Brief Overview about Multiple Sclerosis; Immune mediated Pathogenesis, Presentation and Diagnosis

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Article History: Received 10th June, Accepted 5th July, published online 10th July 2023

Abstract

Background: Multiple sclerosis (MS) is a chronic autoimmune disease characterized by demyelination and neurodegeneration in the central nervous system (CNS). The pathogenesis of MS is complex and incompletely understood. It is an autoimmune disease with combination of both genetic and environmental risk factors. Understanding the immune-mediated mechanisms and the influence of genetic and environmental risk factors may help to further improve therapeutic approaches and prevent disease progression. T regulatory cell expressing the CD4, CD25, and forkhead box P3 (FoxP3)markers is the regulatory subtype of CD4+ T cells , Immunologically Treg cell has the main role in secreting the transforming growth factor- beta (TGF- β) and IL- 10 cytokines, regulating the immune responses against infectious or cancers, suppressing the auto-reactive T cells, and maintaining the immunologic self- tolerance ,The Treg cell dysfunction in MS, followed by breaking down of self- tolerance, led to autoreactive T- cell suppression failure, myelin and neural destruction, then neuroinflammation. Inflammatory lesions of the spinal cord usually appear as acute partial transverse myelitis (APTM) with rapid onset and tend to show asymmetric neurological signs. APTM may be the first manifestation of MS, it also may remain the only neurological effect during life or recur as relapsing myelitis. The possibility of developing MS was shown to be higher after APTM than after optic neuritis. In 2001, Ian McDonald developed a new criteria for diagnosing MS, which is now known as the ‘‘McDonald criteria’’ That replaced the Poser criteria and started the use of MRI as a central tool in the diagnosis of multiple sclerosis. It demanded evidence of dissemination of lesions in both space and time which could be proved clinically or by MRI reinforced by other paraclinical diagnostic methods like cerebrospinal fluid examination to enable the diagnosis of multiple sclerosis in patients with different clinical presentations. In the 2017 revised McDonald criteria is oligoclonal bands was taken as a substitute for DIT, therefore, can be used to start the diagnosis of multiple sclerosis after the first clinical event and a single brain MRI.

Keywords: Multiple Sclerosis, Immune mediated Pathogenesis presentation

Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease characterized by demyelination and neurodegeneration in the central nervous system (CNS). Pathologically, it is characterized by perivascular mononuclear cell infiltrates, demyelination, axonal loss, and gliosis that result in the formation of multiple plaques in the brain and spinal cord . **(1)**

Multiple sclerosis affects young people globally, and divided into four diagnostic types. 85–90% of MS patients develop a relapsing-remitting form of the disease, characterized by periods of exacerbation

followed by remission. As the disease progresses, 50% of patients develop a **secondary progressive** form, characterized by progressive, irreversible neurological disability. 10–15% of patients develop a progressive clinical course from the onset that is termed **primary progressive**, while the smallest group of patients develop **progressive relapsing** form characterized by both progression and relapses. **(2).**

Epidemiology:

Kurtzke categorized MS in three zones (low, Medium and high), Wade proposed a five-zone classification system to avoid grouping countries with prevalence rates which are incomparable: **(1)very high** 170–350/100,000, **(2) high**(70-170/100,000),**(3) Medium**(38-70/100,000 ,**(4) low** 13-38/100,000 and **(5) very low risk** 0-13/100,000 **(3)**

There is increasing incidence and prevalence of MS in both developed and developing countries affecting more than 2.8 million people around the world.There is an increasing in the prevalence of MS with increasing latitude. North European countries and North America constitute the high-risk MS prevalence zone, with prevalence of more than 100 cases per 100,000 population. Low MS risk areas are centered around the equator, with less than 30 cases per 100,000 population and Medium MS risk areas are located in between with prevalence within a similar range **(4).**

Data from Middle East showed low to medium prevalence rate for MS among Arab countries. In 2006, the overall reported prevalence rate in Jordan was 39 per 100,000**.** Mutiple sclerosis is associated with the high rates of unemployment in Egypt The prevalence of MS in Egypt has been reported to be 13.7/100,000 and 25/100,000 in two studies, respectively.Egypt got the highest number of multiple sclerosis (MS) patients in the Middle East region with estimated number of 25,000 subjects. In 2018 there were 7,000 patients diagnosed and treated with high economic burden due to delay in both diagnosis and treatment adding to that financial burden **(5)**.

According to the MS International Federation, one of every 3,000 individuals worldwide has MS. In Egypt, 9,244 new cases are diagnosed annually (10 new cases/100,000 population/year). Egypt is one of the few countries where the reported prevalence of MS has tripled from 20/100,000 in 2013 to 59.7/100,000 in 2020. In view of that, one of every 1,500 Egyptians has MS . **(5)**.

Multiple sclerosis is three times more prevalent in women than men and this ratio may be increasing, In Egypt The female to male ratio is 2.57**(5)**. Gender differences is important in the progression and the inflammatory activity of the disease, Women experience more frequent relapses in RRMS forms, while men mount up disability faster, reach disability milestones more rapidly, and show poorer recovery after early disease relapse.**(6)**

Multiple sclerosis usually occurs between the ages of 20 and 50. In Egypt the Mean age is 31.87 years ,While mean age at onset of MS symptoms was 26.1 years (range 9–52 years), with a peak at age 20–29 years. **(5)**.

Pathogenesis and risk factors:

The pathogenesis of MS is complex and incompletely understood. It is an autoimmune disease with combination of both genetic and environmental risk factors. Understanding the immune-mediated mechanisms and the influence of genetic and environmental risk factors may help to further improve therapeutic approaches and prevent disease progression (**7).**

Defects in self-tolerance leads to autoimmunity in MS ,The loss of self-tolerance eventually leads to the generation of autoreactive T and B cells capable of producing pathogenic effector molecules that drive tissue destruction **(8)**.

Multiple sclerosis is a two-stage disease, with an early inflammation responsible for relapsing–remitting disease and a delayed neurodegeneration causing non-relapsing progression, i.e. secondary and primary progressive MS **(8)**.

Immune Dysregulation in the Development of Multiple Sclerosis

MS is a cell-mediated autoimmune disease directed against CNS myelin antigens that includes both CD4+ and CD8+ cells and autoantibodies may play a secondary role. Auto reactive T cells against the myelin components exist in normal individuals but not a disease and may even have a brain-protecting properties.

MS is stimulated when pathogenic Th17- and Th1-type and CD8 myelin autoreactive T cells are induced **(9).**

Immune-mediated mechanisms in the pathogenesis of multiple sclerosis

An important result in MS lesion is the disruption of the blood brain barrier (BBB), So understanding this barrier is essential to understand the pathogenesis of the disease. It is a functional and anatomical barrier separating the blood from neurons in the CNS. It consists of both the vascular wall, CNS astrocytes covering these with glia limitans, and the perivascular space in between. Inflammation is caused due to migration of leukocytes across post-capillary venules into perivascular space, then through the glia limitans into the brain parenchyma . **(10).**

Focal immune cell infiltration and their cytokines are the initial cause of damage in MS. The inflammatory infiltrates contain T-lymphocytes, dominated by MHC class I, restricted CD8+T-cells, B-cells and plasma cells are also present, although in much lower numbers **,** damage of Oligodendrocyte and demyelination occur as a result of inflammation. Axons are relatively preserved in the early stages of the disease , However, as disease progresses irreversible axonal damage occurs **(11)**

These lesions can disrupt the correct transmission of nerve impulses leading to neuronal dysfunction such as autonomic and sensorimotor defects, visual disturbances, ataxia, fatigue, difficulties in thinking, and emotional problems. **(11)**

T regulatory cell expressing the CD4, CD25, and forkhead box P3 (FoxP3)markers is the regulatory subtype of CD4+ T cells , Immunologically T_{reg} cell has the main role in secreting the transforming growth factor- beta (TGF- β) and IL- 10 cytokines, regulating the immune responses against infectious or cancers, suppressing the auto-reactive T cells, and maintaining the immunologic self- tolerance ,The Treg cell dysfunction in MS, followed by breaking down of self- tolerance, led to autoreactive T- cell suppression failure, myelin and neural destruction, then neuroinflammation **(12)**

In most autoimmune diseases, the ratio of Th17 and Treg cells determines the progression or protection outcome of disease. Studies showed that the imbalanced levels of Th17 and Treg cells, as well as the Treg cell dysfunctional, result in MS development **(12)**

Immunological studies proved that increased levels of Th1 and Th17 cells, higher levels of proinflammatory cytokines. The presence of auto reactive B cells, and dysfunction of Treg cell, supports the idea that the immune system plays a crucial role in MS and its progression. It has been proved that T-cell responses and their inflammatory products against myelin antigens have important role in MS pathogenesis by degenerating the myelin sheaths of central neurons **(8)**.

Th17 cells as well may further increase permeability of the BBB by disrupting the endothelial tight junctions by the secretion of IL-17 and IL-22, and through interactions with endothelium allowing further attraction of $CD4^+$ subsets as well as other immune cells. Consequently, initiating pathological cascade of inflammation, perivascular infiltrates and damage to neurons and glia cells **(10).**

Various dysregulated miRNAs, including miR- 17,miR- 27, and miR- 146a, are considerably associated with MS pathogenesis and its biological process. These miRNAs can regulate the responses of immune cells like Treg cells and change the presentation of target antigens. **(12)**

Immune mechanisms associated with relapse and remission:

Better understanding of mechanisms underlying RRMS has led to development of different disease-modifying therapies, reducing both severity and frequency of new relapses by suppressing or altering the immune system **(13)**

Systemic infections **(13)**, increased osteopontin, lower serum vitamin D (Vit D) levels, reduced interleukin-10-producing B cells, and finally decreased levels of terminally differentiated autoregulatory CD8þ T cells (CD8þ T_{regs}) are important factors for relapse.Despite the clinical difference between RRMS and progressive MS, pathological inflammatory changes are seen in both, but with an additional degree in relapsing–remitting disease. They are similar in the composition of the inflammatory infiltrate, with more proportion of B-cells and plasma cells in progressive MS **(11)**

In active lesions, which is the main in the relapsing–remitting stage of MS, low numbers of T cells are present during the prephagocytic stage of lesion formation at the sites of the initial tissue injury ,This inflammation is indicated by the infiltration of inflammatory cells into the CNS, resulting in intense damage to the blood–brain barrier (BBB), which has been confirmed with gadolinium-enhanced magnetic resonance imaging of lesions. **(14)**

Relapses are not always increasing processes, as protective counter regulatory mechanisms are activated in response to inflammatory demyelination to influence disease remission. Remission is associated with remyelination, especially during the early disease stages**.** By myelin internalization and subsequent induction of peroxisome proliferator-activated receptor b/d**,** proinflammatory M1 macrophages acquire an anti-inflammatory M2 phenotype which plays a crucial role in remission by removing myelin debris, and oligodendrocyte differentiation during the remyelination **(15),** So a shift in the balance of M1 toward M2 microglia /macrophages triggers remyelination.

Other important mechanisms which can promote remission included deposition of amyloid-forming proteins (aB- crystallin , A b, tau) which inhibits the proinflammatory cells at the neuroinflammation site, an increase in $CD_{4þ}$ CD25þ CD127 low Fox P3þ CD39þ T_{regs}**,** which inhibits Th_{17} expansion, increase in novel granulocytic myeloid-derived suppressor cells, which can decrease autologous CD4þ T-cell activation and proliferation through programmed cell death ligand-1; or other soluble mediators**.** With increasing the disease duration these relapses are more and more overlaid by the progressive disease process that leads to an irreversible accumulation of motor, sensory and cognitive deficits. This progressive phase of MS is still only incompletely understood **(16)**

Immune mechanisms associated with disease progression

Most cases convert over time to a secondary chronic progressive type of MS (SP-MS). While around 15 % of cases present with a primary progressive disease course (PP-MS) In which the relapsing stage is absent and the disease starts with uninterrupted progression from its onset. A small percentage of patients has a progressive relapsing MS disease course (PR-MS) with fast progressive type of disease **(17)**

Clinical progression in both (SP-MS) and (PP-MS) is widely suggested to begin at around 40 years of age and then proceed at approximately the same rate . It is widely suggested that an increasing axonal loss in white matter tracts of the brain and spinal cord is the major pathological substrate of progressive clinical disability **,**MRI findings suggest that inflammatory lesions become less prominent as MS enters the progressive phase, while neuropathology studies show the persistence of focal infiltrates of peripheral immune cells and actively demyelinating lesions **(17)**

Inflammation is frequently seen around vessels with intact blood brain barrier **(14)** The majority of active lesions in the progressive stage of MS differ from those lesions in patients with acute or relapsing MS by having an inactive lesion core, which is surrounded by a narrow rim of microglia activation and macrophages infiltration **(18)**

In the progressive stage cortical lesions arise where a lymphocytic inflammation is predominantly present in the meninges covering the demyelinating area, while perivascular and parenchymal T- or B-cell infiltrates are rare or absent. The relative contribution of B-cells and plasma cells is higher in patients with progressive MS. Subpial cortical demyelination is a specific feature of multiple sclerosis pathology, not present in other inflammatory diseases of the central nervous system **(14)**

Genetic and environmental factors involved in Multiple Sclerosis-associated immune dysregulation

Multiple sclerosis is an autoimmune inflammatory disorder of CNS of unknown etiology probably involves interaction between genetic, environmental, and other factors triggering an autoimmune attack resulting in damage to myelin and axons. Studies of the interactions between these two kinds of factors and their combined effects will lead to a better understanding of the etiology of MS. Although studies of epigenetic changes in MS have only begun in the last decade, a growing body of literature suggests that epigenetic changes may be involved in the development of MS, possibly by mediating the effects of environmental risk factors such as **EBV infection** , **smoking**, and **vitamin D deficiency (19).**

The prevalent suggestion of **genetic risk** is that there is a number of different genes increase susceptibility to the disease (i.e. MS is a polygenic disease) Genes. within the HLA complex are the strongest genetic risk

,factors for MS. The HLA class II and I genes are particularly relevant modifiers of disease risk. Variants of class II genes encode products that present. antigens to CD4+ T lymphocytes, and class I products present antigens to CD8+ lymphocytes **(20)** .

Epstein-Barr virus is one of the strongest risk factors for MS with**.** Primary EBV infection at an early age is typically asymptomatic, but primary .infection during adolescence or adulthood often shows as infectious mononucleosis, which has been associated with a two- to threefold increased risk of MS **(21)**

Smoking is a risk factor for the development, severity, progression, disability, and early death in MS. Tobacco contains high amounts of free radicals which can cause mutations in genetic material. Cigarette smoke acts on the cellular level of the immune system, resulting.in the development. of proinflammatory cytokines (**22)**

Smokers have high levels. Of. proinflammatory cytokines (e.g., IL-6), higher levels of. C-reactive protein, fibrinogen, and other inflammatory markers contribute to .persistent autoimmunity. People with MS have higher levels of NO, which .can cause mitochondrial damage, oligodendrocyte necrosis, and axonal degeneration, eventually leading to impairment in axonal conduction , Also the Exposure to harmful gases like carbon monoxide (CO) affects tissue oxygenation and can lead to demyelination **(22)**

Another recognized environmental risk factors of MS is Vitamin D deficiency. Hypovitaminosis D may increase the immunological stigmata of a past infection with EBV or increase susceptibility to the disease with the coexistence of some HLA groups **(23)**

The effect of vitamin D on the immune response in general could be an amplification of innate immunity combined with regulation of adaptive immunity **(23)**

Activated T and B lymphocyte and Macrophages cells contain vitamin D receptors and vitamin D appears to control activation of human T cells, regulatory T lymphocyte cells and cytokines play main roles in autoimmunity.1,25-dihdroxycholecalciferol inhibits in vitro production of inflammatory cytokines and stimulates the development of regulatory T lymphocyte cells expressing cytotoxic T lymphocyte antigen 4 (CTLA-4) and forkhead box P3 (FoxP3), leading to an anti-inflammatory effect This approves different valuable immunological effects previously reported using $1,25(OH)_2D$ in vitro **(23)**

Common presentations of MS:

Optic Neuritis

20 % of multiple sclerosis patients have their early presentation as optic neuritis, and 50 % of patients with multiple sclerosis can ultimately present with optic neuritis during the course of the disease **(24)**

Myelitis

Inflammatory lesions of the spinal cord usually appear as acute partial transverse myelitis (APTM) with rapid onset and tend to show asymmetric neurological signs. APTM may be the first manifestation of MS, it also may remain the only neurological effect during life or recur as relapsing myelitis. The possibility of developing MS was shown to be higher after APTM than after optic neuritis **(25)**

Brainstem syndromes

Brainstem syndromes can present with oscillopsia, diplopia, vertigo ,facial sensory loss, and dysarthria. Typical findings include an isolated sixth nerve palsy, gaze evoked nystagmus or an internuclear ophthalmoplegia. While Bilateral internuclear ophthalmoplegia is pathognomonic of MS (**26)**

Motor symptoms

Tremor is a major component of multiple sclerosis (MS), effecting between 25% to 58% of the patients with MS**.** After tremors, paroxysmal dystonia is the second most commonly seen movement disorder in MS Also known as tonic spasms, these episodes consist of abrupt onset and stereotyped involuntary dystonic posturing. **(27)**

Sensory impairment

Dysesthesia is the term used to describe unpleasant cutaneous symptoms without any primary skin condition such as burning, tingling, anesthesia, itching, and pain. Dysesthesia which involves the trunk or extremities caused by lesions affecting the posterior column of the spinal cord, while that which attacks head and face are caused by lesions affecting trigeminal or occipital nerves **(28)**

Imbalance

The cerebellum and its afferent and efferent pathways are commonly affected in MS**.** Cerebellar signs and symptoms represent the principal clinical manifestation in 11–33 % of patients with MS. It may cause a wide range of signs and symptoms including tremor, truncal ataxia , gait, slurred speech, incoordination of voluntary movements, different kinds of nystagmus, ocular dysmetria, and an inability to perform rapid alternating movements properly (dysdiadochokinesia). Patients may have one or a combination of signs and symptoms depending on the extent of involvement. Also, patients who show clinical signs of cerebellar damage early in the disease course tend to develop more quickly severe disability. **(29)**

Cognitive impairment

45% frequency of cognitive impairment was found in MS. Cognition represents the function of several neural pathways involved in the processing of information in the brain, including several cognitive domains such as executive function, perceptual-motor function, learning and memory, complex attention, language, and social cognition, as defined by the Diagnostic and Statistical Manual of Mental Disorders 5th edition **(30).**

Depression

There is evidence that depression is more prevalent in persons with MS than in the general population of U.S. adults. The lifetime prevalence of depression in patients with MS ranges between 24% and 54% **(31)**

Fatigue

Fatigue occurs in 75–95% of MS patients and has a substantial negative effect on the quality of life of patients **(32)**

Bladder and bowel dysfunction

Neurogenic bowel dysfunctions in the form of functional constipation and/or fecal incontinence are seen in up to 73% of MS patients**.** Adult neurogenic lower urinary tract dysfunction, is a result of the demyelinating damage to the central nervous system, including the brain and spinal cord. This may result in lower urinary tract symptoms including voiding symptoms including (urinary incontinence, urgency, and nocturia),or storage symptoms as(urinary retention, urinary hesitancy, sensation of incomplete emptying, and frequency) , or both of them. By 10 years of disease duration, 80% of Patients with MS report some degree of bladder/bowel dysfunction, While 22% report moderate or severe dysfunction **(33).**

Heat sensitivity

Increase in body temperature in MS results in transient worsening of clinical symptoms**.** Between 60 and 80% of individuals affected by (MS) experience heat sensitivity or Uhthoff's phenomenon, a characteristic transient worsening of clinical symptoms resulting from an increase in body (core) temperature of as little as 0.5°C . It consists of visual disturbances during or after the elevation of body temperature. Uhthoff's phenomenon is a reflection of ineffective transmission of electrical impulses due to impaired myelin functions triggered by routine daily life activities, such as light physical work, exercise or exposure to sunlight **(34)**

Headache

Several studies showed that headache is more common in (MS) with prevalence in patients with MS higher than 50%. Especially migraine and tension-type headache are the most common primary headaches reported in MS patients **(35).**

Diagnosis of MS:

The first physician who described the clinical features for MS was Jean-Martin Charcot by a triad of intention tremor, Nystagmus, and scanning speech presented in 1868. For many years Charcot's triad was thought to be characteristic of MS. But turned out, that this group of symptoms typically occurred in the advanced stages of the disease, and also appeared in other neurological disorders, particularly those associated with damage to the cerebellum. Schumacher developed the first modern diagnostic criteria for MS **(16)** Then Poser et al. created a new diagnostic criteria for MS in 1983 for clinical trials. Poser criteria allowed the clinical diagnosis of MS to be made if there were at least two relapses (dissemination in time) (DIT) and if there was clinical evidence of damage to at least two structures of the CNS (Dissemination in space) (DIS).**(36)**

In 2001, Ian McDonald developed a new criteria for diagnosing MS, which is now known as the ‘‘McDonald criteria’’ That replaced the Poser criteria and started the use of MRI as a central tool in the diagnosis of multiple sclerosis. It demanded evidence of dissemination of lesions in both space and time which could be proved clinically or by MRI reinforced by other paraclinical diagnostic methods like cerebrospinal fluid examination to enable the diagnosis of multiple sclerosis in patients with different clinical presentations. In the 2005 revision of the McDonald criteria of 2001, DIT diagnosed with MRI scan, which was performed at least 30 days (instead of 90 days in the 2001 criteria) **(37)**
Then the major accomplishment of the 2010 revision of the McDonald criteria was that MS can be diagnosed with a single baseline MRI at the time of first clinical manifestation **(25)**
In the 2017 revised McDonald criteria is oligoclonal bands was taken as a substitute for DIT, therefore, can be used to start the diagnosis of multiple sclerosis after the first clinical event and a single brain MRI **(38)**
Also the 2010 McDonald criteria did not allow symptomatic spinal cord or brainstem lesions to prove DIT or DIS to avoid what is called double counting. Since several studies showed that the inclusion of symptomatic lesions increased the diagnostic sensitivity with slight affection on specificity **(38)**

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