sclerosis (MS), a chronic autoimmune disorder, causes demyelination of neurons in the central nervous system (CNS) leading to a severe disability.[1,2] MS can occur at any age but is usually diagnosed between the ages of 20 and 40 years and reported mostly in women (approximately 3 times more often than in men).[3,4] About 2.5 million people are affected with MS worldwide. To date, no large-scale studies have been conducted to accurately determine the incidence and prevalence of MS in India.[5,6] Some scattered studies have reported the prevalence of MS in the regions of India [Table 1]. However, in the last few years, increase in the number of practicing neurologists and easy and affordable availability of magnetic resonance imaging (MRI) have led to an increase in the reported prevalence of MS.[6,16]

The epidemiology of MS is complex and involves interaction between environmental and genetic factors.[5] Environmental factors such as minimized exposure to sunlight, i.e., lack of Vitamin D, smoking, and infections (Epstein–Barr virus) increase the susceptibility to MS.[17-22] Some studies have also stated that there is a genetic susceptibility for MS; HLA-DR2 is a common haplotype in about 40% of patients with MS.[23-25] The proposed immune-pathogenesis for MS can be well-described as an inflammatory autoimmune disorder caused by activation of autoreactive peripheral blood T cell lymphocytes. This leads to a cascade of events which are responsible for demyelination of the nerve fibers leading to chronic neurodegeneration.[26]

MS affects a patient's mental, emotional, and socioeconomic well-being.[27] Moreover, complexity of MS, its presentation, associated burden, diagnosis, poor referral of patients to the physicians, and management pose a bigger challenge.[28,29] Major goals of management of MS comprise modification

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Table 1: Studies showing the prevalence of multiple sclerosis in India

Author name, year	Study population	Findings
Singhal, 1985[7]	105 MS patients and 14 NMO patients	The prevalence rate of 0.17-1.33 per 100,000 people affected with MS in India
Jain and Maheshwari, 1985[8]	354 MS patients	4.15 MS cases from North India and 3.2 MS cases from South India, per year
Bharucha *et al*., 1988[9]	14,010 people of Parsi community from Mumbai	21 cases per 100,000 people affected with MS
Wadia and Bhatia, 1990[10]	16 MS patients (14 in Mumbai and 2 in Pune) from a total Zoroastrian population of 50,053 from Mumbai and 3399 from Pune	Prevalence ratio as 26 per 100,000 in Mumbai and 58 per 100,000 in Pune
Mani *et al*., 1999[11]	31 MS patients	Hospital incidence of 0.85% of total 3639 admissions in neurology unit in Western India
Syal *et al*., 1999[12]	100 MS patients	Increasing number of neurological admissions of MS patients in the hospitals of Northwest India from 1.58% to 2.54%
Gangopadhyay *et al*., 1999[13]	45 MS patients	Incidence of MS as 0.32% of all hospital admissions and 0.62% per 100,000 of neurology clinic patients
MSIF, 2013[14]	Extensive worldwide study	About 85,000 people are affected with MS in India in the year 2013
Pandit and Kundapur, 2014[15]	79 patients	The prevalence rate for MS as 8.3 per 100,000 and age-standardized prevalence of MS relative to the world population as 7.8 per 100,000
Singhal and Advani, 2015[16]	Review	About 7-10 per 100,000 people affected with MS in India

MS=Multiple sclerosis, NMO=Neuromyelitis optica, MSIF=Multiple Sclerosis International Foundation

of the disease course by reducing number and severity of relapses, decreasing accumulation of lesions, and slowing down the progression of disability. To date, there is no cure for MS; however, several disease-modifying therapies (DMTs) that help in reduction of relapse rate, delaying disability, and reducing MRI lesion load are available for the treatment of patients with MS[30] [Table 2].

The aim of this review is to present the challenges associated with overall management of MS in India including those related to diagnosis, treatment, and adherence to the treatment. The article also presents suggestions from members gathered in a series of company-sponsored advisory board meetings.

Challenges Associated with Multiple Sclerosis

The discussion is focused on insights obtained from advisory board meetings on the current challenges associated with the management of patients with MS and devising solutions to resolve them. Literature search aided in documenting the gaps in diagnosis and treatment of MS, optimizing treatment methods and issues with patient adherence to MS therapy as the key challenges in recognition and treatment of MS.

Gaps in the diagnosis of multiple sclerosis

Early diagnosis and intervention are important to potentially limit the disability and preserve patient's health status.[31,32]

Lack of early diagnosis and intervention

Suboptimal referral of patients with MS to neurologists is a crucial barrier in the early diagnosis of MS in India. Due to overlapping conditions such as optic neuritis, patients with visual symptoms are treated by ophthalmologists, and not referred to the neurologists. Different study groups have reported the probability of occurrence of MS in patients with optic neuritis to be as high as 58% (in about 15 years).[8,33] Besides optic neuritis, other symptoms in the initial stages of MS include ocular motor syndromes (internuclear ophthalmoparesis and nystagmus), ataxia, dysarthria, sensory or motor signs, partial myelitis, and bowel or bladder dysfunction.[34]

It is also difficult to diagnose MS because of its multiple subtypes, interpatient variations in the clinical presentation and pseudorelapses.[25,29] A variant of MS, neuromyelitis optica (NMO) involves demyelination of optic nerves and spinal cord and is also a cause of serious illness in various countries including India.[35,36] NMO may lead to uncertainties in the diagnosis of MS. Certain patients of MS with NMO have additional symptoms that are not due to optic nerve or spinal cord inflammation or have MS-like lesions in MRI. In addition, some patients with MS were mistakenly diagnosed with NMO inspite of having a consequent course distinct from prototypic MS.[37,38] Several other disorders are known to have a clinical presentation similar to MS such as acute disseminated encephalomyelitis, Schilder's disease, Balo's concentric sclerosis, Eale's syndrome, sarcoidosis, vasculitis, CNS lupus, Sjogren's syndrome, and Behçet's disease. Even the MRI findings of these diseases show a resemblance to T2 white matter lesions. The presence of nonspecific white matter lesions is reported in people affected with migraine, hypertension, and diabetes. Furthermore, there are no specific guidelines in India that can assist in the management of patients with MS. Nevertheless, use of established and up-to-date revised 2010 McDonald criteria is recommended to make the diagnosis after exclusion of alternative diagnoses.

Table 2: Currently used disease-modifying drugs for the treatment of multiple sclerosis

Therapies (chemical name)	Dose	FDA approval
Interferon beta-1a	30 mcg i.m. once weekly	Slow down the accumulation of physical disability and reduce the frequency of clinical exacerbations, and for patients who have experienced a first clinical episode and have MRI features consistent with MS Approved: 1996 US; 1998 CAN Pregnancy Category C
Interferon beta-1b	0.25 mg s.c. every other day	Reduces the frequency of clinical exacerbations; and for patients who have experienced a first clinical episode and have MRI features consistent with MS Approved for RRMS: 1993 US; 1995 CAN Approved for SPMS: 1995 CAN Pregnancy Category C
Glatiramer acetate	20 mg s.c. every day or 40 mg s.c. three times per week	For the treatment of relapsing forms of MS Approval: 1996 US; 1997 CAN Pregnancy Category B
Glatiramer acetate, generic equivalent OF Copaxone 20 mg)	20 mg s.c. every day	For the treatment of relapsing forms of MS Approval: 2015 US Pregnancy Category B
Pegylated interferonbeta-1a	125 mcg s.c. every 14 days	For the treatment of relapsing forms of MS Approval: 2014 US Pregnancy Category C
Interferon beta-1a	22 mcg or 44 mcg s.c. three times per week	Reduces the frequency of clinical exacerbations and delay the accumulation of physical disability Approval: 1998 US; 2002 CAN Pregnancy Category C
Daclizumab	150 mg once a month	The FDA indication includes a statement that this medication should generally be reserved for people who have had an inadequate response to two or more disease-modifying therapies Approval: 2016 US
Teriflunomide	7 mg or 14 mg pill once daily	For the treatment of relapsing forms of MS Approval: 2012 US; 2013 CAN Pregnancy Category X
Fingolimod	0.5 mg capsule once daily	Reduces the frequency of clinical exacerbations and to delay the accumulation of physical disability 2010 US; 2011 CAN Pregnancy Category C
Dimethyl fumarate	120 mg capsule taken twice daily for 1 week, followed by 240 mg capsule taken twice daily thereafter	For the treatment of relapsing forms of MS 2013 US; 2013 CAN Pregnancy Category C
Alemtuzumab	12 mg per day for 5 consecutive days, followed by 12 mg per day on 3 consecutive days 1 year later	The FDA indication includes a statement that this medication should generally be reserved for people who have an inadequate response to two or more DMTs Approval: 2014 US; 2014 CAN Pregnancy Category C
Mitoxantrone	12 mg/m² every 3 months. Lifetime cumulative dose limit of approximately 8-12 doses over 2-3 years (140 mg/m²)	For reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting MS Approval: 2000 US Pregnancy Category D
Natalizumab	300 mg once every 28 days	Used as a monotherapy (not in combination with any other MS DMT or other immune suppressant drugs) for the treatment of patients with relapsing forms of MS. Approval: 2006 US; 2006 CAN Pregnancy Category C
Ocrelizumab	Start dose: 300 mg IV infusion followed 2 weeks later by a second 300 mg IV infusion Subsequent doses: 600 mg IV infusion every 6 months	Indicated for the treatment of patients with relapsing or primary progressive forms of multiple sclerosis Approval: 2017 US

Category B=Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, Category C=Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant the use of the drug in pregnant women despite potential risks, Category D=There is a positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks, Category X=Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits, IV=Intravenously, s.c.=Subcutaneously, i.m.=Intramuscularly, MS=Multiple sclerosis, MRI=Magnetic resonance imaging, RRMS=Relapsing-remitting multiple sclerosis, SPMS=Secondary progressive multiple sclerosis, FDA=Food and Drug Administration, DMT=Disease-modifying therapies

Lack of an early diagnosis of MS due to these overlapping or misleading conditions is coupled with a lack of an early intervention, i.e., even if the patients with MS reach neurologists, it is not certain that treatment will be initiated.[14]

Misinterpretation of magnetic resonance imaging findings

MRI plays a vital role in the diagnosis and treatment of MS. MRI of CNS can support as well as complement the clinical presentation of MS.[39-42] However, dissonance between position of lesions and their clinical presentation is a major limitation of MRI. Furthermore, depending on number of lesions and their area, MRI shows great variation in the diagnosis of MS as far as sensitivity and specificity are concerned. Some MRI reports have also demonstrated nonspecific white matter lesions; however, these were compatible with MS. This is particularly valid for primary progressive MS, which may not demonstrate the exemplary discrete lesions of relapsing-remitting MS.[43-46]

Schumacher criteria, developed in 1965 was the first official clinical symptom-based criteria for the diagnosis of MS.[47] Poser criteria (1983) was established on the basis of outcomes of additional tests, including visual-evoked potential and cerebrospinal fluid analysis.[48] McDonald criteria (amended in 2010) is currently used and is a well-established diagnostic criteria for the diagnosis of MS. The revised McDonald criteria use MRI findings as well as clinical parameters for making an early diagnosis of the disease with high specificity and sensitivity, which support initiating an early treatment and better management of patients with MS.[49-52] McDonald diagnostic criteria emphasizes the need to demonstrate the dissemination of lesions in space (DIS) and time (DIT) and to exclude alternative diagnosis for MS. DIS can be demonstrated with at least one T2 lesion in at least two of the four locations considered characteristic for MS and as specified in the original McDonald Criteria (juxtacortical, periventricular, infratentorial, and spinal cord), with lesions within the symptomatic region excluded in patients with brainstem or spinal cord syndromes. Whereas, DIT can be demonstrated by an appearance of a new T2 lesion on a scan compared to a reference or baseline scan performed at least 30 days after the onset of initial clinical event and simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time.[53] Figure 1 represents the McDonald diagnostic criteria to detect patients with MS.

Challenges in the treatment of multiple sclerosis

Lack of early initiation of treatment

MS can have devastating effects on the patients and if it is left untreated, these may occur earlier or can be more severe. It has been reported that about 90% of patients that are left untreated will have disability later in their lives (20–25 years after getting affected).[54] Treatment with DMTs should be started as early as possible considering the disabling nature of disease.[55-57]

Initiating an early treatment limits the progression of disability, thereby moderating overall treatment cost and improving the clinical outcomes of patients with MS.[58] In general, patients are not aware of the consequences of MS and related cost if the treatment gets delayed. With the progression of disease and an increasing disability level, there is an increase in the direct and indirect costs involved. This increment in cost is generally related to relapses and productivity cost rather than the direct cost involved in using DMTs.[59,60] The issue of higher cost is a complex problem when considered at an individual level. Patients usually neglect treatment when cost-sharing exceeds beyond their limit.[61] Moreover, the treatment plans that negatively affect initiation and adherence may be responsible for increased use of health resources, relapse risks, progression of disease, and ultimately, disability in patients.[61]

Lack of continuous treatment

Chronic diseases such as MS require continuous treatment. A discerned lack of efficacy, financial constraints, distress, and curiosity of the patient to adopt other available therapies might also lead to a poor treatment adherence.[62-64] The major contributing factor for noncompliance among patients with MS is the delayed symptomatic presentation after initial diagnosis. It has been found that after an initial diagnosis of MS, there is no significant relapse or development of new symptoms in some patients for few months or years, which in turn increases the chances of patient's denial of accepting the disease, understanding the need for routine therapy as well as adapting it.[62,64]

Nonadherence or poor adherence to treatment regimens is the most common challenge in the treatment of patients with chronic conditions. Nonadherence might result from complex treatment regimens as well as the adverse effects associated with them (fatigue, flu-like symptoms, and reactions at injection site) or lack of awareness/negligence among the patients and some injection-related issues (fear/anxiety, pain, and discomfort).[62-64] A global survey conducted among 331 patients diagnosed with MS found 31% patients to deliberately break the treatment course for 1 day or longer, whereas about 19% patients had completely evaded taking their medications.[65] This discontinuation in the treatment was reported due to associated adverse effects (42%), emotional fatigue (13%), practical issues related to the treatment (9%), lack of efficacy (9%), or lack of symptoms (6%). On forwarding the same questionnaire to some other neurologists, it was found that 17% patients took treatment breaks majorly due to associated adverse effects (82%).

There may be an underestimation of the incidence of poor adherence of patients to treatment by some physicians.[65] Studies conducted for the evaluation of adherence to injectable therapies reported approximately 80% adherence in about 80% patients for initial 6 months,[66] followed by a decrease to 60%–76% in the next 2–5 years.[67]

The availability of newer and easy-to-use therapy systems have helped to overcome the issue of nonadherence to some extent.

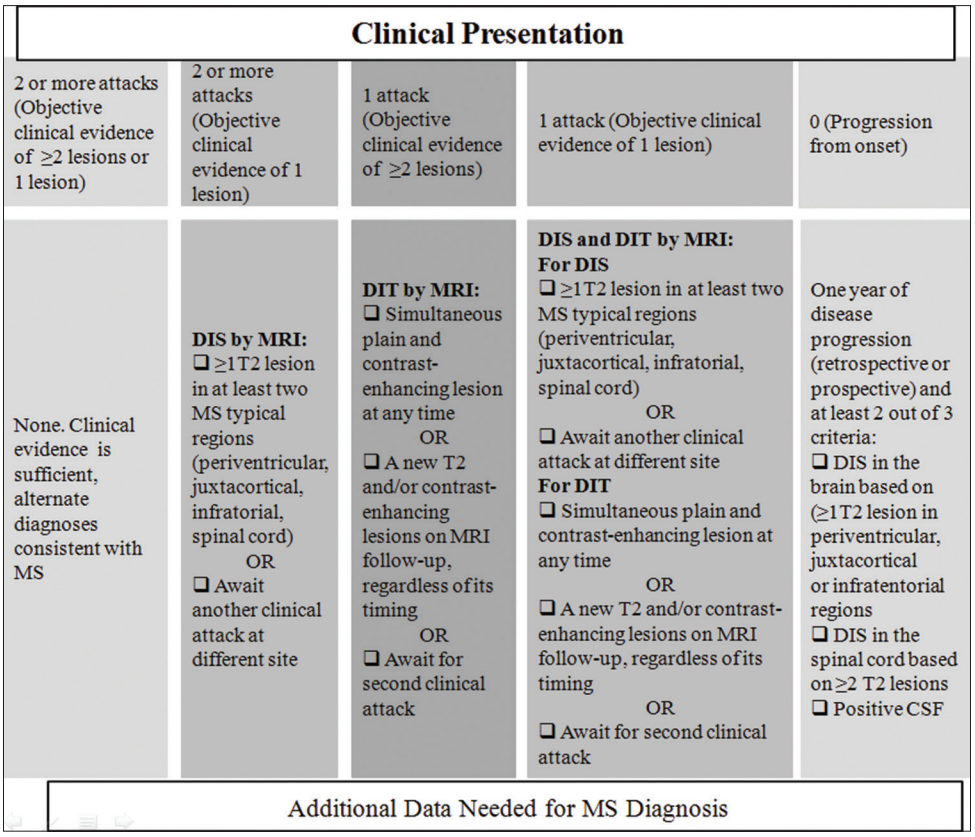

Figure 1: McDonald Criteria (2010) for Diagnosis of Multiple Sclerosis

In the SMART trial, adherence was observed in 97.3% and 93.9% of patients at 3 and 12 months, respectively, who used RebiSmart® (an electronic auto-injector for the subcutaneous administration of interferon β-1a). Common adverse events (AEs) in patients at 3 and 12 months were anxiety, flu-like syndrome, and pain at injection site, weakness, and fatigue.[63]

Expert opinion

Early diagnosis of multiple sclerosis

Making an early diagnosis is of paramount importance so that progression of the disease and disability can be minimized. The advisory board suggested the following key points to be taken into consideration while making diagnosis of patients with MS: [Table 3]

- Timely referral from other physicians to neurologists: Referral of optic neuritis patients to the neurologists should be made on time. In addition, paroxysmal symptoms are very common and patients later on get diagnosed with MS.[68] Therefore, paroxysmal symptoms should not be missed
- Follow-up of the patient with MS: Clinical assessment is of utmost importance and Expanded Disability Status Scale scoring must be done for all patients [Figure 2]. Patients may go to the doctors for medical issues and not for MS. In later, phases of the disease, one MRI a year could be an optimal solution. As per experts' practical experience, MS progression does not always involve MRI lesions (such as in case of clinical progression from relapsing–remitting MS to secondary progressive MS)[69]
- Early diagnosis and diagnostic criteria: The evolving criteria have increased sensitivity greatly which helps in early diagnosis; however, at the same time, specificity must not be neglected. Hence, while diagnosing MS, clinical features are very important. Recommended 2016 MAGNIMS modifications to the 2010 McDonald criteria for MRI in the diagnosis of MS will help to improve early diagnosis[53]
- Exclusion of diseases with similar clinical presentation: All other causes for MS-like lesions on MRI should be excluded before diagnosing a patient with MS. MS should not be confused with NMO due to similar clinical presentations or common symptoms such as fatigue, depression, or dizziness. The diagnosis of MS should be based on diagnostic criteria that are separate from established updated diagnostic criteria for NMO. Further, exclusion of alternative diagnoses should be kept in mind while referring a person with MS to the neurologist.

Improving treatment adherence

Adherence to MS therapy is associated with lower risks of disease-associated hospitalizations, fewer relapses, and less associated medical costs. In the past, limited availability of MS treatment was a barrier to optimal therapy; but today, we have multiple treatment alternatives, although the cost remains a limiting factor. The advisory board suggested that:

- Focus on "3As": Clinicians should focus on "3As", i.e., affordability, accessibility, and availability, to manage MS. It was suggested to make the therapy more affordable and accessible to patients. An important point to consider is the need for pharmacoeconomic studies in MS
- Counseling to be given due importance: Patients are usually concerned about how long this treatment is to be taken. When treating physicians make their patients aware of the duration of treatment, it may add to patients' anxiety. Counseling plays an important role in handling and managing physical as well as an emotional aspect of the disease. It also supports a patient in initiating treatment followed by its adherence, thereby, minimizing the progression to disability
- Factors which matter in choosing the therapy: Injectable and oral therapeutic agents are now available; however, the prescription should be made considering long-term efficacy and safety, and AE profile of the DMDs. Moreover, the patient should be given a chance to contribute to the decision of treatment options. Awareness strategies for the use of injectable therapies must include schemes to manage tolerability to the treatment, such as titration and reduction of dose, injection timings, usage of sleeping aids, nonsteroidal anti-inflammatory drugs or acetaminophen coadministration (before and after injection), and injection techniques. Interferons are the first-line treatment option. In case of disease progression, second- and third-line DMTs are used. However, in relapses, patients are treated with methyl prednisolone, followed by DMT[70]
- Switch for nonresponders: Suboptimal response to a first-line DMT warrants either a lateral/transversal switch in some cases with low-to-moderate level of concern (from one first-line immunomodulatory treatment to another one) or a vertical switch (therapeutic escalation) in more aggressive cases with moderate to high level of concern (from a first-line to a second-or third-line therapy).[31] If more than two relapses have occurred in the previous 2 years, it indicates aggressive disease[71]
- Need for adaptable and cost-effective treatment options: Factors that prevent a patient from administering treatment are multifold: Cost, AEs, and injection phobia. Experts stated that insurance companies do not cover MS related costs. Patients usually seek a lot of information on MS when diagnosed and get worried on explaining that it is noncurable. They seek an opinion from different doctors which may add to the confusion. Cost of the treatment, the most important patient-related consideration also increases with relapses. An easy to use and appealing therapeutic strategy, reduction in the cost of MS therapy and support of MS treatment by the government would largely help in improving patient adherence
- Design robust patient support programs: Designing robust patient support programs might help to improve adherence. A monthly clinic that includes clinical psychologists, psychiatrists, physiotherapists, and physicians specialized in all areas of neurology, mental health, and rehabilitation to guide and treat patients could be a good option
- Promote educational activities: Educational activities, MS programs such as organizing educational camps for patients and caregivers, might help in an easy understanding of complexity associated with the disease, as well as the importance of adherence to prolonged treatment regimen. Social media can act as an effective mode to spread awareness about early diagnosis and treatment of patients with MS. Educational activities among MS affected the population, and physicians can play a critical role in patient adherence. Focused continuing medical education on an annual basis may help to increase awareness
- Use of social media and applications to help patients and doctors: Patients should be encouraged to use calendars to improve adherence to the therapy. Usage of web applications or dedicated applications for doctors and patients would be helpful.

Table 3: Challenges observed in the diagnosis and management of patients with multiple sclerosis and expert opinion

Challenges in the diagnosis management	Expert opinion
Suboptimal referral of patients with MS	Timely referral by treating ophthalmologist to the neurologists
Misleading clinical presentation	Appropriate counseling in the language that the patient understands
Misinterpretation of MRI findings	Focus on "3As": Affordability, accessibility, and availability of therapy while deciding treatment regimen for the patient
Lack of early initiation of treatment	Need for timely follow-up
Poor adherence to treatment	Switch strategy for nonresponders
Higher cost of treatment	Need of robust patient support programs and disease awareness activities

MS=Multiple sclerosis, MRI=Magnetic resonance imaging

Conclusion

Timely referral and early initiation of treatment of MS are critical for a reduction in the relapse rate and disability. To achieve treatment adherence, it is essential to provide proper counseling and assurance to patients regarding the benefits of therapy. This requires a legitimate evaluation of relative risks, cost, and advantages of therapy for achieving desirable therapeutic outcomes. Further, accessibility to an easy-to-use therapy delivery system could also be beneficial in attaining an adequate treatment adherence for better outcomes. Going forward, there is still a need for considerable awareness, rehabilitation facilities,

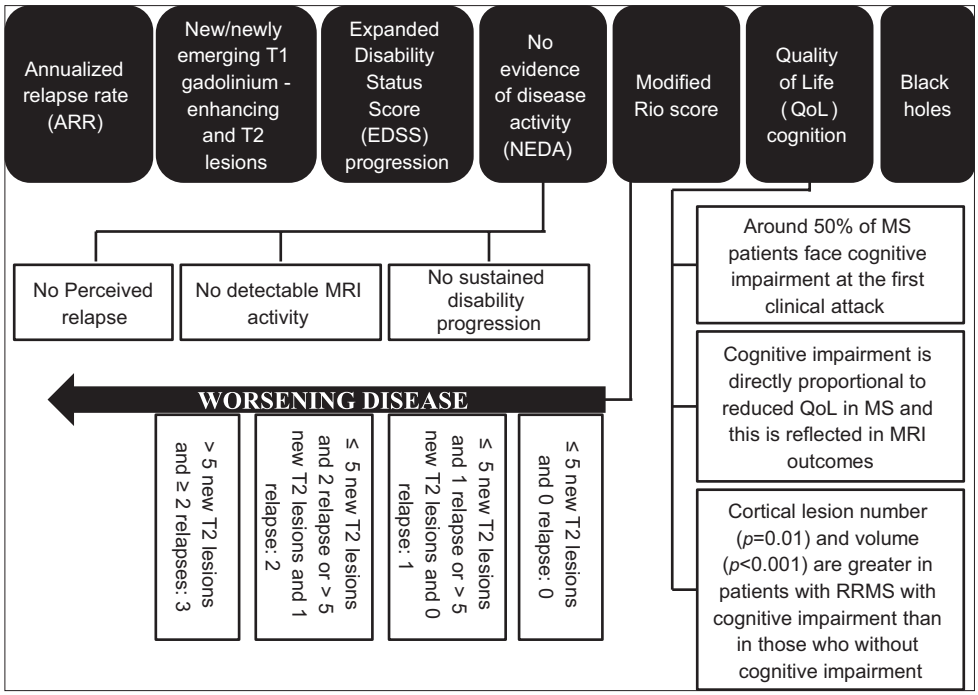

Figure 2: Assessment Parameters to Evaluate Effectiveness of Various Multiple Sclerosis Associated Therapeutic Options[39,54,72]

well-equipped MS clinics in the institutions, registry of MS patients, insurance coverage, and accessibility to effective and economical DMTs in India.

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Conflicts of interest

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References

1. Compston A, Coles A. Multiple sclerosis. Lancet 2002;359:1221-31.
2. Dutta R, Trapp BD. Mechanisms of neuronal dysfunction and degeneration in multiple sclerosis. Prog Neurobiol 2011;93:1-2.
3. Jobin C, Larochelle C, Parpal H, Coyle PK, Duquette P. Gender issues in multiple sclerosis: An update. Womens Health (Lond) 2010;6:797-820.
4. Myhr KM. Diagnosis and treatment of multiple sclerosis. Acta Neurol Scand Suppl 2008;188:12-21.
5. Bhatia R, Bali P, Chaudhari RM. Epidemiology and genetic aspects of multiple sclerosis in India. Ann Indian Acad Neurol 2015;18:S6-S10.
6. Gupta S, Tewari AK, Nair V. Multiple sclerosis: Indian perspective. Ch. 120. Available from: http://www.apiindia.org/medicine_update_2013/chap120.pdf. 548-51. [Last accessed on 2016 May 21].
7. Singhal BS. Multiple sclerosis – Indian experience. Ann Acad Med Singapore 1985;14:32-6.
8. Jain S, Maheshwari MC. Multiple sclerosis: Indian experience in the last thirty years. Neuroepidemiology 1985;4:96-107.
9. Bharucha NE, Bharucha EP, Wadia NH, Singhal BS, Bharucha AE, Bhise AV, *et al.* Prevalence of multiple sclerosis in the parsis of Bombay. Neurology 1988;38:727-9.
10. Wadia NH, Bhatia K. Multiple sclerosis is prevalent in the Zoroastrians (Parsis) of India. Ann Neurol 1990;28:177-9.

11. Mani J, Chaudhary N, Ravat S, Shah PU. Multiple sclerosis: Experience in neuroimaging era from Western India. Neurol India 1999;47:8-11.
12. Syal P, Prabhakar S, Thussu A, Sehgal S, Khandelwal N. Clinical profile of multiple sclerosis in North-West India. Neurol India 1999;47:12-7.
13. Gangopadhyay G, Das SK, Sarda P, Saha SP, Gangopadhyay PK, Roy TN, *et al.* Clinical profile of multiple sclerosis in Bengal. Neurol India 1999;47:18-21.
14. MS International Federation. Atlas of MS; 2013. Available from: https://www.msif.org/about-us/advocacy/atlas/. [Last accessed on 2016 Sep 12].
15. Pandit L, Kundapur R. Prevalence and patterns of demyelinating central nervous system disorders in urban Mangalore, South India. Mult Scler 2014;20:1651-3.
16. Singhal BS, Advani H. Multiple sclerosis in India: An overview. Ann Indian Acad Neurol 2015;18:S2-5.
17. Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part II: Noninfectious factors. Ann Neurol 2007;61:504-13.
18. Handel AE, Williamson AJ, Disanto G, Dobson R, Giovannoni G, Ramagopalan SV, *et al.* Smoking and multiple sclerosis: An updated meta-analysis. PLoS One 2011;6:e16149.
19. Høglund RA, Maghazachi AA. Multiple sclerosis and the role of immune cells. World J Exp Med 2014;4:27-37.
20. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA 2006;296:2832-8.
21. Thacker EL, Mirzaei F, Ascherio A. Infectious mononucleosis and risk for multiple sclerosis: A meta-analysis. Ann Neurol 2006;59:499-503.
22. Wingerchuk DM. Environmental factors in multiple sclerosis: Epstein-barr virus, Vitamin D, and cigarette smoking. Mt Sinai J Med 2011;78:221-30.
23. Bandari DS, Sternaman D, Chan T, Prostko CR, Sapir T. Evaluating risks, costs, and benefits of new and emerging therapies to optimize outcomes in multiple sclerosis. J Manag Care Pharm 2012;18:1-7.
24. Barcellos LF, Oksenberg JR, Begovich AB, Martin ER, Schmidt S, Vittinghoff E, *et al.* HLA-DR2 dose effect on susceptibility to multiple sclerosis and influence on disease course. Am J Hum Genet 2003;72:710-6.
25. Compston A, Sawcer S. Genetic analysis of multiple sclerosis. Curr Neurol Neurosci Rep 2002;2:259-66.
26. Comabella M, Khoury SJ. Immunopathogenesis of multiple sclerosis. Clin Immunol 2012;142:2-8.
27. Benito-León J, Morales JM, Rivera-Navarro J, Mitchell A. A review about the impact of multiple sclerosis on health-related quality of life. Disabil Rehabil 2003;25:1291-303.
28. Perrin Ross A. Management of multiple sclerosis. Am J Manag Care 2013;19:s301-6.
29. Ross AP, Hackbarth N, Rohl C, Whitmyre K. Effective multiple sclerosis management through improved patient assessment. J Neurosci Nurs 2008;40:150-7.
30. Michel L, Larochelle C, Prat A. Update on treatments in multiple sclerosis. Presse Med 2015;44:e137-51.
31. Miller JR. The importance of early diagnosis of multiple sclerosis. J Manag Care Pharm 2004;10:S4-11.
32. Noyes K, Weinstock-Guttman B. Impact of diagnosis and early treatment on the course of multiple sclerosis. Am J Manag Care 2013;19:s321-31.
33. Optic Neuritis Study Group. Multiple sclerosis risk after optic neuritis: Final optic neuritis treatment trial follow-up. Arch Neurol 2008;65:727-32.
34. Frohman EM, Goodin DS, Calabresi PA, Corboy JR, Coyle PK, Filippi M, *et al.* The utility of MRI in suspected MS: Report of the therapeutics and technology assessment subcommittee of the American academy of neurology. Neurology 2003;61:602-11.
35. Barhate KS, Ganeshan M, Singhal BS. A clinical and radiological profile of neuromyelitis optica and spectrum disorders in an Indian cohort. Ann Indian Acad Neurol 2014;17:77-81.
36. Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, Fujihara K, *et al.* A serum autoantibody marker of neuromyelitis optica: Distinction from multiple sclerosis. Lancet 2004;364:2106-12.
37. de Seze J, Lebrun C, Stojkovic T, Ferriby D, Chatel M, Vermersch P, *et al.* Is devic's neuromyelitis optica a separate disease? A comparative study with multiple sclerosis. Mult Scler 2003;9:521-5.
38. Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. Neurology 2006;66:1485-9.
39. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, *et al.* Recommended diagnostic criteria for multiple sclerosis: Guidelines from the international panel on the diagnosis of multiple sclerosis. Ann Neurol 2001;50:121-7.
40. Paty DW, Oger JJ, Kastrukoff LF, Hashimoto SA, Hooge JP, Eisen AA, *et al.* MRI in the diagnosis of MS: A prospective study with comparison of clinical evaluation, evoked potentials, oligoclonal banding, and CT. Neurology 1988;38:180-5.
41. Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, *et al.* Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald criteria". Ann Neurol 2005;58:840-6.
42. Thompson AJ, Montalban X, Barkhof F, Brochet B, Filippi M, Miller DH, *et al.* Diagnostic criteria for primary progressive multiple sclerosis: A position paper. Ann Neurol 2000;47:831-5.
43. Traboulsee AL, Li DK. The role of MRI in the diagnosis of multiple sclerosis. Adv Neurol 2006;98:125-46.
44. Lebrun C, Bensa C, Debouverie M, Wiertlevski S, Brassat D, de Seze J, *et al.* Association between clinical conversion to multiple sclerosis in radiologically isolated syndrome and magnetic resonance imaging, cerebrospinal fluid, and visual evoked potential: Follow-up of 70 patients. Arch Neurol 2009;66:841-6.
45. Okuda DT, Mowry EM, Beheshtian A, Waubant E, Baranzini SE, Goodin DS, *et al.* Incidental MRI anomalies suggestive of multiple sclerosis: The radiologically isolated syndrome. Neurology 2009;72:800-5.
46. Sellner J, Schirmer L, Hemmer B, Mühlau M. The radiologically isolated syndrome: Take action when the unexpected is uncovered? J Neurol 2010;257:1602-11.
47. Schumacher GA, Beebe G, Kibler RF, Kurland LT, Kurtzke JF, Mcdowell F, *et al.* Problems of experimental trials of therapy in multiple sclerosis: report by the panel on the evaluation of experimental trials of therapy in multiple sclerosis. Ann N Y Acad Sci 1965;122:552-68.
48. Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, *et al.* New diagnostic criteria for multiple sclerosis: Guidelines for research protocols. Ann Neurol 1983;13:227-31.
49. Barkhof F, Rocca M, Francis G, Van Waesberghe JH, Uitdehaag BM, Hommes OR, *et al.* Validation of diagnostic magnetic resonance imaging criteria for multiple sclerosis and response to interferon beta1a. Ann Neurol 2003;53:718-24.
50. CHAMPS Study Group. MRI predictors of early conversion to clinically definite MS in the CHAMPS placebo group. Neurology 2002;59:998-1005.
51. Dalton CM, Brex PA, Miszkiel KA, Hickman SJ, MacManus DG, Plant GT, *et al.* Application of the new McDonald criteria to patients with clinically isolated syndromes suggestive of multiple sclerosis. Ann Neurol 2002;52:47-53.
52. Tintoré M, Rovira A, Río J, Nos C, Grivé E, Sastre-Garriga J, *et al.* New diagnostic criteria for multiple sclerosis: Application in first demyelinating episode. Neurology 2003;60:27-30.
53. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, *et al.* Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69:292-302.
54. Trojano M, Paolicelli D, Bellacosa A, Cataldo S. The transition from relapsing-remitting MS to irreversible disability: Clinical evaluation. Neurol Sci 2003;24 Suppl 5:S268-70.
55. Comi G. Early treatment. Neurol Sci 2006;27 Suppl 1:S8-12.
56. Flachenecker P. Disease-modifying drugs for the early treatment of multiple sclerosis. Expert Rev Neurother 2004;4:455-63.
57. Frohman EM, Havrdova E, Lublin F, Barkhof F, Achiron A, Sharief MK, *et al.* Most patients with multiple sclerosis or a clinically isolated demyelinating syndrome should be treated at the time of diagnosis. Arch Neurol 2006;63:614-9.
58. Burks J. MS: The treatment paradigm, a pathway to success for improved patient outcomes. J Manag Care Med 2008;12:26-31.
59. Naci H, Fleurence R, Birt J, Duhig A. Economic burden of multiple

sclerosis: A systematic review of the literature. Pharmacoeconomics 2010;28:363-79.
60. Owens GM, Olvey EL, Skrepnek GH, Pill MW. Perspectives for managed care organizations on the burden of multiple sclerosis and the cost-benefits of disease-modifying therapies. J Manag Care Pharm 2013;19:S41-53.
61. Palmer L, Abouzaid S, Shi N, Fowler R, Lenhart G, Dastani H, *et al*. Impact of patient cost sharing on multiple sclerosis treatment. Am J Pharm Benefits 2012;4:SP28-36.
62. Costello K, Kennedy P, Scanzillo J. Recognizing nonadherence in patients with multiple sclerosis and maintaining treatment adherence in the long term. Medscape J Med 2008;10:225.
63. Di Battista G, Bertolotto A, Gasperini C, Ghezzi A, Maimone D, Solaro C, *et al.* Multiple sclerosis state of the art (SMART): A Qualitative and quantitative analysis of therapy's adherence, hospital reliability's perception, and services provided quality. Mult Scler Int 2014;2014:752318.
64. Treadaway K, Cutter G, Salter A, Lynch S, Simsarian J, Corboy J, *et al.* Factors that influence adherence with disease-modifying therapy in MS. J Neurol 2009;256:568-76.
65. Riñon A, Buch M, Holley D, Verdun E. The MS choices survey: Findings of a study assessing physician and patient perspectives on living with and managing multiple sclerosis. Patient Prefer Adherence 2011;5:629-43.
66. Turner AP, Kivlahan DR, Sloan AP, Haselkorn JK. Predicting ongoing adherence to disease modifying therapies in multiple sclerosis: Utility of the health beliefs model. Mult Scler 2007;13:1146-52.
67. Río J, Porcel J, Téllez N, Sánchez-Betancourt A, Tintoré M, Arévalo MJ, *et al.* Factors related with treatment adherence to interferon beta and glatiramer acetate therapy in multiple sclerosis. Mult Scler 2005;11:306-9.
68. Bsteh G, Ehling R, Walchhofer LM, Hegen H, Auer M, Wurth S, *et al.* Paroxysmal and unusual symptoms as first clinical manifestation of multiple sclerosis do not indicate benign prognosis-the PaSiMS II study. PLoS One 2017;12:e0181458.
69. Masek M, Vaneckova M, Krasensky J, Danes J, Havrdova E, Hrebikova T, *et al.* Secondary-progressive form of multiple sclerosis: MRI changes versus clinical status. Neuro Endocrinol Lett 2008;29:461-6.
70. Wiendl H, Meuth SG. Pharmacological approaches to delaying disability progression in patients with multiple sclerosis. Drugs 2015;75:947-77.
71. Goodin DS, Frohman EM, Garmany GP Jr., Halper J, Likosky WH, Lublin FD, *et al.* Disease modifying therapies in multiple sclerosis: Report of the therapeutics and technology assessment subcommittee of the American academy of neurology and the MS council for clinical practice guidelines. Neurology 2002;58:169-78.
72. Sacco R, Bisecco A, Corbo D, Della Corte M, d'Ambrosio A, Docimo R, *et al*. Cognitive impairment and memory disorders in relapsing-remitting multiple sclerosis: The role of white matter, gray matter and hippocampus. J Neurol 2015;262:1691-7.