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Multiple Sclerosis: Promising New Treatment - A Clinical Review

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ABSTRACT

Objective: In this update on multiple sclerosis, the main clinical aspects and the basic features of the diagnosis including the new McDonald criteria, symptoms, pathophysiology, therapy and multiple sclerosis status in Saudi Arabia is discussed. **Method:** reviewed available diagnosis methods and therapies. **Conclusion:** A new McDonald criterion is useful tool for the diagnosis of multiple sclerosis. An initial symptom of multiple sclerosis is weakness in one or more limbs (40%).demyelination is the main pathophysiological event. Disease-modifying treatment focuses on the long term management of the disease with the aim to reduce relapse rates, lessen severity, and to slow the progression of disability and cognitive decline. Multiple sclerosis is not common in Saudi Arabia, it may be fairly prevalent, under-diagnosed and in increasing. there is need to educate the common community mostly rural community by awareness, attitude and knowledge about multiple sclerosis in order to enhance patient's adherence to treatment and his/her quality of life.

Key Words: multiple sclerosis, diagnosis, treatment

INTRODUCTION

Multiple sclerosis is an autoimmune disease thatinvolves an attack on the central nervous system (CNS) (1). Myelin, which is a substance that surrounds and protects the nerve fibers, is damaged which leads to the formation of scar tissue, or sclerosis. Although multiple sclerosis was first described in the late 1800s, the cause of the disease still remains a mystery, and there is no known cure (2). Due to the time frame in which multiple sclerosis typically develops, there is a large economic burden associated with this disease. This can be in terms of treatment costs, or in terms of a patient's lost wages due to their reduced ability to work. One study estimated that in 2009, the annual cost of multiple sclerosis was about $24,000 per patient in treatment costs alone (3). Multiple sclerosis is a disease that affects more women than men at about a 2:1 ratio (1). When it comes to determining the risk of developing the disease, the most important factors to consider include: geography, age, environmental influences, and genetics (1, 4). multiple sclerosis is typically diagnosed between the ages of 15 to 45 years (1). One of the unique aspects of this disease is its apparent uneven distribution across the world (5). Traditionally, the disease affects white people of Nordic origin who live in temperate climates (5). In general, the prevalence of multiple sclerosis increases the further one goes away from the equator (1). Other factors that have been implicated include environment and viruses (6). Some other researchers believe that a reduced vitamin D level may affect the risk of developing multiple sclerosis (7). Vitamin D is naturally produced when a person's skin is exposed to sunlight and people who live closer to the equator are exposed to greater amounts of sunlight which may reduce the risk of multiple sclerosis. Familial recurrence rate of multiple sclerosis is about 5% with the mostcommonly reported relationship being that of siblings (1). This too is consistent with the idea that an environmental agent is importantin the etiology, but it also hints that one or more genes may play arole as well.

Four Different Courses of multiple sclerosis

Neurologists group patients into four major categories based on the course of the disease. (4, 8) the four major categories are: relapsing-remitting, secondary progressive, primary progressive, and progressive-relapsing.

1. Relapsing-remitting: this is the most common form of multiple sclerosis with about 85% of patients initially diagnosed with this course (4). It is characterized by flare-ups (exacerbations) of symptoms followed by periods of remission. These exacerbations are clearly defined attacks of worsening neurological function (9). In remission the symptoms either improve or are not present (4).

2. Secondary-progressive: This course of the disease follows an initial period of relapsingremitting multiple sclerosis. After this initial period, the disease begins to worsen steadily, with or without periods of remission (9). The time to conversion from relapsing-remitting multiple sclerosis varies from person to person, but an average time frame is 20-25 years after initial onset and diagnosis (4).

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Since this presentation of the disease is not initially diagnosed, there are is no information regarding the percentage of patients who will develop this course of the disease.

3. Primary progressive: This course is characterized by slowly worsening neurologic function from the onset of the disease with no distinct period of remission (4). About 10% of patients are initially diagnosed with this course of the disease, and it is most commonly diagnosed in individuals who are older than 50 at the time of onset (4). This form of multiple sclerosis is more resistant to the medications typically used to treat the disease (4). The rate of the progression of the disease varies from person to person (9).

4. Progressive-relapsing: this is the rarest course of the disease with about 5% of patients initially diagnosed (9). This course is characterized by being progressive from the start with intermittent exacerbations present along the way (4). This course of the disease differs from primary progressive multiple sclerosis due to the presence of the exacerbations. These exacerbations are not present in primary progressive multiple sclerosis. No two individuals will have exactly the same experience when it comes to their course of multiple sclerosis, so the courses may vary from person to person (9).

Symptoms

Variability and diversity characterize the symptoms and presentation of multiple sclerosis. There is virtually no neurologic complaint that has not been ascribed to multiple sclerosis. In a significant number of patients who later develop typical multiple sclerosis, the clinical onset is with an acute or sub-acute episode of neurologic disturbance due to monoregional involvement of the CNS. This form of presentation is known as clinically isolated syndrome (CIS). These may consist of optic neuritis, isolated brain stem, partial spinal cord syndrome, or hemispheric syndromes. The incidence of the initial symptom was weakness in one or more limbs (40%), optic neuritis (22%), paraesthesiae (21%), diplopia (12%), vertigo (5%), disturbance of micturition (5%), or other (5%) (10). Diagnosis: The diagnosis of multiple sclerosis typically occurs between the ages of 15and 45 years, there is no single specific test to diagnose multiple sclerosis; however, there are a variety of techniques that are used to aid in the diagnosis. These techniques include the following: magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analysis, and the use of evoked potentials (1, 11). • MRI: this test is used to reveal areas of damage in the CNS caused by multiple sclerosis plaques. This is the preferred imaging technique, and it is more sensitive than computed tomography (CT) scans. Not only is this tool useful for the diagnosis of the disease, it is also useful for determining the prognosis as well (11). • CSF analyses: this test is used to determine the levelsof immunoglobulin G (IgG) in an individual's CNS. Patients with multiple sclerosis have an increased synthesis of IgG in the CNS whereas serum IgG levels are normal. The IgG index is used to evaluate the level of IgG in the CNS and is a calculated value represented by the formula: (CSF IgG / CSF Albumin) / (Serum IgG / Serum Albumin) (12). Therefore, it is an indicator of the amount of CSF IgG compared to serum levels. Studies of the CSF have also shown that IgG separates into small bands called oligoclonal bands (1). Five or more of these bands are present in 90-95% of patients with multiple sclerosis. Although the use of MRI is more common in determining the diagnosis of multiple sclerosis, CSF analysis can be useful if MRI results are inconclusive. • Evoked potentials: this test measures the electricalactivity that is produced by the stimulation of certain nerve pathways. It is useful in establishing areas of demyelination. This test is considered less sensitive and specific compared to MRI or CSF analysis, but it can be useful in aiding the diagnosis. As more information has become available about multiple sclerosis, the clinical guidelines have evolved as well. In the 2005 guidelines by the International Panel on the Diagnosis of multiple sclerosis, also known as the McDonald Criteria, a diagnosis of multiple sclerosis could only be made if an individual "had an appearance of a new lesion on a scan compared to a baseline scan at least 30 days after the onset of the initial clinical event" (13). The McDonald Criteria was revised in 2010 and now allows for the use of MRI to fulfill the criteria of a diagnosis when a new lesion is discovered regardless of when the timing of the baseline MRI occurred. The goal of this change in criteria was to diagnose patients sooner so that treatment couldbe initiated earlier in the course of the disease. The McDonald criteria also states that CSF findings can aid in the diagnosis and help evaluate alternative diagnoses. These findings include an elevated IgG index or the presence of two or more oligoclonal bands. With primary-progressive multiple sclerosis, the McDonald Criteria

states that a diagnosis can be made "when there is continuous progression of neurological symptom during a one year period with characteristic MRI and CSF findings." According to the new McDonald criteria, the diagnosis of multiple sclerosis requires objective evidence of lesions disseminated in timeand space: MR imaging findings may contribute to the determination of dissemination in time or space; other supportive investigations include CSF and visual evoked potentials (VEPs); diagnostic categories are possible multiple sclerosis, multiple sclerosis, or not multiple sclerosis. For dissemination in space, McDonald criteria include the Barkhof-Tintore MR imaging criteria (14, 15), which require 3 of the following 4 elements: (1) at least one gadolinium-enhancing lesion or 9 T2 hyperintense lesions; (2) at least one infratentoriallesion; (3) at least one juxtacortical lesion; (4) at least 3 periventricular lesions. A spinal cord lesion can substitute for any of the above brain lesions. If there are immunoglobulin abnormalities in the CSF, the MR imaging criteria are relaxed to only 2 T2 lesions typical of multiple sclerosis. For dissemination in time, the MR imaging can be equally useful. If an MR imaging scan of the brain performed at ≥3 months after an initial clinical event demonstrates a new gadolinium-enhancing lesion, this would indicate a new CNS inflammatory event, because the duration of gadolinium enhancement in multiple sclerosis is usually less than 6 weeks. If there are no gadolinium-enhancing lesions but a new T2 lesion (presuming an MR imaging at the time of the initial event), a repeat MR imaging scan after another 3 months is needed with demonstration of a new T2 lesion or gadolinium-enhancing lesion (15). Pathophysiology: Although there is little evidence to confirm an environmentaltrigger or virus in relation to the disease, the autoimmune hypothesis for multiple sclerosis is considered to be well established. (16) This hypothesis states that the pathophysiology of multiple sclerosis is related to myelin antigen-specific CD4+ T cells which become activated. The exact trigger for the activation of the T cells is still unknown. One theory suggests that T cells might become activated by crossreacting with a particular antigen, such as a microbial agent, known as "molecular mimicry". This theory explains why some viruses have been studied as a possible trigger for the disease. These cells then cross the blood-brain barrier, recognize myelin basic protein, attack the neuronal myelinsheaths, and trigger the onset of muscular symptoms and can lead to cognitive decline. These areas of axonal damage are known as lesions. The actual mediator of myelin and axonal destruction has not been established, but it may reflect a combination of macrophages, antibodies, cytokines, and reactive oxygen intermediates (1).

Therapy

The most important goal of multiple sclerosis therapy is to prevent permanentneurologic disability. The treatment of multiple sclerosis is subdivided into 3 categories which include: symptomatic, acute attacks, and disease modifying (1). Symptomatic treatment revolves around helping to maintain a patient's quality of life. This can be difficult since many of the symptoms of multiple sclerosis do not respond to drug therapy. The following symptoms will most likely benefit from pharmacologic management and should be initiated as the symptoms appear: spasticity, tremor, bowel and bladder symptoms, sexual dysfunction, and fatigue. Bladder frequency and urgency typically improve with oxybutynin, whereas pain and spasms typically respond to Baclofen (17). About half of patients diagnosed with multiple sclerosis will become depressed, so it is important to be aware of mood changes and treatment and counseling may be necessary (18). Treatment of acute attacks is centered on the treatment of exacerbations that affects a patient's functional ability. The American Academy of Neurology recommends an IV injection of high-dose corticosteroids. The preferred agent is methylprednisolone at a dose of 500-1,000 mg/day for 3-10 days. Large doses of oral steroids may show comparable results; however, further studies are needed to validate this notion (17). Disease-modifying treatment focuses on the long term management of the disease with the aim to reduce relapse rates, lessen severity, and to slow the progression of disability and cognitive decline (1). Treatment is highly variable and differs for patients based on disease severity, cost, side effect profiles, and patient and prescriber preference. Currently there are nine FDA approved agents that can reduce disease activity and progression in patients with relapsing forms of multiple sclerosis (4). These agents are: • Interferon beta-Ia (Avonex®) • Interferon beta-Ia (Rebif®) • Interferon beta-Ib (Betaseron®) • Interferon beta-Ib (Extavia®) • glatiramer acetate (Copaxone®) • mitoxantrone (Novantrone®) • natalizumab (Tysabri®) • fingolimod (Gilenya™) • teriflunomide(Aubagio®) The anti-

inflammatory properties of the beta Interferons are thought to be beneficial, but their mechanism of action is unknown in respect to multiple sclerosis (4).

Multiple Sclerosis in Saudi Arabia

In 1988, Yaqub et al. published a paper about multiple sclerosis in Saudi Arabia, stating that there are indications of increasing incidence of multiple sclerosis in Saudi Arabia. Out Of 806 neurology inpatients, 16 had multiple sclerosis, 21 myasthenia gravis and 10 amyotrophic lateral sclerosis with an ratio of 1:1.3:0.6 respectively. The symptomatology and site of lesions are similar to that seen in the west, but the course and evolution might be different. The main course was remissions and relapses but without transformation to chronic progressive disease, and the main disability was partial or complete bilateral visual loss, seen in 19% of the patients (19). Ten years later, Daif et al. published another paper about the pattern of presentation of multiple sclerosis in Saudi Arabia, stating also that it resembles the western type of multiple sclerosis (20). In an unpublished communication, Prof. Bohlega estimated the prevalence of multiple sclerosis in Saudis to be 40/100,000 in 2008. ‘‘Although it used to be thought that multiple sclerosis is not common in Saudi Arabia, it is now clear that it is fairly prevalent, underdiagnosed and in increase’’ stated Prof. Bohlega (21).

New Treatment for Multiple Sclerosis

Teriflunomide (Aubagio)

A main goal of MS treatment is to slow down the progression of the disease. Drugs that do this are called disease-modifying medications. One such medication is the oral drug Teriflunomide (Aubagio). It was approved for use in people with MS in 2012. A study published in The New England Journal of Medicine found that people with relapsing MS who took Teriflunomide once a day showed significantly slower disease progression rates and fewer relapses than those who took a placebo. People given the higher dose of Teriflunomide (14 mg vs. 7 mg) experienced decreased disease progression. Teriflunomide was only the second oral disease-modifying medication approved for MS treatment (22).

Dimethyl Fumarate (Tecfidera)

A third oral disease-modifying drug became available to people with MS in March of 2013. Dimethyl fumarate (Tecfidera) was formerly known as BG-12. It stops the immune system from attacking itself and destroying myelin. It may also have a protective effect on the body, similar to the effect that antioxidants have. The medication is available in capsule form. Dimethyl fumarate is designed for people who have relapsing-remitting MS (RRMS). RRMS is a form of the disease in which a person typically goes into remission for a period of time before their symptoms worsen. People with this type of MS can benefit from twice-daily doses (22).

Dalfampridine (Ampyra)

MS-induced myelin destruction affects the way nerves send and receive signals. This can affect movement and mobility. Potassium channels are like pores on the surface of nerve fibers. Blocking the channels can improve the nerve conduction in affected nerves. Dalfampridine (Ampyra) is a potassium channel blocker. Studies published in The Lancet found that Dalfampridine (formerly called Fampridine) increased walking speed in people with MS. The original study tested walking speed during a 25-foot walk. It didn’t show Dalfampridine to be beneficial. However, post-study analysis revealed that participants showed increased walking speed during a six-minute test when taking 10 mg of the medication daily. Participants who experienced increased walking speed also demonstrated improved leg muscle strength (22).

Alemtuzumab (Lemtrada)

Alemtuzumab (Lemtrada) is a humanized monoclonal antibody (lab produced protein that destroys cancer cells). It’s another disease-modifying agent approved to treat relapsing forms of MS. It targets a protein found on the surface of the immune cells called CD52. Though it’s not known exactly how Alemtuzumab works, it’s believed to bind to CD52 on T and B lymphocytes (white blood cells) and cause lysis (break down of the cell). The drug was first approved to treat leukemia at a much higher dosage. Lemtrada had a hard time getting approval for MS in the United States. The Food and Drug Administration (FDA) rejected the application for Lemtrada’s approval in early 2014. They cited the need for more clinical trials showing that it does not cause serious side effects. Lemtrada was later approved by the FDA in November 2014, but it comes with a warning about serious autoimmune conditions, infusion reactions, and increased risk of malignancies like melanoma and other cancers. It was compared to EMD Serono’s MS drug, Rebif, in two phase III trials. The trial found that it was better at reducing the relapse rate and the worsening of disability over two years. Due to its safety profile, the FDA recommends that it only be prescribed to

patients who have had an inadequate response to two or more other MS treatments (22).

Modified Story Memory Technique

MS affects cognitive function as well. It can negatively affect memory, concentration, and executive functions like organization and planning. Researchers from the Kessler Foundation Research Center found that a modified story memory technique (mSMT) can be effective for people who experience cognitive effects from MS. Learning and memory areas of the brain showed more activation in MRI scans after mSMT sessions. This promising treatment method helps you retain new memories. It also helps you recall older information by using a story-based association between imagery and context. Modified story memory technique might help someone with MS remember various items on a shopping list, for example (22).

CONCLUSION

Multiple sclerosis is a progressive disease with no cure so far. Although treatments are available to manage the disease course, they are only partially effective. A combination of drugs and physical, speech, and occupational therapies; exercise; rest; and healthful nutrition may relieve symptoms and promote a satisfactory quality of life. The past few years have seen increasing improvement in the development of laboratory and imaging approaches to study multiple sclerosis, leading to a better understanding of the pathogenesis, pathology, and genetics of the disease. We look forward to patient education, awareness, attitude and knowledge that should be made by the neurologist and follow up by a trained multiple sclerosis nurse in order to enhance patient's adherence to treatment and his/her quality of life.

REFERENCES

1. Bainbridge JL, Corboy JR. Multiple Sclerosis. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: A pathophysiologic approach. 8th ed. New York: McGraw-Hill Medical; c2011. p. 963-78.
2. Research: History of MS [homepage on internet] National Multiple Sclerosis Society; [cited 2013 Mar 2] Available from: http:// www.nationalmssociety.org/research/how-far-weve-come/index.aspx.
3. 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(1-a):S41-53.
4. Goldenberg MM. Multiple sclerosis review. P&T; 2012 Mar;37(3):175-84.
5. Koch-Henriksen N, Sorensen PS. The changing demographic pattern of multiple sclerosis epidemiology. Lancet Neurol. 2010; 9:520-32.
6. Maghzi AH, Marta M, Bosca I, Etemadifar M, Dobson R, Maggiore C, Giovannoni G, Meier UC. Viral pathophysiology of multiple sclerosis: a role for Epstein-Barr virus infection? Pathophysiology. 2011; 18:13-20.
7. About MS: What causes MS? [homepage on internet] National Multiple Sclerosis Society; [cited 2013 Mar 4] Available from: http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/what-causes-ms/index.aspx.
8. Ryan M. Multiple Sclerosis. In: Alldredge BK, Corelli RL, Ernst ME, Guglielmo BJ, Jacobson PA, Kradjan WA, Williams BR, editors. Koda-Kimble and Young's applied therapeutics: the clinical use of drugs. 10th ed. Philadelphia: Wolters Kluwer Lippincott Williams & Wilkins; c2013. p. 1323-36.
9. About MS: Four Disease Courses of MS [homepage on internet] National Multiple Sclerosis Society; [cited 2013 Feb 22] Available from: http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/what-is-ms/four-disease-courses-ofms/index.aspx .
10. McAlpine D. *Multiple sclerosis: a reappraisal.* Edinburgh: Churchill Livingstone; 1972
11. About MS: Diagnosing MS [homepage on internet] National Multiple Sclerosis Society; [cited 2013 Feb 22] Available from: http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about ms/diagnosing-ms/index.aspx .
12. Cerebrospinal Fluid (CSF) IgG Index [internet]. Mayo Foundation For Medical Education And Research; [cited 2013 Mar 4]. Available from:

http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/8009.

13. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, Fujihara K, Havrdova E, Hutchinson M, Kappos L, Lublin FD, Montalban X, O'Connor P, Sandberg-Wolheim M, Thompson AJ, Waubant E, Weinshenker B, Wolinsky JS. Diagnostic criteria for multiple sclerosis:2010 revisions to the McDonald criteria. Ann Neurol. 2011; 69:292-302.
14. Barkhof F, Filippi M, Miller DH, et al. Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. *Brain* 1997; 120:2059–69.
15. Tintore M, Rovira A, Martinez MJ, et al. Isolated demyelinating syndromes: comparison of different MR imaging criteria to predict conversion to clinically definite multiple sclerosis. *AJNR Am J Neuroradiol* 2000; 21:702–06.
16. Korn T. Pathophysiology of multiple sclerosis. J Neurol. 2008; 255:2-6.
17. Murray TJ. Diagnosis and treatment of multiple sclerosis. BMJ. 2006; 332:525-7.
18. Feinstein A. The neuropsychiatry of multiple sclerosis. Can J Psychiatry. 2004; 49:157 63.
19. Yaqub BA, Daif AK (1988) Multiple sclerosis in Saudi Arabia. Neurology 38(4):621–623
20. Daif AK, Al-Rajeh S, Awada A, Al Bunyan M, Oqunniyi A, Abdul Jabar M, Al Tahan AR (1998) Pattern of presentation of multiple sclerosis in Saudi Arabia: analysis based on clinical and paraclinical features. Eur Neurol 39(3):182–186.
21. S. Bohlega *et al*. (2013) Multiple sclerosis in the Arabian Gulf countries: a consensus statement. J Neurol 260:2959-2963.
22. Promising New Treatments for Multiple Sclerosis. 2015 March 19; Available from URL: http://www.healthline.com/health/multiple-sclerosis/promising-new-treatments.