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BRIEF REVIEW ON MULTIPLE SCLEROSIS

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ABSTRACT

There is no known cure for multiple sclerosis. Treatments attempt to improve function after an attack and prevent new attacks. Medications used to treat MS, while modestly effective, can have side effects and be poorly tolerated Multiple sclerosis usually starts with an acute episode of neurological disturbance, termed a 'clinically isolated syndrome', followed by an illness phase punctuated by relapses and remissions which may transition after 10 years to a phase of progressive accumulation of disability without relapses. Fifteen to 20% of patients will have a progressive course from the onset. There is significant interpatient variability in prognosis. The main diagnostic criteria are clinical, supported by investigations including magnetic resonance imaging and lumbar puncture and evoked potentials. First line disease modifying agents for relapsing remitting multiple sclerosis include interferon-ß and glatiramer. First line treatment for relapses is usually intravenous methylprednisolone for 3 days. Troublesome symptoms may include spasticity, parasthesias, tremor, erectile dysfunction, depression and anxiety, fatigue and pain. After excluding differential diagnoses, symptomatic management includes pharmacological agents, allied health consultation and continence strategies. Although pregnancy reduces disease activity, there is a higher risk of relapse in the postpartum period.

INTRODUCTION

Multiple sclerosis (**MS**) is a demyelinating disease in which the insulating covers of nerve cells in the brain and spinal cord are damaged.[1] This damage disrupts the ability of parts of the nervous system to communicate, resulting in a range of signs and symptoms, including physical, mental, and sometimes psychiatric problems.[2]

It is possible that multiple factors are involved in causing multiple sclerosis, including DNA defects in nuclear and mitochondrial genomes, viral infection, hypoxia, oxidative stress, lack of sunlight, and increased macrophages and lymphocytes in the brain.[3]

Multiple sclerosis is the most common autoimmune disorder affecting the central nervous system. In 2015, about 2.3 million people were affected globally with rates varying widely in different regions and among different populations. That year about 18,900 people died from MS, up from 12,000 in 1990. The disease usually begins between the ages of 20 and 50 and is twice as common in women as in men.[4]

THE 4 TYPES OF MS

- **Relapsing-Remitting MS (RRMS):** This is the most common form of multiple sclerosis. About 85% of people with MS are initially diagnosed with RRMS. People with RRMS have temporary periods called relapses, flare-ups or exacerbations, when new symptoms appear.
- **Secondary-Progressive MS (SPMS):** In SPMS, symptoms worsen more steadily over time, with or without the occurrence of relapses and remissions. Most people who are diagnosed with RRMS will transition to SPMS at some point.
- **Primary-Progressive MS (PPMS):** This type of MS is not very common, occurring in about 10% of people with MS. PPMS is characterized by slowly worsening symptoms from the beginning, with no relapses or remissions.
- **Progressive-Relapsing MS (PRMS):** A rare form of MS (5%), PRMS is characterized by a steadily worsening disease state from the beginning, with acute relapses but no remissions, with or without recovery[5]

PRESENTATION

Most patients with MS have relapsing-remitting disease, which typically presents in a young adult with a clinically isolated syndrome suggestive of MS such as optic neuritis, long tract symptoms/signs (eg, numbness, paresthesia, or weakness), a brainstem syndrome (eg,internuclear ophthalmoplegia), or a spinal cord syndrome (eg, transverse myelitis). Presentations due to cortical syndromes such as aphasia or visual field disturbances are possible, though much less common. Presenting symptoms and signs may be either monofocal (consistent with a single lesion) or multifocal (consistent with more than one lesion). Approximately 5 to 10 percent of adult patients have the primary progressive form of MS, which presents with gradual accumulation of disability from the onset, without

superimposed acute relapses. The most common clinical presentation of primary progressive MS is a spinal cord syndrome with spastic paraparesis and no clear sensory level[6]

A relapse (also called an attack or exacerbation) is defined as the acute or subacute onset of clinical dysfunction typical of an acute inflammatory demyelinating event in the central nervous system, in the absence of fever or infection. Symptoms and signs associated with a relapse usually reach a peak in days to several weeks, followed by a remission during which the symptoms and signs resolve to a variable extent. The minimum duration for a relapse has been arbitrarily established at 24 hours, though most are much longer. Clinical symptoms of shorter duration are less likely to represent new lesion formation or extension of previous lesion size.[7]

Pregnancy and multiple sclerosis

Pregnancy is known to be associated with an increase in a number of circulating proteins and other factors that are natural immunosuppressants. Additionally, levels of natural corticosteroids are higher in pregnant than nonpregnant women. These may be some of the reasons why women with MS tend to do well during pregnancy.

Women who have gait difficulties may find these get worse during late pregnancy as they become heavier and their center of gravity shifts. Increased use of assistive devices to walk or use of a wheelchair may be advisable at these times. Bladder and bowel problems, which occur in all pregnant women, may be aggravated in women with MS who have pre-existing urinary or bowel dysfunction. MS patients may also be more subject to fatigue.

In general, pregnancy does not appear to affect the long-term clinical course of MS. Women who have MS and wish to have a family can usually do so successfully with the assistance of their neurologist and obstetrician.

CLINICAL SYMPTOMS AND SIGNS

There are no clinical findings that are unique to MS, but some are highly characteristic of the disease. Common symptoms of MS include sensory symptoms in the limbs or one side of the face, visual loss, acute or subacute motor weakness, diplopia, gait disturbance and balance problems, Lhermitte sign (electric shock-like sensations that run down the back and/or limbs upon flexion of the neck), vertigo, bladder problems, limb ataxia, acute transverse myelitis,

and pain. The onset is often polysymptomatic. The most common presenting symptoms are sensory disturbances, followed by weakness and visual disturbances.[8]

Bowel and bladder dysfunction: Approximately 50 percent of patients with MS report bowel dysfunction and up to 75 percent report bladder dysfunction. The extent of sphincter and sexual dysfunction often parallels the degree of motor impairment in the lower extremities. The most frequent urinary complaint is urgency, which is usually the result of uninhibited detrusor contraction due to a suprasegmental lesion.[9]

Cognitive impairment: Frank dementia is an uncommon feature of MS, occurring in fewer than 5 percent of patients. It is usually only encountered in severely affected individuals. However, when evaluated with neuropsychological tests, up to 70 percent of patients have some cognitive impairment. The prevalence of cortical syndromes such as aphasia, apraxia, and agnosia is low. Different disease courses may have different cognitive profiles. As an example, there is evidence that patients with relapsing-remitting MS generally have better cognitive performance than patients with progressive types of MS[10]

Depression: Cross-sectional studies have shown some degree of affective disturbance in up to two-thirds of patients with MS.

Depression may be more common in patients with MS than in others with chronic medical conditions. In addition, the risk of suicide in patients with MS may be increased in comparison with the general population, as shown in most but not all studies. The median life expectancy in patients with MS is reduced by about 5 to 10 years compared with that of the general population suicide probably has only a small effect on this diminution.[11,12,13]

Epilepsy: Epilepsy is more common in patients with MS than in the general population, occurring in 2 to 3 percent of patients. Approximately two-thirds of seizures in patients with MS are primary or secondary generalized seizures, while the remaining one-third are partial. Simple partial seizures are about twice as common as complex partial seizures in patients with MS. This differs from the general population, where complex partial seizures are more frequent than simple partial[14]

Eye movement abnormalities: A host of efferent visual disturbances can occur as manifestations of MS, including the following:[15]

- Abnormalities of voluntary gaze (very common).

•Internuclear ophthalmoplegia.

•Ocular dysmetria and gaze impersistence.

•Horizontal gaze palsy.

•One-and-a-half syndrome.

•Dorsal midbrain syndrome.

•Skew deviation.

●Nystagmus (very common).

•Horizontal.

•Vertical.

•Pendular.

•Periodic alternating.

●Abnormalities of slow phase eye movements (common).

•Disordered smooth pursuit.

●Paroxysmal disorders of eye movements (less common).

•Ocular flutter.

•Square wave jerks.

•Opsoclonus.

●Isolated ocular motor nerve palsies (uncommon).

Fatigue: Fatigue is a characteristic finding in MS, usually described as physical exhaustion that is unrelated to the amount of activity performed. The impact of fatigue is suggested by the findings of a survey of 223 patients with MS; fatigue was the most common currently experienced symptom (86 percent), and it was rated as the worst symptom causing difficulty or distress by 65 percent, higher than any other symptom. Fatigue interferes with daily activities.[16]

Heat sensitivity: Heat sensitivity (Uhthoff phenomenon) is a well-known occurrence in MS; small increases in the body temperature can temporarily worsen current or preexisting signs and symptoms. Transient increases in the frequency or severity of clinical signs and symptoms as a result of elevated body temperature are experienced by 60 to 80 percent of individuals with MS[17]

Motor symptoms: In patients with MS, paraparesis or paraplegia are more common than isolated upper extremity weakness due to the frequent occurrence of lesions in the descending motor tracts of the spinal cord. Severe spasticity can occur, such that extensor spasms of the

legs and sometimes the trunk may be provoked by active or passive attempts to rise from a bed or wheelchair.

Brainstem-related symptoms like dysphagia, dysarthria, and respiratory dysfunction (particularly poor cough and inability to clear secretions) can occur in advanced MS disease.

Incoordination: Gait imbalance, difficulty in performing coordinated actions with the arms and hands, and slurred speech often occur as a result of impairment of cerebellar pathways. Cerebellar signs are usually mixed with pyramidal (corticospinal) tract signs.

Pain: Pain associated with MS can arise from neurogenic and non-neurogenic sources. Neurogenic pain includes paroxysmal pain, persistent pain (eg, burning or ice-cold dysesthesias of the feet, hands, limbs, and trunk), and episodic neuropathic pain. Musculoskeletal and soft tissue pain may be caused by paralysis, immobility, or spasticity.

Pain is a common symptom in patients with MS.[18]

- Headache in 43 percent.
- Neuropathic extremity pain in 26 percent.
- Back pain in 20 percent.
- Lhermitte sign in 16 percent.
- Painful spasms in 15 percent.
- Trigeminal neuralgia in 4 percent.

Sensory symptoms: Sensory symptoms are the most common initial feature of MS and are present in almost every patient at some time during the course of disease. The sensory features can reflect spinothalamic, posterior column, or dorsal root entry zone lesions. Symptoms are commonly described as numbness, tingling, pins-and-needles, tightness, coldness, or swelling of the limbs or trunk. Radicular pains also can be present, particularly in the low thoracic and abdominal regions. An intense itching sensation, especially in the cervical dermatomes and usually unilateral, is suggestive of MS.

Sexual dysfunction— Sexual dysfunction is common in patients with MS. About 50 percent of patients become completely sexually inactive secondary to their disease, and an additional 20 percent become sexually less active.In men with MS, the most common complaints are reduced libido, erectile impotence, the disappearance of early morning erection, premature ejaculation, orgasmic dysfunction, and reduced penile sensation. In women with MS, the

most common complaints are reduced libido, difficulties in achieving orgasm, decreased vaginal lubrication, decreased vaginal sensation, and dyspareunia.[19]

MS TREATMENT OPTIONS

There are various MS treatment options available today that have been shown to decrease the frequency of relapses and to delay disease progression. There are several ways that these treatment options can be taken. Some treatments use an injection either subcutaneous (under the skin) or intramuscular (into the muscle) while others are given intravenously (via an infusion) or orally (by mouth).

Disease-modifying treatment of relapsing-remitting multiple sclerosis in adults

Starting disease-modifying therapy

A number of immunomodulatory agents, including interferon beta preparations, glatiramer acetate, natalizumab, alemtuzumab, ocrelizumab, dimethyl fumarate, teriflunomide, and fingolimod, have important beneficial effects for patients with relapsing-remitting multiple sclerosis (RRMS):

- A decreased relapse rate.
- A slower accumulation of brain lesions on MRI.

Thus, everyone with a diagnosis of definite RRMS should begin disease-modifying therapy (DMT). However, these therapies are not a cure; they are only partially effective for reducing the relapse rate, and whether all or any reduce disability progression is still under investigation. However, some observational studies have found evidence suggesting that the use of DMTs for patients with MS is associated with a lower long-term risk of disease progression.

We recommend disease-modifying therapy (DMT) with one of the effective agents for all patients with RRMS starting as soon as possible. The choice of a specific agent should be individualized according to disease activity and patient values and preferences. Our suggested approach to initial treatment is as follows:

- Infusion therapy with natalizumab for patients with more active disease and for those who value effectiveness above safety and convenience. The evidence that natalizumab is more effective than interferons, glatiramer, or oral DMTs for patients with RRMS is based upon cross-trial comparisons and clinical experience.

●Injection therapy (interferons or glatiramer) for patients who value safety more than effectiveness and convenience. Among these, we prefer intramuscular interferon beta-1a 30 mcg weekly or glatiramer acetate.

●Oral therapy (dimethyl fumarate, teriflunomide, or fingolimod) for patients who value convenience. We prefer dimethyl fumarate in this setting because it may be more effective and have a better safety profile than the other two agents, though the evidence is indirect and inconclusive. In addition, the potential teratogenicity of teriflunomide limits its use for a disease where a substantial portion of patients are of child-bearing age.

Most DMTs are continued indefinitely in clinically stable patients with RRMS unless side effects are intolerable. Exceptions include natalizumab therapy, where the risk of progressive multifocal leukoencephalopathy increases with the duration of treatment, and pregnancy, where the risk of possible adverse effects of DMTs on the fetus must be weighed against DMT discontinuation and increased risk of maternal disease relapses.

For patients initially treated with natalizumab who have an inadequate response, or who become seropositive for anti-JC virus antibodies, we suggest stopping natalizumab and starting one of the following options:

●Dimethyl fumarate.

●Fingolimod monotherapy.

●Teriflunomide.

For patients initially treated with an oral agent who have an inadequate response, we suggest the following options:

●Switch to a different oral agent.

●Switch to injection therapy with an IFNB or glatiramer.

●Switch to infusion therapy with natalizumab.

For patients with RRMS who are poor responders to all first-line treatments, and who develop accumulating disability despite therapy, the following options are available:

●Add intravenous (IV) methylprednisolone 1000 mg monthly

●Switch to fingolimod.

●Switch to alemtuzumab monotherapy.

●Intravenous immune globulin.

●IV pulse cyclophosphamide combined with pulse methylprednisolone.[20]

INJECTABLE THERAPIES — Injectable (intramuscular and subcutaneous) disease-modifying therapies for RRMS include the interferon beta (IFNB) preparations and glatiramer acetate. These are the oldest treatments for RRMS, the first being approved in 1993. They are sometimes called the "platform" therapies for this reason. The available evidence from controlled trials suggests that interferons and glatiramer have similar clinical utility Daclizumab, another self-administered injection therapy, was approved for treating RRMS in 2016.

Interferons: A number of different IFNB preparations are effective for the treatment of RRMS, as presented below.

Interferon beta-1b: The first disease-modifying medication approved for use in MS was recombinant interferon beta-1b. The drug is a cytokine that modulates immune responsiveness through various mechanisms.[21]

Interferon beta-1a: Interferon beta-1a is available in several different formulations, including intramuscular, subcutaneous, and pegylated preparations.

INFUSION THERAPIES: Infusion therapies for RRMS include natalizumab, alemtuzumab, ocrelizumab, and mitoxantrone. Observational data suggest that natalizumab and alemtuzumab have similar benefit for reducing relapse rates. Mitoxantrone is seldom used because of cardiac toxicity and limited evidence of benefit.

Natalizumab — Natalizumab is a highly effective drug for the treatment of RRMS. However, its use is associated with the development of progressive multifocal leukoencephalopathy (PML), a potentially disabling and fatal complication.

However, there are no trials comparing natalizumab directly with other disease-modifying agents. Thus, the relative effectiveness of natalizumab compared with other disease-modifying agents for RRMS cannot be defined confidently.

Testing for anti-JC virus antibodies suggested after one year of natalizumab therapy and discontinuing natalizumab for patients who are seropositive. The rationale for testing at one year is that PML is rare in the first year of natalizumab therapy even among those who are seropositive at baseline for JC virus antibodies. For patients who are JC virus antibody-positive, screening for PML with brain MRI every three to four months is advisable. For

patients who are negative for JC virus antibodies at one year, we suggest checking titers two to three times per year thereafter, with reconsideration of natalizumab in patients who seroconvert. However, in patients with a negative or low JC virus antibody level, 97 percent remain low over an 18-month period.

Natalizumab is given as a 300 mg intravenous (IV) infusion every four weeks. Side effects include infusion-related symptoms (headache, flushing, erythema, nausea, and dizziness), fatigue, allergic reactions, anxiety, infections (mainly urinary tract infection and pneumonia), pharyngitis, sinus congestion, and peripheral edema. Given its efficacy, natalizumab is reasonable as a starting medication for patients with aggressive disease, especially if they are negative for the JC virus antibody.

Alemtuzumab is a humanized monoclonal antibody that causes depletion of CD52-expressing T cells, B cells, natural killer cells, and monocytes. Data from randomized controlled trials show that alemtuzumab is more effective than interferon beta-1a for reducing the relapse rate in RRMS. This benefit is associated with a small increased risk of potentially serious infections and autoimmune disorders, including immune thrombocytopenia (ITP)[23]

ORAL THERAPIES — Approved oral disease-modifying therapies for RRMS are dimethyl fumarate, teriflunomide, and fingolimod.

Dimethyl fumarate — Fumarates may have neuroprotective and immunomodulatory properties. In two large trials, an oral formulation of dimethyl fumarate (BG-12) significantly reduced relapse rates and the development of new brain lesions on MRI in patients with active MS, and results from one of these trials suggest that BG-12 reduces the rate of disability progression

Teriflunomide: The immunomodulator teriflunomide is the active metabolite of leflunomide that inhibits pyrimidine biosynthesis and disrupts the interaction of T cells with antigen presenting cells. The effectiveness of teriflunomide for the treatment of RRMS was demonstrated in several randomized controlled trials.

OTHER TREATMENTS

Azathioprine: early trials of azathioprine for MS were small and conflicting. Nevertheless, in a meta-analysis that identified five randomized controlled trials involving 698 patients with MS, azathioprine compared with placebo was associated with a statistically significant

reduction in the number of patients who had MS relapses during the first, second, and third years of treatment; relative risk reductions for these periods were 20, 23, and 18 percent, respectively. Approximately 55 percent of the pooled patients included in the meta-analysis had RRMS, while the remainder had progressive forms of MS; all of the trials were published prior to 1994.[24]

Cyclophosphamide — Limited observational evidence supports the use of pulse (eg, monthly) intravenous (IV) cyclophosphamide for RRMS. There is a greater experience with pulse cyclophosphamide for progressive forms of MS, but data are conflicting regarding benefit.

Another option under investigation employs high-dose cyclophosphamide as immunoablative treatment without bone marrow transplantation. In an open-label study, nine patients with active inflammatory RRMS were treated with IV cyclophosphamide (50 mg/kg daily) for four days, followed by granulocyte colony-stimulating factor. At a mean follow-up of 23 months, there was a statistically significant improvement in disability and a reduction in the mean number of gadolinium enhancing lesions compared with pretreatment, and there were no serious adverse events. However, two patients developed MS exacerbations and required rescue treatment with other immunomodulatory drugs. Larger studies are needed to determine the effectiveness and safety of this approach, and it is not recommended for use outside of clinical trials.[25]

Glucocorticoids in combination therapy — Monthly IV glucocorticoid bolus, typically 1000 mg of methylprednisolone, is used at many institutions for the treatment of primary or secondary progressive MS alone or in combination with other immunomodulatory or immunosuppressive medications. However, randomized trial data are limited and conflicting with respect to the use of oral or parenteral glucocorticoids in combination with interferon beta preparations for RRMS.[26]

Intravenous immune globulin: although data are equivocal, there is no compelling evidence that intravenous immune globulin (IVIG) is effective for patients with RRMS. Some, but not all early clinical trials reported beneficial effects for IVIG in RRMS. However, these trials generally involved small numbers of patients, lacked complete data on clinical and MRI outcomes, or used questionable methodology. A later multicenter placebo-controlled trial of

127 patients with RRMS found that IVIG treatment conferred no benefit for reducing relapses or new lesions on MRI.[27]

Laquinimod — Laquinimod is a synthetic immunomodulatory compound with high oral bioavailability. The effectiveness of oral laquinimod was evaluated in two large randomized controlled trials.

Clinical trials suggest that laquinimod is modestly effective for reducing the relapse rate and disability progression for patients with RRMS.

Rituximab: Rituximab is a monoclonal antibody directed against the CD20 antigen on B lymphocytes that causes B cell reduction. Limited data suggest the effectiveness of rituximab for RRMS:

●In a preliminary randomized trial of 104 adult patients with RRMS, treatment with intravenous rituximab (1000 mg) given on days 1 and 15 was associated with a significant reduction in both total and new gadolinium-enhancing lesions on brain MRI at 24 weeks when compared with placebo. In addition, rituximab treatment was associated with a significant reduction in the proportion of patients who had a clinical relapse by week 24.

●In an observational study of 256 patients with stable RRMS who switched to rituximab or fingolimod after stopping natalizumab due to JC virus antibody positivity, the rituximab group had lower rates of clinical relapse, adverse events, and treatment discontinuation compared with the fingolimod group.

While these results are promising, further clinical trials are needed to establish the long-term effectiveness and safety of rituximab for RRMS Rare cases of PML have been reported in patients treated with rituximab for other indications. However, it is unknown if rituximab increases the risk of PML, since rituximab is often used to treat patients who have an underlying risk factor for PML.[28]

Stem cell transplantation — Autologous hematopoietic stem cell transplantation (HSCT) has been evaluated for patients with refractory RRMS in several uncontrolled studies. The goal is eliminating and replacing the patient's pathogenic immune system to achieve long-term remission of MS. The process involves mobilizing and harvesting hematopoietic stem cells from the patient's peripheral blood or bone marrow, followed by a conditioning regimen of chemotherapy, sometimes with immune-depleting biologic agents or radiation therapy, to

partially or totally ablate the patient's immune system. The last step is infusing the harvested stem cells to regenerate the immune system.

●In a case series of 156 adults with MS, mainly RRMS (n = 123), treatment with nonmyeloablative HSCT was associated with improvement in disability and other clinical outcomes at two years and four years of follow-up. However, the results must be interpreted with caution due to methodologic limitations of the study; as examples, there was no control group, most patients were treated off protocol, disability assessment was not blinded, and the drop-out rate was high, with follow-up available for only 82 patients at two years and 36 patients at four years.[29]

These reports illustrate the potential benefits and perils of HSCT. More long-term data, preferably from randomized controlled trials, are needed to assess the efficacy and safety of this intervention for the treatment of highly active RRMS.

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