# BRIEF OVERVIEW ABOUT MULTIPLE SCLEROSIS

**Asmaa Arafa Mohamed Hassan[1]*, Amaal Salah Eldien Almotaym[2], Tarek Abdelrahman Gouda[3], Wael Mahmoud Elsayed[4]**

**Article History:** **Received: 10/06/2023** **published online: 10/07/2023** **Accepted: 05/07/2023**

**Abstract**

**Background:** Multiple sclerosis (MS) is the most prevalent demyelinating disease of the central nervous system (CNS) with an autoimmune component affecting young adults in their third decade of life, inflammation, demyelination, and axonal degeneration represent the major pathologic hallmarks of the disease. The broad range of signs and symptoms of MS reflect multifocal lesions in the CNS, including the afferent visual pathways, cerebrum, brainstem, cerebellum, and spinal cord. The hallmark of MS pathology is the focal demyelinated lesion, or "plaque" appear as indurated areas. The location of lesions in the CNS usually dictates the type of clinical deficit. The MS plaques consist of a variety of immunologic and pathologic features, including different degrees of inflammation, demyelination, remyelination and axonal injury.

**Keywords:** Multiple sclerosis

[1*, 2, 3, 4]Neurology Department, Faculty of Medicine, Zagazig University, Egypt,
Email: asmaaalhawary@medicine.zu.edu.eg, asmaalhawary625@gmail.com, arafaasmaa19@gmail.com

***Corresponding Author**: - Asmaa Arafa Mohamed Hassan
[4]Neurology Department, Faculty of Medicine, Zagazig University, Egypt
Email: asmaaalhawary@medicine.zu.edu.eg

**DOI:** 10.53555/ecb/2023.12.Si13.222

**Introduction**

Multiple sclerosis (MS) is the most prevalent demyelinating disease of the central nervous system (CNS) with an autoimmune component affecting young adults in their third decade of life, inflammation, demyelination, and axonal degeneration represent the major pathologic hallmarks of the disease **.** It has a negative impact on patients' physical, psychological and social well-being with a significant economic burden. **( 1)**

It affects about 2.8 million people worldwide, and its prevalence is increasing (**2).** Most of MS patients developed the disease between 20 and 40 years of age and it is between 1.5 to 3 times more prevalent in women, this gender distribution has been rising over the time**.** Most of countries, from the Middle East North Africa (MENA) region fall in the low-to-moderate MS prevalence zone. **(3)**

In Egypt, an epidemiological study in 2013 revealed a prevalence of 13.7/100,000 in Al Quseir city, Red Sea Governorate, possibly reflecting the lower prevalence rates seen in African countries. **(4)**

Other study in Egypt included 950 patients recruited from the project MS database of the MS Unit at Ain Shams University Hospitals found that the clinical characteristics of MS in Egypt were similar to other Arab and western countries, being more common among females, and relapsing remitting MS (RRMS) the most common type. **(5)**

In Sharkia governorate, the frequency of MS is 3.376 / 100,000 /population with the RRMS is the most common type, and the motor symptoms are the most frequent presenting symptoms. **(6)**

The etiology of MS is still unknown, but a complex interactions between genetic susceptibility, lifestyle and environmental factors can be important contributors to disease risk **(2)** . The lifestyle and environmental factors that increase the risk of MS include exposure to tobacco smoke and organic solvents, Epstein–Barr virus (EBV) infection, adolescent obesity, lack of sun exposure or low levels of vitamin D, and working night shifts. **(7)**

**Regarding to the genetic risk factors,** Genetic susceptibility to develop MS is mostly associated with the human leukocyte antigen (HLA) region, the HLA class II alleles DRB1*1501**,** DRB1*0301 and DRB1*1303 **( 8)**

**As regards the environmental risk factors,** EBV associated with infectious mononucleosis and lymphoma, seropositivity, or the presence of antibodies indicating prior exposure, has been consistently shown to be associated with adult and pediatric-onset MS in people of different races and ethnicities. **(9)**

Decreased **vitamin D** levels as well is associated with an increased risk for MS. Its Serum levels were significantly decreased in MS patients and were significantly correlated with MS severity and MRI lesion load**.** Both ultraviolet rays exposure and vitamin D have been shown to be important factors in protecting against MS **Smoking and exposure to passive smoking as well** contribute to increase the risk of MS in a dose-dependent manner. **(10)**

**Obesity** also especially in adolescence and young adulthood, but not later on adult life, seems to be associated with subsequent risk of MS. It induces a chronic low-grade inflammatory state characterized by altered secretion of adipokines especially leptin **(11)**

Serum leptin level was significantly elevated in MS patients, its levels were positively correlated with disease disability, severity and progression which indicates that leptin has a role in MS. **(6)**

Regarding to **Sex Hormones**: MS relapse rates declined during pregnancy, particularly in the third trimester, and rebound in the first 3 months post-partum before returning to the pre pregnancy rate , this has led to the hypothesis that certain female sex hormones may play a protective role in RRMS. **(12)**

The **clinical disease course classification** comprises the clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS) and progressive MS, which is divided into primary progressive MS (PPMS) and secondary progressive MS (SPMS) **(13)**

**The Clinically isolated syndrome:** describes a first clinical event highly suggestive of demyelinating CNS disease, but not meeting dissemination in time for diagnosis of clinical definite MS. **(13)**

**The Relapsing-remitting MS** is the most common MS phenotype found in about 85% of MS patients, it is characterized by alternating periods of neurological dysfunctions called relapses and periods of relative clinical stability free of new neurological symptoms called remissions. **(14**

**The Secondary progressive MS considered the** second most common form of MS, One in two RRMS patients will develop SPMS within 15 years and up to two-thirds after 30 years**.** It is distinguished from PPMS by its distinct course, which necessarily includes and follows an initial course of RRMS. **(15)**

**Finally, The Primary progressive MS** accounts for 10–15% of the MS patient population, presents with a disease course that consists mainly of gradual worsening of neurological disability from symptom onset, although relapses may occur. **(16)**

**Clinical Manifestations:**
The broad range of signs and symptoms of MS reflect multifocal lesions in the CNS, including the afferent visual pathways, cerebrum, brainstem, cerebellum, and spinal cord. **(17)**

**The commonest clinical presentations are:** acute demyelinating **optic neuritis** is the presenting symptom in about 20% of MS patients and affects about half of MS patients at some point in the disease course. It is diagnosed clinically based on a history of sub-acute visual blurring or loss, evolving over hours to days, typically associated with painful eye movements, Color vision problems, especially red desaturation.

The Patients may also complain from a "blind spot" or "blurry spot" within the visual field corresponding with a scotoma.**(18)**
During the acute phase of optic neuritis, in two-thirds of the cases, the optic disc appears normal on funduscopic examination (retro bulbar optic neuritis); in the other third of cases, the optic nerve appears swollen (papillitis). **(18)**

**Numbness and paresthesia** are also common **sensory symptoms** experienced by MS patients. Sensory complaints affect about 87% of MS patients at some point in the disease course and are part of the presenting syndrome in 34% .**(19)**

**Pain** is a frequent symptom as well in MS, in some cases; it is caused by an injury in the area of entry of the fifth cranial nerve (trigeminal neuralgia), the dorsal root entrance area (root pain). Usually the pain has neuropathic features such as burning, electrical or sharp sensations. **.(20)**

**Lhermitte's symptom** – an electrical-shock-like sensation running down the spine upon neck flexion – occurs in up to one-third of MS patients at some point in the disease ,the neuroanatomical localization of Lhermitte's symptom is the posterior column in the cervical or upper thoracic spinal cord . **(20)**

**Myelitis** that occurs in MS is typically partial and usually presents sub acutely. Partial myelitis is defined as involvement of one or more, but not all, of these functional spinal tracts. (**21)**. The occurrence of a band-like tightening sensation around the chest or abdomen (the so-called MS "hug") is a typical symptom of myelitis and suggests involvement of the posterior columns of the spinal cord. **(22)**

By contrast, a complete transverse myelitis should prompt a detailed evaluation for other potential causes, especially if it is hyper acute in the onset, longitudinally extensive (involves three or more vertebral segments on T2-weighted MRI images), accompanied by prominent radicular pain, or associated with absent reflexes. **(23)**

**Weakness** is a constant symptom in advanced MS and affects up to 89% of MS patients at some point in the disease. Its severity can vary from a slight difficulty in walking to a complete inability to walk, making necessary the use of support devices or a wheelchair**.(20)**

Patients with MS often describe the sensation of being off-balance, or unsteady, these symptoms can arise from **cerebellar dysfunction** (tremor, dysmetria, dysdiadochokinesia, gait ataxia, eye movement abnormalities), sensory impairment (sensory ataxia), vestibular dysfunction, or weakness. **(23)**

**Cognitive deficits** are common, particularly in advanced cases, and include memory loss, impaired attention and problem-solving difficulties The most common domains affected in MS on formal neuropsychological testing are slowed information processing, executive dysfunction, and impairment of long-term verbal and visual memory**.** Cognitive impairment in MS is associated with white-matter involvement and brain atrophy. **(24)**

The brainstem is commonly affected in MS. The clinical syndromes produced by its involvement include double vision (cranial nerves III, IV, VI), internuclear ophthalmoplegia (medial longitudinal fasciculus), facial weakness or myokymia (cranial nerve VII), vertigo (cranial nerve VIII. Less common **brainstem symptoms** in MS include hearing loss and severe bulbar signs. Acquired pendular nystagmus in MS is thought to be caused by a disruption of the cerebellopontine networks

involved in neural integration and maintenance of gaze. **(25**)

**Fatigue** is one of the most debilitating symptoms in MS and the patients often describe it as a general sense of low energy**.** It can persist between the clinical relapses, but often worsens in association with disease activity. However, it is always important in the evaluation of MS patients with fatigue to exclude alternate causes, particularly depression, hypothyroidism, anemia and sleep disorders. (**26)**

Persons with MS often experience an increase in symptoms of fatigue or weakness when exposed to high temperatures due to hot weather, exercise, hot showers or baths or fever. **Heat intolerance**, may result in blurring of vision (Uhthoff sign) usually in an eye previously affected by ON. These symptoms result from elevation of core body temperature, which further impairs conduction by demyelinated nerves. **(27)**

Impairment of **bowel and bladder control** also occurs in more than 75% of patients in advanced stages of the disease and correlates, in most cases, with the degree of motor involvement in the lower extremities. The most frequent alterations are increased micturition frequency, urinary urgency, and incontinence secondary to hyperactivity of the detrusor muscle, which is present in about two-thirds of MS patients who undergo formal urodynamic testing. **(27)**

Atypical or red flag presentations that may suggest an alternative diagnosis: **(28)**

- Bilateral optic neuritis or unilateral optic neuritis with a poor visual recovery.
- Complete gaze palsy or fluctuating ophthal-moparesis .
- Intractable nausea, vomiting, or hiccups.
- Complete transverse myelopathy with bilateral motor and sensory involvement.
- Encephalopathy.
- Headache or meningism .

**Pathologic features of MS:**

The hallmark of MS pathology is the focal demyelinated lesion, or "plaque" appear as indurated areas. The location of lesions in the CNS usually dictates the type of clinical deficit. The MS plaques consist of a variety of immunologic and pathologic features, including different degrees of inflammation, demyelination, remyelination and axonal injury. **(29)**

During the **early stages** of the RRMS course, the pathology characterized mainly by demyelination and a variable degree of axonal loss and reactive gliosis. **(29)**

In the **progressive course**, MS is dominated by diffuse gray and white matter atrophy and characterized by low-grade inflammation and microglial activation at the plaque borders. **(30)**

In **active plaques**, the dominant cell is the myelin-laden macrophage, with participation of systemic infiltrating monocytes and lymphocytes cells mainly CD8+ T cells with few CD4+ T cells. B cells and plasma cells are limited.**(31)**

In **late chronic disease plaques** show little inflammation and highly reactive microglia at their rim. Chronic inactive plaques are marked by demyelination with little to no inflammation and are surrounded by an astrocytic scar. **(32)**

Many studies found that axonal injury including transection occurs in early stages of MS, within both active and chronic plaques. Axon pathology correlates with the degree of inflammation. During axon injury, there are sodium influx, activation of calcium-dependent proteases, up regulation of voltage-gated calcium channels, and destruction of the axon cytoskeleton. In mature myelinated axons, neurofilaments are the single most abundant protein. Damage to CNS neurons and physiologic turnover lead to neurofilaments release. This results in elevated its levels in the CSF and eventually blood, where the concentration reflects the rate of release from neurons. **(32)**

Based on the trafficking of other proteins degraded in the CNS, it is likely that partially degraded fragments of neurofilaments drain directly into CSF and blood via multiple routes which include direct drainage into CSF and blood via arachnoid granulations as well as drainage into the subarachnoid spaces and perivascular spaces. **(33).**

**References**

1. Battaglia MA, Bezzini D, Cecchini I, Cordioli C, Fiorentino F, Manacorda T and Patti F (2022): Patients with multiple sclerosis: a burden and cost of illness study. J Neurol, 269(9), 5127-5135.
2. Walton C, King R, Rechtman L, Kaye W, Leray E, Marrie RA and Baneke P (2020): Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS. Mult Scler J, 26(14), 1816-1821.
3. Yamout BI, Assaad W, Tamim H, Mrabet S and

Goueider R (2020): Epidemiology and phenotypes of multiple sclerosis in the Middle East North Africa (MENA) region. Mult. scler. j., exp., 6(1): 1-9
4. El-Tallawy N , Farghaly M , Badry R, Metwally A, Shehata A, Rageh T and Kandil M (2016): Prevalence of multiple sclerosis in Al Quseir city, Red Sea governorate, Egypt. Neuropsychiatr Dis Treat, 155-158.
5. Zakaria M, Zamzam D A, Hafeez M A A, Swelam MS, Khater SS, Fahmy M and Gadallah M (2016): Clinical characteristics of patients with multiple sclerosis enrolled in a new registry in Egypt. Mult. Scler. Relat. Disord. 10, 30-35.
6. Fahmi R, Kamel A, Elsayed D , Zidan A and Sarhan N (2021): Serum levels of leptin and adiponectin in patients with multiple sclerosis. Egypt J Neurol Psychiatr Neurosurg, , 57(1), 1-7.
7. Olsson T, Barcellos LF and Alfredsson L (2017): Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. Nat. Rev. Neurol., 13(1), 25-36.
8. Cotsapas C and Mitrovic M (2018): Genome-wide association studies of multiple sclerosis. Clin. Transl. Immunol., 7(6), 1018 -1026
9. Hempel S, Graham GD, Fu N, Estrada E, Chen AY, Miake-Lye I and Wallin MT (2017) :A systematic review of modifiable risk factors in the progression of multiple sclerosis. Mult Scler J, 23(4), 525-533.
10. Hedström A, Olsson T and Alfredsson L (2016) : Smoking is a major preventable risk factor for multiple sclerosis. Mult Scler J, 22(8), 1021-1026.
11. Marrodan M , Farez M, Balbuena M and Correale J (2021): Obesity and the risk of Multiple Sclerosis. The role of Leptin. Ann. Clin. Transl. Neurol. 8 (2), 406-424.
12. Golden LC and Voskuhl R (2017): The importance of studying sex differences in disease: The example of multiple sclerosis. J Neurosci, 95(1-2), 633-643.
13. Klineova S and Lublin FD (2018): Clinical course of multiple sclerosis. Cold Spring Harb. Perspect. , 8(9), a028928.
14. Marzullo A, Kocevar G, Stamile C, Durand-Dubief F, Terracina G, Calimeri Fand Sappey-Marinier D (2019): Classification of multiple sclerosis clinical profiles via graph convolutional neural networks. Front. Neurosci, 5 (13) 594-601.
15. Chataway J, Murphy N, Khurana V, Schofield H, Findlay J, and Adlard N (2021): Secondary progressive multiple sclerosis: a systematic review of costs and health state utilities. Curr Med Res Opin, 37(6), 995-1004.
16. Hauser SL, Baror A, Comi G, Giovannoni G, Hartung HP, Hemmer B and Kappos L (2017): Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. NEJM, 376(3), 221-234.
17. Disanto G, Zecca C, MacLachlan S, Sacco R, Handunnetthi L, Meier UC and Gobbi C (2018): Prodromal symptoms of multiple sclerosis in primary care. Ann. Neurol., 83(6), 1162-1173.
18. Biousse V, and Newman NJ (2020): Neuro-ophthalmology illustrated (664). J. A. Micieli (Ed.). New York: Thieme.
19. Christogianni A, Bibb R, Davis SL, Jay O, Barnett M, Evangelou N and Filingeri D (2018) : Temperature sensitivity in multiple sclerosis: an overview of its impact on sensory and cognitive symptoms. Temperature, 5(3), 208-223.
20. Moreno-Torres I, Sabín-Muñoz J and García-Merino A (2019): Multiple sclerosis: epidemiology, genetics, symptoms, and unmet needs. R. Soc. Chem. 23(8), 1-32.
21. Mariano R, Flanagan EP, Weinshenker BG and Palace J (2018): A practical approach to the diagnosis of spinal cord lesions. Pract. Neurol., 18(3), 187-200.
22. Bourre B, Zéphir H , Ongagna JC, Cordonnier C, Collongues N., Debette S and de Seze J (2012): Long-term follow-up of acute partial transverse myelitis. Arch. Neurol., 69(3), 357-362.
23. Sand IK (2015): Classification, diagnosis, and differential diagnosis of multiple sclerosis. Current opinion in neurology, 28(3), 193-205.
24. Eijlers A, van Geest Q, Dekker I, Steenwijk M, Meijer K, Hulst, H and Geurts J (2018): Predicting cognitive decline in multiple sclerosis: a 5-year follow-up study. Brain, 141(9), 2605-2618.
25. Thurtell MJ (2020): Nystagmus and Nystagmoid Eye Movements. Albert and Jakobiec's Principles and Practice of Ophthalmology, 1-30.
26. Rudroff T, Kindred JH and Ketelhut NB (2016): Fatigue in multiple sclerosis: misconceptions and future research directions. Frontiers in Neurology, 7, 122-128 .
27. Kister I, Bacon TE , Chamot E, Salter A R, Cutter G R , Kalina J T, & Herbert, J. (2013). Natural history of multiple sclerosis symptoms. Int. J. MS Care, 15(3), 146-156.
28. Solomon AJ (2019): Diagnosis, differential diagnosis, and misdiagnosis of multiple sclerosis. CONTINUUM: lifelong Learning in Neurology, 25(3), 611-635.

29. Lee PW, Severin ME and Lovett-Racke AE (2017): TGF-β regulation of encephalitogenic and regulatory T cells in multiple sclerosis. Eur. J. Immunol, 47(3), 446-453.
30. Hunter SF (2016): Overview and diagnosis of multiple sclerosis. Am J Manag Care, 22(6 Suppl), s141-50.
31. Attfield KE, Jensen LT, Kaufmann M, Friese MA and Fugger L (2022): The immunology of multiple sclerosis. Nature Reviews Immunology, 1-17.
32. Lassmann H (2018): Multiple sclerosis pathology. Cold Spring Harb. Perspect. J, 8(3), a028936.
33. Gafson A , Barthélemy N, Bomont P, Carare R, Durham H , Julien J, Kuhle J, and et al.(2020): Neurofilaments: Neurobiological foundations for biomarker applications. Brain 2020, 143, 1975–1998.