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Review Article

Multiple Sclerosis (MS) – Demyelinating Disorder; It's Overview, Indications, Etiology, Pathophysiology and Clinical Pharmacotherapy

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ABSTRACT

Multiple sclerosis (MS) is also called as demyelinating disorder in which myelin sheath of neurons affected which ultimately affects the cognitive impairment and cause mobility disorders. Worldwide the Multiple sclerosis influences 2.5 million citizens plus 400,000 Americans. The main cause is still unknown but the researchers find that due to genetic, immunologic and environmental factors, myelin sheath could be damage. The treatment protocol depends upon the severity and the symptoms of the disease. Certain medications like Natalizumab, Dimethyl fumarate etc is used to treat relapses in MS. In case of severe illnesses, the patient response is being discontinued then the doctor and pharmacist ought to prefer palliative care for the wellbeing of the patient. The main objective of this review study is to give a glance about the multiple features of this disease state, its morbidity and co-morbidity, types and proper management by appropriate medications in order to avoid any drug interaction and toxicity.

Keywords: Multiple sclerosis (MS), Demyelinating, Myelin sheath, Natalizsumab, Dimethyl fumarate, Palliative care and Medications.

INTRODUCTION

Demyelinating disease of nervous system is also known as multiple sclerosis which is an inflammatory and autoimmune disorder. It generally appears on initial stage, usually in adult stage. Its most recurrent symptoms include loss of balance, numbness, impaired vision, weakness, bladder dysfunction, and psychological changes [1]. First and early symptom of multiple sclerosis is fatigue. Multiple sclerosis is a very complex disease in which myelin sheath is damage. It has more than a single etiopathological entity and has multifactorial etiology. [2]

History: First MS was diagnosed and recorded in Holland on 4th august 1421 but the clear description of this disease begins to appear in early 19th century in 1838. [3]

Etiology: The main cause of MS is unknown but many researchers told that MS is autoimmune as well as genetic. In altered immune response loss of both axons and demyelination occur.

Types: There are four types of MS reported:

Relapsing-remitting MS (RRMS): This is the most prevalent type of disease. About almost 85% of patient originally diagnose with this type. Patient with RRMS have transitory periods called relapses or exacerbations when a new symptoms develop. A relapse pursue for weeks and last for 55 days. A relapse is the occurrence of new symptom or reoccurrence of old symptom last for more than a whole day. The severity and gap between attacks are unpredictable. It is also difficult to determine the severity and about relapse. [4]

Secondary-Progressive MS (SPMS): It is more exacerbated then RRMS because in this relapse maybe appear or not. Once RRMS is diagnose it progress to SPMS. In this type the patient has shown continued deterioration or damage for past six months. In this kind of disease modifying medicines are not longer work. [5]

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Primary-Progressive MS (PPMS): This type of MS is atypical and it occurs in about 10% of people. In this type slowly worsening of neurons but without any attack or relapses. [4]

Progressive-Relapsing MS (PRMS): This type of MS is very rare and almost 5% of people got affected. It is characterized by worsening disease state with or without recovery and with acute relapses. In this disease true neurologic attacks occur. [4]

Signs and symptoms: Following are the frequent sign and symptom of MS:
Weakness, tremor, fatigue, sexual dysfunction, dizziness, numbness vertigo, impaired mobility, bladder and bowel dysfunction, slurred vision, swelling, depression, mild cognitive and memory difficulties with spasticity.

Factors That Contributing Multiple Scleroses:
There are some factors that subsidize MS:

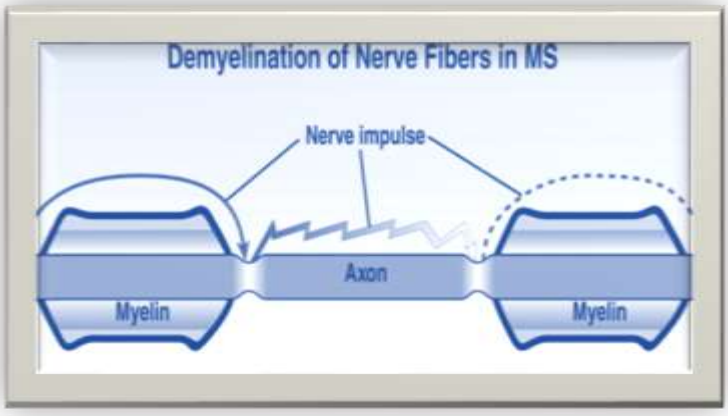
Genetic factor: female has 2 to 3 times more likely to get disease plus family history increase risk of MS.

Environmental factor: it is least common in rural areas and lower class. This disease incensed by much kind of infections (Epstein barr).[7]

Immunologic factor: an abnormal immune mediated response attack the myelin sheath and deteriorate it.

Diagnosis:
On the basis of clinical findings and evidence diagnosis are made upon:
Magnetic resonance imaging: the imaging procedure of choice for confirming the MS.
Evoked potentials: it is used to identify subclinical lesions but results are not specific for MS.
Lumber puncture: it is used when MRI is not working or from MRI, MS is not diagnosed.

Pathophysiology: For normal conduction of nerve impulses, myelin sheath down the axons is necessary. The destruction of the myelin sheath leads to impaired communication between nerve cells and neurological symptoms is the main cause, however early in the disease course, MS involves recurrent course of CNS inflammation that results in damage to both the myelin sheath surrounding axons as well as the axons themselves. Histologic examination reveals severe demyelination, decreased axonal numbers, and gliotic scarring. The exact cause of inflammation remains unclear, but an autoimmune response directed against CNS antigens is suspected. Pathological studies suggest that different patients may have different etiologies for inflammation: some patients appear to have T-cell-plus-antibody-mediated autoimmune responses, while others have a primary disorder with the myelin-producing oligodendrocyte cells.[8] This latter mechanism is evocative of virus- or toxin-induced demyelination rather than autoimmunity in this subset of patients.[9]



Treatment:
The treatment of MS patient involves:
Medications: (Clinical Course)
Many medicines used to treat MS but some medicines given symptomatic. Following are the medicines given to the MS patient:

i. Infused medications
   a. natalizumab
ii. Injectible medications
   a. interferon beta-1a
   b. interferon beta-1b
   c. glatiramer acetate
iii. Oral medications
   a. fingolimod
   b. dimethyl fumarate

Natalizumab: FDA approved natalizumab in November 2004 as monoclonal antibody targeting

cellular adhesion molecule very late antigen. Every 4 weeks it is administered through IV. By blocking VLA-4, fewer inflammatory cells enter the brain and thereby dulled CNS inflammation typical of MS. Natalizumab reduces clinical relapses by 67% and new brain lesions by 83%, in phase III trials [11] making natalizumab the most clinically effective medicine for RRMS to date. It is highly accepted and well tolerated with mild headache, anxiety, fatigue with usually edema observed. In about 2 to 4% patient infusion related hypersensitivity is observed and are thought to be immune mediated hypersensitivity reactions. People who report infusion reaction immediately advice to discontinue natalizumab. [12]

According to new research after the start of natalizumab and 18 month follow up. It has been observed that there is gradually increased in monocytes, erythroblast (16%) and neutrophil (6.8%) which shows that hematopoietic precursors are present in natalizumab patients not in normal blood or before using natalizumab.[13] Even according to one research hematopoietic mobilization in body is one of the biomarker for natalizumab. [14]

According to another research researchers evaluate the effects of natalizumab in a cohort study of 24 patients for 3 years on cognitive impairment. In the assessment certain scores was detected which was improvement in memory and attention. This was the neuropsychological assessment. [15]

Interferon beta-1a/1b: In the body many natural proteins is produced and has function to modulate the immune system. Interferon interacts with non-infected cells thus promote different antiviral proteins that prevent further infection. They belong to the cytokine class. Treatment with interferon results in the development of neutralizing antibodies. [16] According to research IFN-b treatment reduced the inflammatory potential and proliferation of cultured cells. [17]

Glatiramer acetate: To reduce the prevalence of relapses glatiramer acetate is used. Glatiramer acetate is thought to act by modifying immune processes that are believed to be responsible for the pathogenesis of MS. It has affinity with myelin so it can easily divert autoimmune response. According to the research GA is use as the first line agent for RRMS in United States since 1996. More than 100,000 patients use GA by themselves for MS because of its safety and tolerability. 18]

Fingolimod: Fingolimod is an Immunomodulatory agent used to treat multiple sclerosis. It is a sphingosine 1 phosphate receptor modulator. It works by reducing the circulating lymphocytes in CNS which causes damage of nerves and causes inflammation. It is used for reducing the occurrence of physical disability in patients with MS. According to research 2 doses of Fingolimod compared with each other in clinical trials and result shows that 1.25 mg as compare to 0.5mg has greater reduction in relapses. [19]

Dimethyl fumarate or DMF: In March 2013 it is approved by FDA for orat treatment of multiple sclerosis.It is has both anti-inflammatory and neuroprotective effects. A very similar drug, being dimethyl fumarate in combination with three other fumaric acid esters, has been used for many years as a treatment for the skin condition psoriasis, which is also thought to be an autoimmune inflammatory disease. [20-22] According to research DMF shown reduction in relapses, disability progression and lesions. [23]

Table 1.1 Show summaries of medications:

Name	Class or category	Mechanism of action	uses	Adverse effects	references
Natalizumab	Anti integrin	humanized IgG4 antibody directed at α4 subunit integrin, which blocks the α4β1 and α4β7 integrins, expressed on all leukocytes,	Multiple sclerosis Crohn disease	fast heartbeat, puffiness or swelling of the eyelids or around the eyes, face, lips, or tongue, shortness of breath, skin rash, hives, or itching, tightness in the chest	[24-26]
Interferon beta 1a	Cytokine	Regulate and mediate immunity, inflammation and hemotopoesis by regulate NK cells	Multiple sclerosis	chest pain, chills, cough, diarrhea, fever, flu-like symptoms, headache, joint pain, muscle aches, nausea, pain	[27]
Interferon beta 1b	Cytokine	Regulate and mediate immunity, inflammation and hemotopoesis by regulate NK cells	Multiple sclerosis	depressed mood, anxiety, trouble sleeping, restlessness, or thoughts of suicide or hurting yourself	[27]
glatiramer acetate	Immunomodulatory agent	partial activation and tolerance induction of MBP-specific T cells	Multiple sclerosis	Anxiety, bleeding, hard lump, hives or welts, itching, pain, redness, or swelling at the place of injection, chest pain, cough	[28]
Fingolimod	Immunosuppressant	binds to a receptor on a proportion of circulating lymphocytes and reversibly traps them in lymph nodes	Multiple sclerosis	Chills, cough, cough-producing mucus, diarrhea, difficult or labored breathing, dizziness, fever	[29]
Dimethyl fumarate	Radio sensitizer	activating the nuclear erythroid 2-related factor 2 (nuclear factor erythroid-derived 2-like 2; Nrf2)	Multiple sclerosis Psoriasis	fever or chills, lower back or side pain, painful or difficult urination	[30]

Symptomatic treatment of MS is as follows:

Table 1.2 show summary of symptomatic treatment:

Pain	**NSAIDS (Gabapentin 300mg PO)**
Bladder dysfunction	Propantheline 7.5mg PO q3-q4h Oxybutynin chloride 5mg PO tid-qid
Constipation	Laxative suppositories, stool softeners, bulk-producing agent
Depression	Antidepressant agent such as SSRIs
Paranoia or mania	Haloperidol lithium or antipsychotic
Dysesthesias	Carbamazepine 100-200mg PO
Spasticity	Baclofen 5mg PO tid Diazepam 2-5mg Hs

Rehabilitation:

1) Physical therapy: In this therapist evaluate the movement of body, walking, and balance posture.
2) Cognitive rehabilitation: it is used to evaluate the process of thinking, concentrate and remember.
3) Speech therapy: it is used to treat the problems of speech the goal of therapy is enhance easiness in communication.

Palliative care: Palliative is used to enhance the physical, social and emotional spirit of patients. It is done by any health care professionals. It promotes quality of life in serious patients. Palliative care is provided to the patient with severe multiple sclerosis. The main goal of therapy is to increased quality of life among MS patients.[32, 33]

RESULTS AND DISCUSSIONS

Multiple sclerosis is the most prevailing and complicating disorder, due to incompliance of the patient, less awareness in the society and improper medications it could be life threatening. In this piece of writing we outlined and analyze the diverse facets of this disorder with discussing all its type, epidemiology and its pharmacotherapy. Hence for this auto immune disease the medications should be prompt and accurate. The Health care panel which includes Pharmacist should also incorporate as by the proper medication and drug monitoring it could be controllable. The palliative care department should be sound enough and through its proper management it can be handy to some extent as the main task for the doctors and pharmacist is to supervise and improved the quality life of the suffering patient.

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