Original Article

General Overview About Multiple Sclerosis

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Abstract

Background: Recently there is no doubt that the Multiple sclerosis (MS) became a part of primary neurodegenerative disorders. It is a serious neurological disorder which is characterized pathologically by an autoimmune attack directed primarily at myelin, the protective insulation surrounding nerve fibers in the brain and spi- nal cord, and is progressively disabling. It is characterized by the presence of inflammation, neurodegeneration, and demyelinating lesions of white and gray matter. Several evidences suggested that genetics showed factors have a prominent role in the development of multiple sclerosis. The (prevalence) of familial MS is 13% for all MS phenotypes, the risk of MS is 3% in first-degree relatives (siblings 5%, parents 2%, and children, 2%), and only 1% in second and third-degree relatives. EBV is one of the most important risk factors of MS, as a history of EBV infection or triggered acute infectious mononucleosis, stand at an increased risk to develop MS. Elevated serum and CSF anti-EBV antibodies correlate not only to disease onset but also correlate with MS disease activity, and the occurrence of increased EBV loads in patients with MS. The question of whether MS originates in the periphery or in the CNS is still to be comprehensively undetermined, although it is clear that there is a developing immune response. In pathologic specimens, immune cells infiltrate the CNS parenchyma, these cells in association with activated microglia and astrocytes, promote demyelination, oligodendrocyte and axonal injury, the demyelinating lesions of MS, called plaques, appear as indurated areas—hence the term sclerosis. Examination of the demyelinating lesions in the spinal cord and brain of patients with MS shows myelin loss, destruction of oligodendrocytes, and reactive astrogliosis, often with relative sparing of the axon cylinder. In some MS patients, however, the axon is also aggressively destroyed. The clinical presentation of MS is heterogeneous and depends on the loca- tion of demyelinating lesions within the CNS. Symptoms of a clinical attack typically show an acute or sub-acute onset, worsen over days or weeks, reach a peak severity within 2–3 weeks and remit completely or to a variable degree, ranging from minimal resolution to complete recovery normally 2–4 weeks after reaching maximum deficit.

Keywords: Multiple Sclerosis

INTRODUCTION

Recently there is no doubt that the Multiple sclerosis (MS) became a part of primary neurodegenerative disorders. It is a serious neurological disorder which is characterized pathologically by an autoimmune attack directed primarily at myelin, the protective insulation surrounding nerve fibers in the brain and spi- nal cord, and is progressively disabling. It is characterized by the presence of inflammation, neurodegeneration, and demyelinating lesions of white and gray matter. **(1)**

At first most of patients it is often starting with relapsing remitting neuro- logical symptoms regardless the first-time presenting picture. With increasing disease duration these relapses are more and more superimposed by a progressive disease process that leads to an irreversible accumulation of motor, sensory and cognitive deficits. Whatever the clinical course is, MS will result in a serious disability of the patient and not just a gradual worsening in their quality of life, but also in a severely elevated mortality risk if the disease is left untreated. Despite the great success of new therapies in the last two decades, MS is still an incurable condition and will remain so. **(2)**

Studies well documented that MS can severely impact health related qual- ity of life (HRQoL) and impose high levels of psychological stress and financial strains on affected persons. Loss of HRQoL in MS is multifactorial, being poten- tially driven by fatigue, depression, pain, reduced mobility, or sexual and sphinc- ter dysfunction. In addition, persons with MS suffer from secondary conse- quences of symptoms, such as job loss or increasing isolation **(3)**

Epidemiology of multiple sclerosis:

The estimated number of people with MS worldwide has increased to 2.8 million in 2020. When applying the same methodology 8 years ago, the rate now is 30% higher than that time. In 2020, the global prevalence is 35.9 per 100,000 people. Only 14% of countries with data at both time points, reported stable or declining prevalence. The incidence rate of MS across 75 countries was 2.1 per 100,000 persons/year. So, It was reported that there is one every 5 minutes is diagnosed with MS. Prevalence of MS ranges from 2 per 100,000 individuals in Asia to 1 per 1,000 individuals in Western countries, although a prevalence of 1 per 400 individuals has been reported in some countries with a high latitude in many studies, a higher latitude correlates with increased prevalence and incidence of MS. **(4)**

Middle Eastern and North African countries are located in a low- to moderate-risk zone for MS based on the 2013 MS Atlas. In Arab countries, epidemiologic, clinical, radiological and laboratory features of MS are well documented among the Caucasian population. A number of studies have characterized the incidence, prevalence and clinical patterns of MS in different Arab populations such as those of Kuwait, Jordan, Egypt, Libya, Saudi Arabia, Iraq, Lebanon and Oman. Some studies showed only minor differences from other western studies, e.g. a higher family history of MS in The kingdom of Saudi Arabia, Qatar and Dubai which is probably related to more consanguineous marriages but the overall pattern of the disease was similar. Hashem stated that alt- hough Egypt is the largest Arab country. The clinical characteristics of MS in Egypt are similar to the rest of the Arab countries, and also similar to the western countries. MS is more common among females in Egypt, with RRMS being the most common presentation **(2)**

In Egypt, MS represents about 1.41% of all neurological diseases with maximum distribution of cases was in Cairo 83.48% and the reported prevalence ranged from 0.4% at Assuit, while it was 1.78% at Cairo. In a community-based survey in Al Quseir, Egypt, has found an MS prevalence of 13.74/100,000. The annual MS incidence rate in the Middle East and North African countries was only reported in few studies ranging from lowest 0.8 in Libya to highest 9.1/100,000 in Iran. The mean age at disease onset ranging from lowest are: 25.2 in Kuwait, to highest one 32.5 in Northeastern Iran **(5)**

Globally, females are twice as likely to have MS as males, in some countries the ratio of female to male is as high as 4:1, the increased female preponderance of MS suggests a possible role of many environmental risk factors that mainly affect women that will be mentioned later. Most, but not all, patients presenting in later life (>60 years) are progressive form. It was reported that the global distribution of multiple sclerosis generally increases with increasing distance from the equator, although there are exceptions, Canada, Norway, and Sweden have some of the highest prevalence rates of MS in the world. However, there are exceptions; some countries that are farther away from the equator, such as Russia, have low prevalence. **(6)**

Etiology and risk factors of Multiple Sclerosis:

The causation of multiple sclerosis is multifaceted and varied, but inevita- bly there are interactions between genetic, epigenetic, and environmental risk fac- tors.

Genetics of Multiple sclerosis:

Several evidences suggested that genetics showed factors have a prominent role in the development of multiple sclerosis. The (prevalence) of familial MS is 13% for all MS phenotypes, the risk of MS is 3% in first-degree relatives (siblings 5%, parents 2%, and children, 2%), and only 1% in second and third-degree relatives. That risk of recurrence within families are variable in twins' patterns, its increases with the percentage of genetic sharing; for example, the age-adjusted risk in monozygotic twins is 35%, as compared with 6% in dizygotic twins and 3% in siblings. Interestingly, disease risk is also transferred more from unaffected females to their offspring than from males, raising the possibilities of the involvement of mitochondrial genes, epigenetic effects, or a pathogenic role of intrauter- ine exposure to exogenous risk factors **(7).**

The heritability of MS is polygenic and involves polymorphisms in several genes. Among these genes, polymorphisms in human leucocyte antigen (HLA genes) convey the highest risk of MS. A Polymorphisms in genes involved in T cell activation and proliferation (such as IL2 and IL7R) are a major features of the disease, together with poly- morphisms in other components of adaptive and innate immunity (such as genes that modulate tumor necrosis factor (TNF) which involved in T cells activation as well. **(7)**

Epstein-Barr virus (EBV) in Multiple Sclerosis:

EBV is one of the most important risk factors of MS, as a history of EBV infection or triggered acute infectious mononucleosis, stand at an increased risk to develop MS. Elevated serum and CSF anti-EBV antibodies correlate not only to disease onset but also correlate with MS disease activity, and the occurrence of increased EBV loads in patients with MS. The CSF accumulation of EBV-specific CD8 T cells in early MS supports an EBV-MS linkage, and MS progression may be triggered by EBV reactivation, as EBV lytic-phase genes were preferentially expressed during relapse and increased cluster of differentiation 8 (CD8) responses to lytic EBV antigens were detected in MS patients. **(8).**

Vitamin D deficiency in Multiple Sclerosis:

A lot of prospective studies showed a 50-60% reduced risk of MS with Vit D levels ≥75 nmol/L, and a 2-fold increased risk of

MS with levels of Vit D <30 nmol/L. **(9)**
In addition, higher Vit D is predictive of reduced relapse rate, fewer new active lesions, and reduced T2 lesion volume. Alternative explanations for these associations include immunosuppressive effects of Vit D. **(10)**
Obesity in Multiple Sclerosis:

Elevated body mass index (BMI) in young adults increases the risk of developing MS across a range of observational studies. Genetic factors that influence BMI similarly increase the odds of MS, strengthening BMI's position as an MS risk factor, and found the hyperlipidemia. increases relapse rate, disease activity and disability progression. BMI also affects paraclinical measures of progression, being negatively correlated with grey matter volume and brain parenchymal fraction in people with RRMS and clinically isolated syndrome. Another study reported that obesity has pro-inflammatory effects in many autoimmune diseases but the most pertinently is MS. **(9)**

Cigarette smoking in Multiple Sclerosis:
Smoking is associated with increased MS susceptibility and increase inten- sity,duration and progression of the disease. Studies found that smoking interacts with some of the strongest associated risk genes (such as the presence of HLA-DRB1*15:01 and absence of HLA- A*02). Smoking is additionally associated with a worse disease course, with the development of antibodies to interferon-β-1a and natalizumab, while smoking cessation has been shown to delay the conversion to SPMS. **(11)**

Pathology of multiple sclerosis
The question of whether MS originates in the periphery or in the CNS is still to be comprehensively undetermined, although it is clear that there is a de- veloping immune response. In pathologic specimens, immune cells infiltrate the CNS parenchyma, these cells in association with activated microglia and astro- cytes, promote demyelination, oligodendrocyte and axonal injury, the demye- linating lesions of MS, called plaques, appear as indurated areas—hence the term sclerosis. Examination of the demyelinating lesions in the spinal cord and brain of patients with MS shows myelin loss, destruction of oligodendrocytes, and

reactive astrogliosis, often with relative sparing of the axon cylinder. In some MS patients, however, the axon is also aggressively destroyed. Multiple sclerosis is characterized by perivenular infiltration of lympho- cytes and macrophages. Infiltration of inflammatory cells occurs in the paren- chyma of the brain, brainstem, optic nerves, and spinal cord. The elevated immunoglobulin G (IgG) level in the cerebrospinal fluid, which can be demonstrated by an oligoclonal band pattern on electrophoresis, suggests an important humoral immunity (i.e., B-cell activation) component to MS. Many studies have suggested immune system (T lymphocytes and adaptive immune responses) which initiated by interaction between antigen presenting cells (APCs) with T lymphocytes play an important role, not only in the initiation, but also in progression of MS. **(12)**
Many studies have shown that the cluster of differentiation 4 and 8 (CD4 and CD8) play major role in MS pathogenesis. Other studies showed the CD8+ T cells (Cytotoxic T cells) can be found in MS lesions as well. These cells prov- ocation of inflammatory process through the production of cytolytic proteins, in- crease vascular permeability, glial cells destruction and triggering oligodendro- cytes death. Pathogen-associated molecules bind to a receptor on APCs and production of specific cytokines that include interleukin (IL)-12, IL-23 and IL-4 which in- duce T cell differentiation. Also interferon gamma (IFNγ) or type II interferon and tumor necrosis factor alpha (TNF-α) are proinflammatory cytokines that pro- mote cells destruction. B lymphocytes and their cytokines such as transforming growth factor beta (TGF-β) and (TNF-α) promotes inflammation. In addition, these cells are capable of producing IL-10 which is an anti-inflammatory cytokine. Hence, Blymphocytes have both positive and negative effects in the development of MS
(13).

Clinical picture of Multiple Sclerosis:
The clinical presentation of MS is heterogeneous and depends on the loca- tion of demyelinating lesions within the CNS. Symptoms of a clinical attack typ- ically show an acute or sub-acute onset, worsen over days or weeks, reach a peak severity within 2–3 weeks and remit completely or to a variable degree, ranging from minimal resolution to complete recovery normally 2–4 weeks after reaching maximum deficit.
Table (1): Clinical features of multiple sclerosis **(14).**

Cerebrum Cognitive impairment Deficits in attention, reasoning, and executive function (early); dementia (late)
Hemi sensory and motor Upper motor neuron signs
Affective (mainly depression)
Epilepsy (rare)
Focal cortical deficits (rare)
Optic nerve Unilateral painful loss of Vision Scotoma, reduced visual acuity, color vision, and relative afferent pupillary defect
Cerebellum and cerebellar Pathways Tremor Postural and action tremor, Dysarthria
Clumsiness and poor Balance Limb incoordination and gait ataxia
Brainstem Diplopia, oscillopsia Nystagmus, internuclear and another complex ophthalmoplegias
Vertigo
Impaired swallowing Dysarthria

Impaired speech and emotional labiality Pseudo bulbar palsy
Paroxysmal symptoms
Spinal cord Weakness Upper motor neuron signs

Stiffness and painful Spasms Spasticity
Bladder dysfunction
Erectile impotence
Constipation
Other Pain
Fatigue
Temperature sensitivity and exercise intolerance

Several “red flags” in neurologic examinations can provide valuable infor- mation that helps to accurately diagnose and direct the care of patients with mul- tiple sclerosis (MS) who complain about certain symptoms. These red flags may “aid in diagnosis of disease, detect improvements or worsening of symptoms, and discover unexpected deficits in the patient we may not even be aware of that re- quire explanation.

Table (2): Red flags in the diagnosis of multiple sclerosis **(15).**
Clinical presentations:

- No dissemination in time/space.
- Onset < 10 or > 55 years of age.
- Prominent fever/headache, impairment of consciousness.
- Abrupt hearing loss.
- Non-scotomatous field defect.
- Cortical features (seizures, aphasia, and cortical blindness).
- Encephalopathy.

Optic neuritis:

- Bilateral presentation.
- Severe pain that restricts movement or awakens patient Very severe visual loss without recov- ery after 1 month Uveitis.
- Retinal exudates or hemorrhages, severe optic disc edema and vitreous reaction.
- History of cancer.

Transverse myelitis:

- Hyper acute non-progressive onset.
- Complete involvement of the spinal segment.
- Progressive myelopathy in the absence of bladder involvement.
- Anterior spinal artery distribution.
- Radicular pain.
- Cauda Equina Syndrome.
- Co-existing lower motor neuron (LMN) signs.

Brainstem/cerebellar:

- Hyper acute onset in a vascular territory.
- Fluctuating or fatigable ocular or bulbar symptoms.
- Complete external ophthalmoplegia.

MRI:

- Brain: normal, small lesions 53 mm, prominent gray matter involvement, hydrocephalus, ab- sence of callosal or periventricular lesions, symmetric confluent WM lesions, meningeal en- hancement, or simultaneous enhancement of all lesions.
- Spine: extensive lesion spanning 3 or more segments, swelling, full thickness lesions, lep- tomeningeal enhancement.

CSF:

●Normal.

●Absence of OCB (by isoelectric focusing technique).

●White blood cell count >50.

● Protein > 80 mg/dl.

*LMN: lower motor neuron *WM: white matter *OCBs: oligoclonal bands

Cognitive impairment in Multiple Sclerosis:

Cognitive impairment is a common feature in MS affecting 43%–72% of patients, these impairments depending on several factors, such as disease du- ration and age at disease onset. The most frequently affected cognitive func- tions are attention, speed of information processing, memory, executive func- tions, and visuospatial abilities. **(3)**

Neuropsychological dysfunction severely affects the patients' lives, their ability to keep their jobs, and they require greater assistance with daily living activities, cognitively compromised patients are also more likely to have prob- lems with socialization. **(16)**

Cognitive impairment has been strongly associated with non-somatic symptoms of depression and anxiety, these finding supports the importance of evaluating depressive symptoms when cognitive impairment is suspected in pa- tients with RRMS. Also, there is evidence that the high levels of anxiety related. **(16)**

MS are associated with poor performance in cognitive tasks, especially pro- cessing speed, working memory, and visual–spatial memory. Cognitive defects can pre-date the appearance of other neurological symp- toms and signs of MS. In a prospective study found that male participants who later developed multiple sclerosis showed significantly lower intelligence quo- tients than did healthy controls at ages 18–19 years, which occurs several years before their first MS symptoms. Patients with clinically isolated syndrome (CIS) or relapsing-remitting multiple sclerosis (RRMS) show similar neuropsychological profiles with prom- inent involvement of cognitive processing speed (CPS), whereas in progressive forms of the disease, impaired memory and executive function are more common. Patients with benign multiple sclerosis (BMS), which is defined by an Ex- panded Disability Status Scale (EDSS) score of less than 3.0 after at least 15 years since disease onset, can present with cognitive impairment despite preservation of motor and other neurological functions. **(17)**

Multiple sclerosis phenotypes:

An international consensus has classified MS to different categories ac- cording to clinical features, course, frequency, and disease progression in addi- tion to MRI findings, into **(17):**

Clinically isolated syndrome (CIS):

It was not included in the initial MS clinical descriptors, but now CIS recognized as the first clinical presentation of a disease that shows characteristics of. inflammatory demyelination that could be MS but has yet to fulfill criteria of dissemination in time. **(18)**

Radiologically isolated syndrome (RIS):

A more complicated situation, where incidental imaging findings suggest inflam- matory demyelination in the absence of clinical signs or symptoms. RIS is not considered an MS subtype if the clinical evidence of demyelinating disease is absent. However, RIS may raise the suspicion of MS, depending on the morphol- ogy and location of detected MRI lesions. Changes of brain imaging that are highly suggestive of demyelinating pathology carry the greatest risk of future MS clinical symptoms. Asymptomatic spinal cord lesions, gadolinium-enhancing lesions, or posi- tive CSF findings enhance the likelihood of an eventual MS diagnosis. There is a fact that 10% of RIS patients develop a primary progressive (PP) disease course. **(19)**

Relapsing remitting MS:

It's the most common MS phenotype, found in about 85% of MS patients, RRMS characterized by alternating periods of neurological dysfunction, relapses, and periods of relative clinical stability free of new neurological symptoms, re- missions. Some studies reported that the frequency of relapses can vary from pa- tient to patient but generally does not exceed 1.5 per year. Various neurological symptoms can be present during the relapse, these symptoms lasting at least 24 hours in the absence of infection or metabolic derangement. Relapses result in residual deficits in almost half of episodes, leading to stepwise accrual of impair- ment. Many potential relapse triggers have been investigated over years to iden- tify potential interventions to prevent an acute attack. Infections, stress, as well as pregnancy and their association with relapse, are the most relevant factors to everyday clinical practice. Many studies pointed that the number of relapses within first 2 years of diagnosis can influence the median time onset of disease progression. Another study identified the short inter-relapse period after the first attack considered the strongest predictor for the time to onset of disability **(20).**

Progressive phenotypes of Multiple Sclerosis:

Primary progressive Multiple Sclerosis (PPMS):

About 10%–20% of patients will develop this phenotype. PPMS is characterized by worsening neurologic function

(accumulation of disability) from the onset of symptoms, without early relapses or remissions. PPMS can be further characterized as either active (with an occasional relapse and/or evidence of new MRI activity over a specified period of time) or not active, as well as with progression (evidence of disability over time, with or without relapse or new MRI activity) or without progression. **(14).**

Secondary progressive Multiple Sclerosis (SPMS):
The majority of untreated RRMS patients could eventually progress into SPMS, and research data suggested that the median time to progressive phase of about 19 years after the onset of RRMS. A few predictors of the conversion to SPMS have been identified, such as higher age at RRMS onset that associated with earlier progression to SPMS, as well as male gender, spinal cord symptoms and incomplete relapse recovery have also been shown to shorten the time to progression. Phenotypically, the course of SPMS is not uniform and consists of periods of progression with possible superimposed relapse activity but also periods of relatively stable disability. The pathology involved in SPMS is poorly understood and most likely complex, involving some degree of persistent inflammation, combined with neurodegeneration caused by mitochondrial dysfunction and resultant axonal damage. **(21)**

Diagnosis of multiple sclerosis
Early detection of MS is important because it gives us the opportunity to seek treatment and plan for the future. Basically, the diagnosis of multiple sclerosis is based on the integration of proper medical history, clinical examination, imaging, laboratory findings of cerebrospinal fluid (CSF), myelin basic protein and immunoglobulin gamma (IgG) determinations, as well as Evoked potentials test that includes visual, auditory, and somatosensory evoked potentials offer information about demyelination in the optic nerve and CNS. **(22)**

McDonald diagnostic criteria for multiple sclerosis:
It's a clinical, radiographic, and laboratory criteria used in the diagnosis of multiple sclerosis. **(23)**

Criteria:

The diagnosis of multiple sclerosis can be made if there is fulfillment of any of these five categories of criteria, depending on how many clinical attacks have occurred.

- ≥2 clinical attacks
  - with ≥2 lesions with objective clinical evidence

  - with no additional data needed
- ≥2 clinical attacks
  - with 1 lesion with objective clinical evidence and a clinical history suggestive of a previous lesion
  - with no additional data needed
- ≥2 clinical attacks
  - with 1 lesion with objective clinical evidence and no clinical history suggestive of a previous lesion
  - with dissemination in space evident on MRI
- 1 clinical attack (i.e., clinically isolated syndrome)
  - with ≥2 lesions with objective clinical evidence
  - with dissemination in time evident on MRI or demonstration of CSF-specific oligoclonal bands
- 1 clinical attack (i.e., clinically isolated syndrome)
  - with 1 lesion with objective clinical evidence
  - with dissemination in space evident on MRI
  - with dissemination in time evident on MRI or demonstration of CSF-specific oligoclonal bands

Dissemination in space requires ≥1 T2-hyperintense lesions (≥3 mm in long axis), symptomatic and/or asymptomatic, that are characteristic of multiple sclerosis in two or more of the four following locations.

- periventricular (≥1 lesion, unless the patient is over the age of 50 in which case it is advised to seek a higher number of lesions)
- cortical or juxtacortical (≥1 lesion)
- infratentorial (≥1 lesion)

- spinal cord (≥1 lesion)

Notably, T2-hyperintense lesions of the optic nerve, such as those in a patient presenting with optic neuritis, cannot be used in fulfilling the 2017 revised McDonald criteria 5.
Dissemination in time can be established in one of two ways.

• a new T2-hyperintense or gadolinium-enhancing lesion when compared to a previous baseline MRI scan (irrespective of timing)
• simultaneous presence of a gadolinium-enhancing lesion and a non-en- hancing T2-hyperintense lesion on any one MRI scan.
(23)

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