The Egyptian Journal of Hospital Medicine (January 2018) Vol. 70 (11), Page 2008-2015

Approach in Diagnosis and Management and Common Mistakes in Diagnosis of Multiple Sclerosis

[1]Anas Rafik Mohamed Elshaer, [2]Mohamed Ahmed Hassan Kallab,
[2]Shurouq H. S. Alqrinawi, [3]Osama Ahmed Abdelsalam
[1]King Fahad Hospital, [2]Dammam Medical Complex ,[3]Neurology Department, Mansoura University
Corresponding author: Anas AlShaer, E-mail: ashaer93@yahoo.com

ABSTRACT

Background- Augustus d'Este, the grandson of England's King George III, is now thought to have MS based on a diary he kept until his death in 1848, in which he described symptoms that sound much like MS, including blurred vision, weakness and numbness in his limbs, tremors and nocturnal spasms. Twenty years after d'Este's death, the Parisian neurologist Jean-Martin Charcot was the first to identify and name MS. A female patient of Charcot's was suffered from tremors, slurred speech and abnormal eye movements. He attempted to treat her, but with no avail. After her death, Charcot examined the patient's brain and discovered the telltale plaques of MS the hardened scar tissue around nerve fibers. He was concerned with the discovery of MS. **Aim of the work:** multiple sclerosis is considered as one of the great imitators as it features various nonspecific symptoms such as sensory loss, spinal cord symptoms (Motor and autonomic), cerebellar symptoms, eye symptoms, optic neuritis, trigeminal neuralgia, psychiatric as well as constitutional symptoms and may be confused with a number of other diseases. In this project we aimed to identify problems and mistakes for diagnosis of MS in order to achieve early diagnosis and prevention of misdiagnosis and advancement of the disease. **Patients and Methods:** we have collected data about cases of multiple sclerosis disease from two major hospitals in Saudi Arabia (Saudi German Hospital, Madinah, Dammam Medical Complex, Dammam) during the year 2017. Among these cases we found 4 cases misdiagnosed as multiple sclerosis. The first case 48 years old female diagnosed with multiple sclerosis and treated with Imuran for 8 month with no benefit then patient came again with the same symptoms and MRI done for him with no change in MRI findings, thus the patient condition was not fit for the diagnostic criteria of multiple sclerosis and diagnosed as primary lateral sclerosis. Second case 37 years old patient came with acute onset paraplegia and diagnosed as transverse myelitis then came after 4 months; the patient developed symptoms of optic neuritis. The third case 42 years old female came with left sided hemiplegia and diagnosed as ischemic stroke and treated with vascular therapy without benefit then came again after 6 months with right sided hemiplegia and incoordination then diagnosed as multiple sclerosis. Fourth case 30 years old female came with acute diminution of vision and diagnosed as optic neuritis and treated without benefit then patient came again with the same presentation and diagnosed as clinically isolated syndrome. **Results:** MRI findings are not enough in diagnosis of multiple sclerosis and should be accompanied by good clinical expertise; lab tests as well as exclusion of any other condition could be misdiagnosed as multiple sclerosis. **Conclusion:** multiple sclerosis (MS) is an immune-mediated inflammatory disease that attacks myelinated axons in the central nervous system, destroying the myelin and the axon in variable degrees and producing significant physical disability within 20-25 years in more than 30% of patients. The hallmark of MS is symptomatic episodes that occur months or years apart and affect different anatomic locations.

Keywords: multiple sclerosis, misdiagnosis, immune modulatory, MacDonald criteria.

INTRODUCTION

Multiple sclerosis (MS) is an immune-mediated inflammatory disease that attacks myelinated axons in the central nervous system (CNS), destroying the myelin and the axon in variable degrees. In most cases, the disease follows a relapsing-remitting pattern, with short-term episodes of neurologic deficits that resolve completely or almost completely. A minority of patients experience are steadily progressive neurologic deterioration [(1,2).]

Pathology

The exact aetiology is poorly known although it is believed to have both genetic and acquired contributory components. An infectious agent (i.e EBV) or at least a catalyst, has long been suspected due to the geographic distribution and presence of clusters of cases; however, no agent has yet been firmly confirmed [(3).] A study also suggested that chronic cerebrospinal venous insufficiency can cause or exacerbate MS but this theory has not been proven by further investigations [(3).] Multiple sclerosis is believed to result from a cell-mediated autoimmune response against one's own myelin components, with loss of oligodendrocytes, with little or no axonal degeneration in the acute phase; however, in later stages, loss of oligodendrocytes results in axonal degeneration. Demyelination occurs in discrete

Received: 20/12/2017 DOI: 10.12816/0044859
Accepted: 30/12/2017

perivenular foci, termed plaques, which range in size from a few millimeters to a few centimeters [3]. Each lesion goes through three pathological stages: [3]

Early acute stage (Active plaques).
-Active myelin breakdown
-Plaques appear pink and swollen
Subacute stage
-Plaques become paler in color (Chalky)
-Abundant macrophages
Chronic stage (inactive plaques/gliosis).
-Little or no myelin breakdown
-Gliosis with associated volume loss
-Appear grey/translucent

Approach Considerations

MS is diagnosed on the basis of clinical findings and supporting evidence from ancillary tests. It is primarily diagnosed clinically. The core requirement for the diagnosis the demonstration of central nervous system lesion dissemination in time and space, based upon either clinical findings alone or a combination of clinical and MRI findings. The history and physical examination are most important for diagnostic purposes. MRI is the test of choice to support the clinical diagnosis of MS [2].

Multiple sclerosis signs and symptoms may differ greatly from person to person and over the course of the disease depending on the location of affected nerve fibers [2]. They included:

- Numbness or weakness in one or more limbs that typically occurs on one side of your body at a time, or the legs and trunk.
- Partial or complete loss of vision, usually in one eye at a time, often with pain during eye movement.
- Prolonged double vision.
- Tingling or pain in parts of your body.
- Electric-shock sensations that occur with certain neck movements, especially bending the neck forward (Lhermitte sign).
- Tremor, lack of coordination or unsteady gait.
- Slurred speech.
- Fatigue.
- Dizziness.
- Problems with bowel and bladder function.
- Sexual dysfunction.

Classification

The first presentation of MS is often a clinically isolated syndrome (CIS). A CIS most often presents in adults or children with long tract symptoms/signs, optic neuritis, or brainstem, cerebellar, spinal cord syndrome. In some children, and rarely in adults, MS may present with symptoms of encephalopathy (i.e headache, vomiting, seizure, or altered consciousness) [4].

MS is divided into the following categories, principally on the basis of clinical criteria, including the frequency of clinical relapses, time to disease progression, and lesion development on MRI :

- Relapsing-remitting MS (RRMS): Approximately 85% of cases.
- Secondary progressive MS (SPMS).
- Primary progressive MS (PPMS).
- Progressive-relapsing MS (PRMS).

The following 2 subgroups are sometimes included in RRMS:

- Clinically isolated syndrome (CIS): A single episode of neurologic symptoms.
- Benign MS: MS with almost complete remission between relapses and little if any accumulation of physical disability over time [4].

Tests included the following:

- **Blood tests:** to help rule out other diseases with symptoms similar to MS. Tests to check for specific biomarkers associated with MS are currently under development and may also aid in diagnosing the disease [5].
- **Magnetic resonance imaging:** the imaging procedure of choice for confirming MS and monitoring disease progression in the CNS [5].
- **Evoked potentials:** which record the electrical signals produced by the nervous system in response to stimuli; t is used to identify subclinical lesions. Results were not specific for MS [5].
- **Lumbar puncture (spinal tap)** in which a small sample of fluid is removed from the spinal canal for laboratory analysis. This sample can show abnormalities in antibodies that are associated with MS. May be useful if MRI is unavailable or MRI findings are no diagnostic; CSF is evaluated for oligoclonal bands and intrathecal immunoglobulin G (IgG) production. Spinal tap can also help rule out infections and other conditions with symptoms similar to MS [5].

Diagnostic criteria for MS developed in the early 1980s (the Poser criteria) considered clinical characteristics and a number of laboratory studies which included cerebrospinal fluid analysis, evoked potentials and neuroimaging. These findings were then used to place patients in categories ranging from clinically definite to laboratory supported definite to clinically probable to laboratory supported probable MS. The Poser criteria were developed primarily to ensure that only MS patients were included in research studies. They have been supplanted by the McDonald criteria, which were developed in 2001 and

subsequently revised in 2005 and 2010. Future revisions are likely [5,6].

The McDonald criteria were revised again in 2010 in order to incorporate newer evidence and to simplify the use of neuroimaging while preserving the sensitivity and specificity of the criteria [5,6]. The core requirement of the diagnosis is the objective demonstration of dissemination of central nervous system lesions in both space and time, based upon either clinical findings alone or a combination of clinical and MRI findings [5,6].

The author added that dissemination in space is demonstrated with MRI by one or more T2 lesions in at least two of four MS-typical regions of the central nervous system (periventricular, juxtacortical, infratentorial, or spinal cord) or by the development of a further clinical attack implicating a different central nervous system site. For patients with brainstem or spinal cord syndromes, symptomatic MRI lesions are excluded from the criteria and do not contribute to lesion count [5,6].

The author added that dissemination in time is demonstrated with MRI by the simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time, or a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan, or by the development of a second clinical attack [5,6].

The author added that McDonald criteria can only be applied after careful clinical evaluation of the patient. Additional data needed to confirm the diagnosis of MS depend upon the clinical presentation:

- For patients with two or more attacks who have objective clinical evidence of two or more lesions or objective clinical evidence of one lesion with reasonable historical evidence of a prior attack, generally no additional data are required. However, it is desirable to confirm the diagnosis of MS through imaging or laboratory testing.
- For patients with two or more attacks who have objective clinical evidence of one lesion, the criteria require evidence of dissemination in space.
- For patients with one attack who have objective clinical evidence of two or more lesions, the criteria require evidence of dissemination in time.
- For patients with one attack who have objective clinical evidence of one lesion (i.e a clinically isolated syndrome [CIS]), the criteria require evidence of dissemination in space and time.
- For patients who present with insidious neurological progression suggestive of primary progressive MS, the criteria require evidence of the one year of disease progression (retrospectively or prospectively determined) plus two of the three following criteria (for patients with brainstem or spinal cord syndromes, symptomatic MRI lesions are excluded from the criteria and do not contribute to lesion count):

1. Dissemination in space in the brain based upon one or more T2 lesions in at least one area characteristic for MS (periventricular, juxtacortical, or infratentorial).
2. Dissemination in space in the spinal cord based upon two or more T2 lesions in the cord.
3. Positive cerebrospinal fluid findings with isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index.

The author added that the attack should be confirmed by a neurologic examination, but some historical events with symptoms and evolution characteristic for MS, for which no objective neurologic findings are documented, can provide reasonable evidence of a prior demyelinating event. Paroxysmal symptoms should consist of multiple episodes occurring over a minimum of 24 hours. Before a definite diagnosis of MS can be made, at least one attack must be confirmed by findings on either neurologic examination, visual evoked potential response in patients with prior visual disturbance, or MRI consistent with demyelination in central nervous system region associated with the prior neurologic symptoms [5,6].

The author added that McDonald criteria assigned diagnostic confidence as follows:

- The diagnosis of "MS" is given if the criteria are fulfilled and there is no better explanation for the clinical presentation.
- The diagnosis of "possible MS" is given if MS is suspected but the criteria are not completely met.
- The diagnosis of "not MS" is given if another diagnosis better explains the clinical presentation [5,6].

Problems in diagnosis of MS

Getting a correct diagnosis of multiple sclerosis (MS) can be a challenge and even experienced doctors make mistakes. Even with improved testing tools and more detailed diagnostic criteria, Misdiagnosis of multiple sclerosis (MS) is becoming an increasingly recognized worldwide problem in the field with significant consequences. says Jack Burks, MD, a neurologist and chief medical officer for the Multiple Sclerosis Association of America. The diagnosis can also require eliminating the possible MS mimicker diseases he says. That leads to an MS diagnosis by exclusion [7,8].

Misdiagnosis is too common in Multiple sclerosis

Rates of MS misdiagnosis range from 6 percent to 35 percent, based on a number of studies published between 1985 and 2005. There are several possible diseases that a person misdiagnosed with MS might have instead. Two of the most common missed diagnoses in these studies were psychiatric disease (23-27 %) and migraine (9-10 %) [7,8].

Potential causes of misdiagnosis

There is no highly specific biomarker for MS, so diagnosis continues to rely upon the interpretation of clinical and radiographic data with healthy doses of critical thinking and clinical skills [7,8].

During his session at CMSC, Dr. Solomon stressed that MRI criteria weren't specifically developed to differentiate MS from other conditions, but instead to identify patients at high risk for MS after initial typical presentations of MS-like symptoms. MS diagnostic criteria were also not rigorously validated in clinically atypical presentations [7,8].

The problem of misdiagnosis is not confined to non-specialists, however. Out of 110 misdiagnosed patients identified in the 2012 survey, a surprising twenty-four percent had been misdiagnosed by a neurologist with MS fellowship training or who worked in an MS-focused medical practice. Thirty-two percent had been misdiagnosed by a neurologist without MS training; three percent were diagnosed by a non-neurologist; and forty-two percent had been diagnosed by a physician for whom their training was unknown [7,8].

Hazards of misdiagnosis

Thirty-three percent of the patients had been living with their misdiagnosis for more than 10 years; 29 percent for three to nine years and 38 percent for less than three years. Neurologists surveyed indicated that patients misdiagnosed with MS actually suffered from several other conditions, including: nonspecific white matter abnormalities (NWMA), small vessel ischemic disease (SVID), migraine, psychiatric disease, neuromyelitis optica spectrum disorder (NMOSD), and fibromyalgia [7,8].

Misdiagnosis of MS means the patient is suffering from an undiagnosed, untreated condition that could lead to unnecessary risk and even death. Patients may be exposed to potentially harmful therapies that carry a risk of progressive multifocal leukoencephalopathy (PML) or may be burdened with the financial risk of expensive DMTs, routine imaging, and clinical care they do not need [7,8].

مرجع

More than 70 percent of the misdiagnosed patients identified in the 2012 survey had received disease-modifying therapy (DMT) for MS, included 36 percent who had used two or more DMTs. Twenty-nine percent of the patients had been using a DMT for more than 10 years; 29 % for three to nine years; and 42 percent for less than three years. The most commonly used medications were interferon beta (53 percent), glatiramer acetate (40 percent), or natalizumab (13 percent). Four percent of the misdiagnosed patients had even participated in clinical trials of disease-modifying therapies [7,8].

Here are some of the conditions that are sometimes mistaken for multiple sclerosis:

Lyme disease is a bacterial infection transmitted through a tick bite. Early symptoms include fatigue, fever, headaches, and muscle and joint aches. Later symptoms can include numbness and tingling in the hands and feet, as well as cognitive problems such as short-term memory loss and speech issues. If you live in an area that's known to have Lyme disease or have recently traveled to one, your doctor will want to rule out the possibility [9].

Migraine is a type of headache that can cause intense pain; throbbing; sensitivity to light, sounds, or smells; nausea and vomiting; blurred vision; and lightheadedness and fainting. A study published online in Neurology in August 2016 [9] found that a migraine was the most common correct diagnosis in study subjects who had definitely or probably been misdiagnosed with MS, occurring in 22 percent of them. That said, headaches and migraines in particular are commonly occur with. Migraines can be difficult to diagnose, and doctors use some of the same tools to diagnose the headaches as they do for MS, including taking a medical history and performing a thorough neurological examination [9].

Conversion and **psychogenic disorders** are conditions in which psychological stress is converted into a physical problem such as blindness or paralysis for which no medical cause can be found. In the Neurology study on MS misdiagnosis, 11 percent of subjects definitely or probably misdiagnosed with MS actually had a conversion or psychogenic disorder [9].

Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory disease that, like multiple sclerosis, attacks the myelin sheaths, the protective covering of the nerve fibers of the optic nerves and spinal cord. But, unlike MS, it usually spares the brain in its early stages. Symptoms of NMOSD which include sudden vision loss or pain in one or both eyes, numbness or loss of sensation in the arms and legs, difficulty controlling the bladder and bowels, and uncontrollable vomiting and hiccups tend to be more severe than symptoms

of MS. Treatments for MS are ineffective for and can even worsen NMOSD, so getting an accurate diagnosis is extremely important. A blood test known as the NMO IgG antibody test can help to differentiate between MS and NMOSD [(9).]

Lupus is a chronic, autoimmune disorder that, like MS, affects more women than men. It can cause muscle pain, joint swelling, fatigue, and headaches. The hallmark symptom of lupus is a butterfly-shaped rash covering the cheeks and bridge of the nose, but only about half of people with lupus develop this rash. There is no single diagnostic test for lupus and because its symptoms are similar to those of many other conditions, it is sometimes called "the great imitator" [(9).]

Rheumatologists (physicians specializing in diseases of the muscles and joints) typically diagnose lupus based on a number of laboratory tests and the number of symptoms characteristic of lupus that a person has [(9).]

Stroke occurs when a portion of the brain stops receiving a steady supply of blood, and consequently doesn't get the oxygen and nutrients it needs to survive. Symptoms of a stroke include loss of vision; loss of feeling in the limbs, usually on one side of the body; difficulty walking; and difficulty speaking — all of which can also be signs of an MS flare. The age of the person experiencing the symptoms may help to pin down the correct diagnosis. While, MS can occur in 70-year-olds, if the person is older, you tend to think of stroke, not MS, Burks says [(9).]

Fibromyalgia and MS have some similar symptoms, including headaches, joint and muscle pain, numbness and tingling of extremities, memory problems, and fatigue. Like MS, fibromyalgia is more common in women than in men. But unlike MS, fibromyalgia does not show up as brain lesions on an MRI [(9).]

Sjögren's syndrome is another autoimmune disorder, and the symptoms of many autoimmune disorders overlap, Burks says. Sjögren's causes fatigue and musculoskeletal pain and is more common in women than in men. But the telltale signs are dry eyes and dry mouth, which are not associated with MS [(9).]

Vasculitis is an inflammation of the blood vessels that can mimic MS, says Kathleen Costello, an adult nurse practitioner and at The Johns Hopkins MS Center in Baltimore and vice president of healthcare access at the National Multiple Sclerosis Society. Depending on the type of vasculitis, symptoms can include joint pain, blurred vision, and numbness, tingling, and weakness in the limbs [(9).]

Myasthenia gravis is a chronic autoimmune disease that causes muscle weakness that typically comes and goes, but tends to progress over time. The weakness is caused by a defect in the transmission of nerve impulses to muscles. In many people, the first signs of myasthenia gravis are drooping eyelids and double vision. Like MS, it can also cause difficulty with walking, speaking, chewing, and swallowing. If a doctor suspects myasthenia gravis, a number of tests can help to confirm or rule out the diagnosis [(9).]

Sarcoidosis is another inflammatory autoimmune disease that shares some symptoms with MS, including fatigue and decreased vision. But sarcoidosis most commonly affects the lungs, lymph nodes, and skin, causing a cough or wheezing, swollen lymph nodes, and lumps, sores, or areas of discoloration on the skin [(9).]

Vitamin B12 deficiency can cause MS-like symptoms such as fatigue, mental confusion, and numbness and tingling in the hands and feet. That's because vitamin B12 plays a role in the metabolism of fatty acids needed to maintain the myelin sheath. Vitamin B12 deficiency can be identified with a simple blood test [(9).]

Acute disseminated encephalomyelitis (ADEM) is a severe inflammatory attack affecting the brain and spinal cord. Symptoms include fever, fatigue, headache, nausea, vomiting, vision loss, and difficulty walking. A very rare condition, ADEM typically comes on rapidly, often after a viral or bacterial infection. Children are more likely to have ADEM, while MS is more likely to occur in adults [(9).]

Clinically evident misdiagnosed cases included:

1st case

History:

48 years old female experienced slowly progressive dysarthria, speech difficulty of 13 month duration associated with bilateral upper and lower limb stiffness and weakness with fatigue and bilateral shoulder pain, no other associated symptoms including visual, ocular, facial cerebellar or autonomic and no urine or stool incontinence

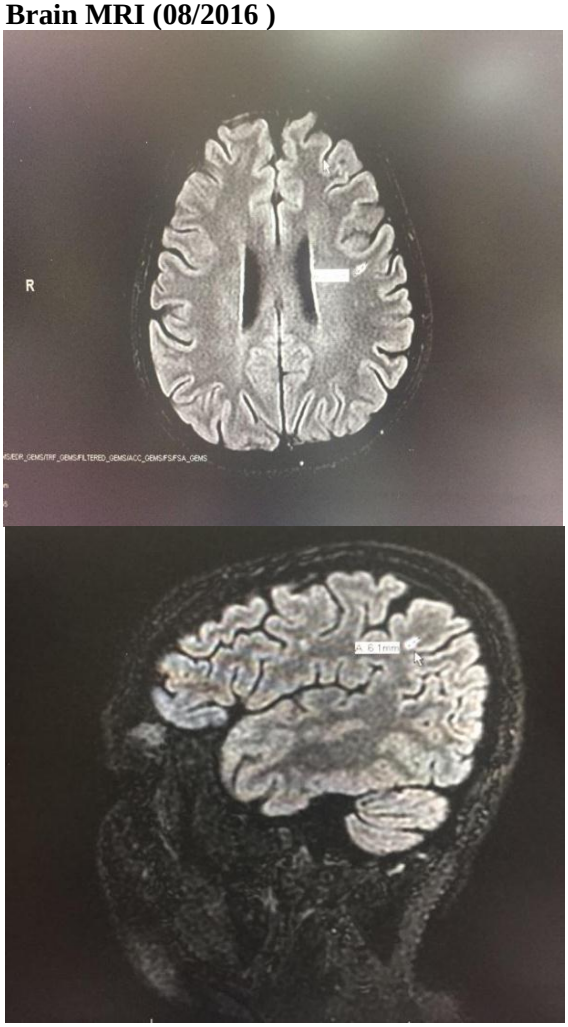
Physical Examination:

Neurological examination revealed normal fundus examination, extraocular movement and no facial weakness. She has dysarthric nasal speech with exaggerated gag (pseudobulbar palsy). Her motor examination shows symmetrical weakness (4/5 in power) with 3+ reflexes and hypertonia (spastic quadriparesis). She has normal sensory and cerebral examination

Investigation:

CSF study : WBC : 0, RBC : 0, protein : 45, Glu : 61 .
CBC, liver profile, renal profile : negative.
Vasculitic screen : negative.

Brain MRI (08/2016)



Figures 1&2: showing multiple small high signal lesions , seen in subcortical white matter , two in right frontal lobe , two in right occipital , left pareital lobe and left Pareito-occipital junction in flare sequences and show no significant enhancement after IV contrast

Patient diagnosed as Multiple Sclerosis and treated with Imuran for 8 months with no improvement. Patient came with the same presentation after 8 months.

Brain MRI done again (04/2017)

There is no significant change in size or signal intensity of previous described foci .
Patient doesn't fit the diagnostic criteria of multiple sclerosis and the clinical finding and MRI are suggestive for primary lateral sclerosis so patient diagnosed as primary lateral sclerosis

2nd case

37 years old male patient came to ER complaining of acute onset paraplegia with no sensory level

- **Brain MRI** showed no detectable abnormalities.
- Patient diagnosed as **Transverse Myelitis** and treated with pulse steroids and patient condition improved then discharged. 4 month after treatment patient developed symptoms of acute optic neuritis.
- **MRI done again** showed three high signal demylenating patches, seen in supratentorial area and one high signal demylenating patch, seen in infratentorial area.
- **CSF study** showed oligodendrites.
- Patient diagnosed as **Multiple Sclerosis** and treated with immune modulatory therapy (B interferon). Finally patient condition improved with no relapse

3rd case

42 years old female patient came to hospital with acute left sided hemiplegia.

- **CT Brain done** revealed faint hypodensity at the thalamic area.
- Patient diagnosed as **Ischemic Stroke**. She took vascular therapy.
- 6 months after treatment, patient developed right sided hemiplegia with incoordination.
- **MRI Brain done** revealed periventricular high signal demylenatinating patches involving also white matter area and corpus callosal area.
- **CSF study** revealed positive oligochlonal band.
- Patient diagnosed then as **Multiple Sclerosis**

4th case

30 years old female presented by acute diminution of vision, diagnosed as **optic neuritis** and treated with no improvement.

- Patient came again with the same presentation,
- CBC, LFT, KFT, all were negative.
- MRI done with no abnormality detected.
- Patient diagnosed as **clinically isolated syndrome**

How to avoid MS misdiagnosis

Basically, neurologists must rely upon their skilled expertise, knowledge and the correct application of diagnostic criteria as well as specific and sensitive biomarker that distinguishes MS from other diseases to make an early accurate diagnosis to improve the quality of life and to prevent the advancement of the disease and to eliminate

unnecessary investigations and treatment with consequent reduction in morbidity and mortality rates.

Management

Treatment of MS has 2 aspects: immune modulatory therapy (IMT) for the underlying immune disorder, and therapies to relieve or modify symptoms.

Treatment of acute relapses is as follows:

Methylprednisolone (Solu-Medrol) can hasten recovery from an acute exacerbation of MS.

Plasma exchange (plasmapheresis) can be used short term for severe attacks if steroids are contraindicated or ineffective [10].

Dexamethasone is commonly used for acute transverse myelitis and acute disseminated encephalitis.

Most of the disease-modifying agents for MS (DMAMS) have been approved for use only in relapsing forms of MS. The DMAMS currently approved for use by the US Food and Drug Administration (FDA) included the following:

Interferon beta-1a (Avonex, Rebif) [11].

Interferon beta-1b (Betaseron, Extavia) [12].
Peginterferon beta-1a (Plegridy) [13].
Glatiramer acetate (Copaxone) [14].
Natalizumab (Tysabri) [15].
Mitoxantrone [16].
Fingolimod (Gilenya) [17].
Teriflunomide (Aubagio) [18].
Alemtuzumab (Lemtrada) [19].
Daclizumab (Zinbryta) [20].

A single-use autoinjector is also available for self-injection of interferon beta-1a (Rebif) in patients with relapsing forms of MS [21].

The following agents are used for treatment of aggressive MS:

High-dose cyclophosphamide (Cytoxan) has been used for induction therapy.

Mitoxantrone is approved for reducing neurologic disability and/or the frequency of clinical relapses in patients with SPMS, PRMS, or worsening RRMS.

Treatment of the symptoms of MS involves both pharmacologic and nonpharmacologic measures. Lifestyle and home remedies plays important role in mild to moderate MS and help to relieve the signs and symptoms of MS such as:

Rest

Exercise: regular exercise can help improve strength, muscle tone, balance and coordination. Swimming or other water exercises are good options. Other types of mild to moderate exercise recommended for people with MS include walking, stretching, low-impact aerobics, stationary bicycling, yoga and tai chi.

Cool down: MS symptoms often worsen when body temperature rises. Avoiding exposure to heat and using devices such as cooling scarves or vests can be helpful.

Eat a balanced diet: results of small studies suggest that a diet low in saturated fat but high in omega-3 fatty acids, such as those found in olive and fish oils, may be beneficial. But further research is needed. Studies also suggest that vitamin D may have potential benefit for people with MS.

Relieve stress: stress may trigger or worsen signs and symptoms of MS. Yoga, tai chi, massage, meditation or deep breathing may help.

Some symptoms may be amenable to pharmacologic therapy such as:

Fatigue: off-label treatments include amantadine, methylphenidate, and fluoxetine [22].

Depression: selective serotonin reuptake inhibitors are preferred.

Spasticity: baclofen is effective in most cases.

Pain: tricyclic antidepressants are first-line drugs for primary pain [23].

Sexual dysfunction: oral phosphodiesterase type 5 inhibitors (i.e sildenafil, tadalafil, vardenafil).

Optic neuritis: intravenous methylprednisolone may speed recovery [24].

REFERENCES

1. Beth W(2014): A short history of MS. Available on: https://www.everydayhealth.com/multiple-sclerosis/a-short-history-of-multiple-sclerosis/#03

2. Olek MJ (2014): Epidemiology and clinical features of multiple sclerosis in adults. http://www.uptodate.com/home.

3. Nesbit GM, Forbes GS, Scheithauer BW *et al.* (1991): Multiple sclerosis histopathologic and MR and/or CT correlation in 37 cases at biopsy and three cases at autopsy. Radiology,180 (2): 467-474.

4. Lublin FD and Reingold SC (1996): Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society, 46(4):907-911

5. Polman CH, Reingold SC and Edan G (2005): Diagnostic criteria for multiple sclerosis: revisions to the McDonald Criteria. Ann. Neurol.,55:67-69.

6. Polman CH, Reingold SC, Banwell B *et al*. (2011): Diagnostic criteria for multiple sclerosis: **2010** revisions to the McDonald criteria. Ann. Neurol., 69:292-300.

7. Solomon AJ, Klein EP and Bourdette D (2012) : Undiagnosing multiple sclerosis: the challenge of misdiagnosis in MS. Neurology, 12-78-91.

8. Solomon AJ (2016): Problems with misdiagnosis, misdiagnosis of multiple sclerosis: frequency, causes, effects and prevention. Consortium of MS Centers Conference, National Harbor, MD.

https://www.everydayhealth.com/multiple-sclerosis/symptoms/conditions-commonly-mistaken-multiple-sclerosis/

9. Beth W (2016): Conditions Commonly Mistaken for Multiple Sclerosis https://www.everydayhealth.com/multiple-sclerosis/symptoms/conditions-commonly-mistaken-multiple-sclerosis/

10. Cortese I, Chaudhry V, So YT, Cantor F, Cornblath DR and Rae-Grant A (2011): Evidence-based guideline update: Plasmapheresis in neurologic disorders Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology, **76 (3):55-59.**

11. Sanford M and Lyseng-Williamson KA (2011): Subcutaneous recombinant interferon-ß-1a (Rebif®): a review of its use in the treatment of relapsing multiple sclerosis. Drugs, https://reference.medscape.com/medline/abstract/21942977

12. Bayer Healthcare Pharmaceuticals Inc. Montville (2014): Short-term and long-term safety and tolerability of interferon β-1b (Betaseron) in multiple sclerosis Betaseron [package insert]. Montville, NJ**: Bayer Healthcare Pharmaceuticals Inc. website**

13. Calabresi PA, Kieseier BC, Arnold DL, Balcer LJ, Boyko A, Pelletier J *et al.* (2014): Pegylated interferon ß-1a for relapsing-remitting multiple sclerosis : a randomised, phase 3, double-blind study. Lancet Neurol., 13(7):657-665.

14. PA: Teva Pharmaceuticals USA, North Wales (2009): Copaxone approval. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020622s057lbl.pdf

15. Pucci E, Giuliani G, Solari A *et al.* (2011): Natalizumab for relapsing remitting multiple sclerosis. Cochrane Database Syst. Rev., CD007621.

16. Biomed Central (2013): Results from the 5-year, phase IV RENEW (Registry to Evaluate Novantrone Effects in Worsening Multiple Sclerosis) study.doi: 10.1186/1471-2377-13-80

17. Novartis , East Hanover (2010): Gilenya approval. https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/gilenya.pdf

18. Genentech Corp. Cambridge (2012): Aubagio (teriflunomide) approval https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202992s000lbl.pdf

19. Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP *et al*. (2012): Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet, 380: 1819 :1822.

20. Gold R, Giovannoni G, Selmaj K, Havrdova E, Montalban X, Radue EW *et al.* (2013): Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): a randomised, double-blind, placebo-controlled trial. Lancet, 381 :2167-2175.

21. Jeffrey S (2013): FDA approves interferon autoinjector for MS. Available on: http://www.medscape.com/viewarticle/777065

22. Braley TJ and Chervin RD. (2010): Fatigue in multiple sclerosis: mechanisms, evaluation, and treatment. Sleep, (8):1061-1068.

23. Solaro C and Uccelli MM (2011): Management of pain in multiple sclerosis: a pharmacological approach. Nat. Rev. Neurol., 7(9):519-527.

24. Optic Neuritis Study Group(1991): The clinical profile of optic neuritis. Arch Ophthalmol., (12):1673-1682.