Overview of multiple sclerosis diagnosis and management

Khalid Alabbas, Abdullah Omar Aljafaari, Ahmed Abdulhai Alsubahi, Khalid Awaad Alenizy, Saif Alshammari, Salman B. Almobayedh, Mahdi Mana Alabbas. Mansour Mana Alghufaynah, Abdulmajeed Mohammad Alibrahem

Abstract:

In this review we discuss the background of disease, different diagnosis methods and give information about treatment approaches depending on the symptoms and stage of disease. In MEDLINE/PubMed, Cochrane Library, Embase and Web of Science databases search was performed for all studies published throughout December 2017. This search was without language restriction, and involving articles with human subject discussion. MS is a progressive illness with no cure up until now. The unknown etiology, potential condition heterogeneity, and immune system complexity will certainly remain to give difficulties for clinicians treating MS. To date there is no cure for MS, and medications which reduce immunologic features might have significant risks. The short-term efficiency and safety of more recent agents is being explored however the long term risks of these agents, specifically when used in mix or succession will remain uncertain. Furthermore, doctors are faced with the

treating possibly pregnant female and sometimes also children. MS is more usual in young people, and women are predominantly impacted. Likewise, current studies show that MS could take place in children. Although therapies are available to manage the disease course, they are only partially efficient. Therefore, MS worsens in some patients regardless of everything they and their physicians do to prevent it.

Introduction:

Multiple sclerosis (MS) is a chronic inflammatory autoimmune demyelinating illness of the central nervous system. Multiple sclerosis influences around 400,000 people in the United States alone, most of them being young people [1].It reveals itself in four scientific forms: slipping back remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and progressive relapsing MD (PRMS) (See Table 1). Approximately 87% of patients existing with RRMS, characterized by acute assaults (relapses) adhered to by partial or full recuperation (remission) [2].Patients can materialize with a heterogeneous group of signs and symptoms including modifications in vision (unilateral visual loss, diplopia), weakness, dyscoordination, sensory loss or distortions, or modifications in bowel and bladder function. Much less analysis however also disabling signs include cognitive adjustment, exhaustion, and mood disturbance. Progression of disease could at some point result in serious disability. Lots of medications and other measures may be used to ameliorate MS signs. The availability of condition modifying therapies has reinvented the care of patients with the relapsing types of this condition. These medications aid regulate the underlying illness process, probably by reducing immune mediated inflammation. They do not heal the disease or reverse the damage that has occurred with previous occasions. Generally the impacts of these agents appear even more powerful when they are offered to patients prior to extra severe widespread damages and special needs have occurred. As

the number of FDA-approved therapies remains to increase and other investigational and off label utilizes expands, it is handy to assess both the pathogenesis of MS and the results of the pharmacologic agents.

In this review we discuss the background of disease, different diagnosis methods and give information about treatment approaches depending on the symptoms and stage of disease.

Methodology:

In MEDLINE/PubMed, Cochrane Library, Embase and Web of Science databases search was performed for all studies published throughout December 2017. This search was without language restriction, and involving articles with human subject discussion. We search for relevant articles which were discussing the multiple sclerosis diagnosis and management, and mainly those studies which review and evaluate the management approaches.

Discussion:

Table 1. Types of Multiple Sclerosis

Type	**Disease Course**
Relapsing/Remitting	Most common type, accounts for approximate 85% of cases.

Type	Disease Course
Multiple Sclerosis (RRMS)	Characterized by discrete attacks that evolve over days to weeks followed by some decree of recovery over weeks to months. In between attacks, the patient has no worsening neurological function.
Secondary Progressive Multiple Sclerosis (SPMS)	Characterized by initial relapses, followed by gradual neurological deterioration not associated with acute attacks.
Primary Progressive Multiple Sclerosis (PPMS)	Characterized by steady functional decline from the onset of the disease. No relapses ever.
Progressive Relapsing Multiple Sclerosis (PRMS)	Characterized by steady functional decline from onset of the disease with later superimposed acute attacks. PRMS and PPMS cannot be distinguished during early stages, until the relapses occur

- **Clinical Evaluation**

The symptoms and signs of multiple sclerosis (MS) could resemble those of various other problems; for that reason medical diagnosis continuouslies be largely clinical, which establishes the have to use diagnostic criteria. Clinical diagnosis needs full medical history and neurological exam. Patients with MS, specifically on the initial visit, should be examined meticulously with unique dedication. Neurologists treating these patients need to have considerable experience in the management of MS. The Kurtzke Expanded Disability Status Scale (EDSS) is an approach of measuring disability in MS. The EDSS quantifies special needs in eight Functional Systems (FS) and allows neurologists to appoint a Functional System Score (FSS) in each of these. The Functional Systems are: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and others.

Table 2. EDSS steps 1.0 to 4.5 refer to people with multiple sclerosis (MS) who are fully ambulatory. EDSS steps 5.0 to 9.5 are defined by impairment to ambulation (FS, Functional Systems)

0.0	Normal neurological examination
1.0	No disability, minimal signs in one FS

1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS; fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS and more than minimal disability in several others
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability; able to walk without aid or rest some 500 meters
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability; able to walk without aid or rest some 300 meters
5.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (work a full day without special provisions)
5.5	Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting
7.0	Unable to walk beyond approximately five meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms
8.5	Essentially restricted to bed much of the day; has some effective use of arms; retains some self care functions
9.0	Confined to bed; can still communicate and eat
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10.0	Death due to MS

EDSS is gold requirement in assessing special needs in MS patients, however it is criticized for positioning excessive focus on making use of legs and being aloof to scientific adjustment. Still, it has a vital function in the examination of illness development since a number of magnetic resonance imaging (MRI) lesions are scientifically quiet (without signs) [3].However, in facilities with qualified personnel, it is advised to use MS Functional Composite range (MSFC) as exact

measurement of three dimensions at the same time, i.e. leg function/ambulation, arm/hand function and cognitive features in MS patients. Criterion MSFC consists of three testing categories: Timed 25 foot walk Test, 9 Hole Peg Test, and Paced Auditory Serial Addition Test (PASAT 3"). One of the problems that neurologists most frequently have in medical application of this scale is the management of the Paced Auditory Serial Addition Test (PASAT) that calls for a collection of complicated computations. A few of the specialists recommend changing the PASAT with the Symbol Digit Modalities Test in such patients. The lifestyle in MS patients ought to be evaluated by means of SF36 range, at appropriate periods, as figured out by the treating neurologist. Beck depression range should be provided in order to evaluate state of mind disorders and Visual Analog Scale (VAS) in order to review discomfort in MS patients (if it is present) [4].

- **Cerebrospinal Fluid Analysis**

Analysis of CSF need to be included in the workup of MS suspected patient. The existence of oligoclonal bands via isoelectric concentrating should be obtained. This technique specifies and delicate; on the contrary, the usage polyacrylamide gel might produce up to 50% of false-negative outcomes. An additional valuable cerebrospinal fluid (CSF) test to identify MS is the immunoglobulin G index.

CSF evaluation was just one of the major paraclinical diagnostic standards for MS (it is mandatory in the 2010 modification of McDonald requirements for MS); nowadays, it is of terrific significance in differential diagnosis of MS (Table 2) [5], [6].

- **Neuroimaging**

The McDonald criteria as revised by Polman and colleagues have presented adjustments in the presentation of dissemination in time and area through MRI, with subsequent vital modifications with respect to the use and analysis of imaging standards. This has made conventional MRI (cMRI) the most vital paraclinical device in detecting MS and developing prognosis at the scientific beginning of the disease. These are the major reasons why cMRI findings have a major duty in the changed diagnostic requirements for MS. The Consortium of Multiple Sclerosis Centers issued standards on the most proper MRI strategy. These consist of getting weighted pictures at T1 and T2 with gadolinium contrast, sagittal area at T2, coronal section to examine the optic nerve, sagittal section to view the spinal cord, and sagittal section to compare it with the lesions observed elsewhere. If any of the lesions doubt, 0.5-mm slices have to be acquired. Although it is suggested to use 1.5 tesla scanners, where such tools is not readily available, the specialists think about that MRI scans with lower resolution are equally beneficial for medical diagnosis. In centers with magnetization transfer (MT) abilities, these pictures could aid diagnosis, although there are no requirements and longitudinal follow up with MT MRI is difficult in daily professional practice. In spite of the sensitivity of cMRI for spotting MS sores, the connection in between cMRI metrics (i.e. hyperintense lesions on T2- and postcontrast T1-weighted photos, hypointense lesions on T1-weighted images, and atrophy measurements) and medical findings of MS is still limited [7].Amongst the likely factors for this clinical/MRI discrepancy, a significant one is the low pathological specificity of the abnormalities seen on cMRI scans and the inability of cMRI metrics to identify and quantify the degree of damages in normal-appearing mind cells (NABTs). These intrinsic limitations of cMRI have motivated the growth and application of modern quantitative MR methods [MR spectroscopy (1H-MRS), MT MRI, diffusion-weighted (DW) MRI and functional MRI (fMRI)] to the study of MS. Although

these methods have supplied important insight right into the pathobiology of MS, their useful value in the assessment of MS patients in scientific method has yet to be recognized [8] [9].

- **Treatment of Relapses**

An attack should last for at least 24 h and, according to the McDonald criteria there must be expert opinion that the occasion is not a pseudoattack as might be caused by a boost in body temperature level or infection. Numerous episodes of paroxysmal signs, e.g., tonic convulsions or trigeminal neuralgia occurring over not less than 24 h, may likewise make up a relapse. Although most of relapses enhance to some extent, incomplete recovery is a crucial determinant of irreversible neurological problems in MS a minimum of in the earlier stages of MS [10], [11], [12].

Corticosteroids

There is proof from a number of class I researches and meta-analyses for an advantageous impact of glucocorticoid therapy in MS relapses. Treatment with intravenous or oral methylprednisolone in a dose of a minimum of 500 mg daily for 5 days should be taken into consideration for treatment of regressions. Therapy with i.v. methylprednisolone (1 g daily for 3 days) ought to be thought about as a different treatment. Therapy with i.v. methylprednisolone (1 g once daily for 3 days with an oral tapering dose) could be taken into consideration for therapy of acute optic neuritis. There is no evidence for significant differences in the efficacy of methylprednisolone treatment given i.v. or by mouth in regards to clinical efficacy or side effects, but extended oral treatment may potentially be related to a higher prevalence of adverse effects. As a result of a small number of patients consisted of in professional trials, effectiveness differences in between the i.v. and oral route of administration could not be left out. The optimal dosage, the particular

glucocorticoid to be used, and whether to utilize a taper after initial pulse treatment, have not been properly evaluated in randomized, managed tests. These issues must be evaluated in brand-new, randomized researches in order to analyze the risk/benefit ratios and damaging results of details glucocorticoids, dosage, and path of management for the treatment of MS relapses [12], [14].

Immunoglobulins

There are insufficient information to support the use of intravenous immunoglobulin (IVIG) therapy as monotherapy for relapses of MS. IVIG has not met the guarantee indicated by the results of lots of properly designed researches. Four randomized double-blind researches have all revealed an useful impact on disease activity in relapsing-remitting numerous sclerosis (RRMS). IVIG 0.15-0.2 g/kg every 4 weeks throughout 2 years showed noticable reduction in the relapse rate in two placebo-controlled trials. A meta-analysis of 4 researches revealed substantial reduction in the yearly relapse rate and disease progression (class I evidence). The prevention of regressions with IVIG trial (PRIVIG) re-evaluating the impacts of IVIG given 0.2 and 0.4 g/ kg monthly cannot reveal effect on the percentage of relapse-free patients and MRI activity in a sugar pill regulated research study in 127 patients with RRMS. Thus, this test cannot sustain earlier monitorings on an useful effect of IVIG in RRMS. In secondary progressive MS, a large placebo-controlled trial of IVIG 1 g/kg monthly in 318 patients failed to show any type of valuable impact on the regression rate, deterioration in EDSS, and modification in lesion quantity of T2 heavy images.The just useful result was decrease in brain atrophy [13].Little studies with historic controls suggested that IVIG could reduce relapse rate after childbirth [11], [12].

- **Treatment of Clinically Isolated Syndrome**

At the start of the disease training course, MS is characterized by inflammatory demyelination, which may be clinically silent (RIS), as a result patients often existing numerous old inactive lesions on brain and spinal cord MRI at the time of the start of clinical signs. At the time of first medical manifestation (CIS), neurodegenerative changes are already taking place in several patients. The disease after that usually enters the relapsing-remitting program resulting in conversion to second dynamic course. Healing window for current anti-inflammatory treatments is when the inflammatory element is most active.

CIS episode should be treated with high methylprednisolone doses to lower the risk of second assault. The dose varies from 500 mg/day for 5 days to 1 g/ day for 3-5 days.The administration of 2 g/day for 5 days has also been defined. The complete dosage is administered i.v. during 2-4 hrs, and blood pressure and heart rate must be kept an eye on to identify the possible negative effects brought on by corticosteroids such as hypotension at an early stage. In case of serious regressions that do not respond to steroid therapy, or in case of negative occasions, treatment with plasmapheresis might be taken into consideration. In all other instances, there is no evidence to sustain making use of plasmapheresis in the treatment of MS. There is no strong evidence in support of making use of natalizumab, i.v. immunoglobulin, or a 2nd training course of corticosteroids during relapses.

Table 3.summarized treatment methods for multiple sclerosis

	Drug name	**Dosage**
Treatment of relapses [12],[11].	Methylprednisolone Prednisone IVIG Plasma exchange	0.5-1 g per day i.v. (3-7 days) 0.5-1 mg/kg body weight in tapering doses; after 3-6 weeks, 5-10 mg maintenance dose 2.0-0.4 g/kg body weight 2-5 days 1-7 times every other day
First line therapies [15],[16].	Glatiramer acetate Interferon beta 1a and interferon beta 1b	20 mcg per day Avonex 6 MIU once per week, Betaferon 9.6 MIU every other day, Rebif 22 mcg or 44 mcg twice weekly

Second line therapies[17],[18],[19]	Fingolimod Natalizumab Azathioprine Cyclophosphamide	0.5 mg per os per day 300 mg i.v. every 4 weeks 2.5-3 mg/kg body weight per day; 1.5- 2.5 maintenance dose 1-5 mg/kg twice per day 1 g i.v. every month for 6-12 months, then every 5 weeks during 2nd year and every 6 weeks during 3rd year of application

Conclusion:

MS is a progressive illness with no cure up until now. The unknown etiology, potential condition heterogeneity, and immune system complexity will certainly remain to give difficulties for clinicians treating MS. To date there is no cure for MS, and medications which reduce immunologic features might have significant risks. The short-term efficiency and safety of more recent agents is being explored however the long term risks of these agents, specifically when used in mix or succession will remain uncertain. Furthermore, doctors are faced with the treating possibly pregnant female and sometimes also children. MS is more usual in young people, and women are predominantly impacted. Likewise, current studies show that MS could take place in children. Although therapies are available to manage the disease course, they are only partially efficient. Therefore, MS worsens in some patients regardless of everything they and their physicians do to prevent it. Patients with relapsing- remitting MS, the most common kind of MS, experience attacks of worsening neurological performance, followed by durations of remission identified by partial or complete healing. Differential medical diagnoses must be considered on making the diagnosis of MS. Therefore, diagnosis of MS should be established on clinical and radiological diagnostic criteria, cerebrospinal fluid analysis and evoked potentials.

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