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Multiple sclerosis: New insights and trends

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ABSTRACT

Multiple sclerosis (MS) is the most famous autoimmune disease attacking the central nervous system. It attacks people from age 20–50 years old and the females' attacks double than males' attacks. MS is an autoimmune disease affecting principally the central nervous system that cause nerve sheath demyelination followed by axon damage and paralysis. MS symptoms include muscle weakness, weak reflexes, muscle spasm, difficult in move, miss-coordination and unbalance with others. There are many factors may be responsible for MS: microbial, viral, smoking, stress, environmental toxins, contaminated diet, and gout. MS is wide spread in the populations in North Europe and this related to lack of vitamin D due to decrease of sunlight exposure. MS biomarkers include nitric oxide, interleukin-6, nitric oxide synthase, fetuin-A and osteopontin. MS is not a genetic disease where MS occurs when human leukocyte antigen system related genes are changed in chromosome 6. The physiology of MS is monitored by activation of immune-inflammatory, oxidative, and nitrosative stress pathways. MS is including two main steps: (1) myelin sheath destruction and formation of lesions and, (2) inflammation. Four types of MS can be distinguished: relapsing-remitting, primary progressive, secondary progressive and progressive relapsing. Nine treatments have been accepted for relapsing-remitting MS type: interferon β-1a, interferon β-1b, mitoxantrone, natalizumab, glatiramer acetate, fingolimod, dimethyl fumarate, teriflunomide, and alemtuzumab, however, the only treatment used is mitoxantrone for progressive MS but many of MS treatments side effects are recorded. Complementary treatments also used in MS treatments such as: vitamin D, Yoga, medicinal plants, oxygen therapy, acupuncture and reflexology.

1. Introduction

Scientist Jean-Martin Charcot is the first one who discovers the disease in 1868 [1]. It is most famous and pronounced autoimmune disease attacks the central nervous system [2]. According to world health organization reports in 2008; actually 2–2.5 million with multiple sclerosis (MS) disease were recorded in the world [3], and approximately 20000 MS patients died all over the world in 2012 comparing to 12000 died in 1990 [4]. MS starts attacks people from age 20–50 years old and the records investigated that females' attacks double than males' attacks [5,6]. Disseminated sclerosis and encephalomyelitis disseminate are two alternative names of MS. The MS is autoimmune disease combined both genetic and environmental factors such as viral-induced immune disturbances [7]. There are many types of MS, sometimes occurring in isolated neuron (relapsing type) or spreading to few or many neurons (progressive type) [8]. The MS characteristic features are common disability, moving limits, low personal activity-related self-effectiveness, limitation of self-regulatory concepts, socio-demographic factors restrictions, decline employment state, and decrease educational level [9]. The MS symptoms may occur and disappear completely where the permanent neurological problems happen when the disease timely advances [8]. MS symptoms occur when the nerve cells myelin sheath in the central nervous system (brain and spinal cord) start to injure and consequently damaged. MS is associated with many symptoms and these include: physical, mental, and sometimes psychiatric disturbances [10–12], due to the neural damage occurs which block the communication among different parts of the nervous system.

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The mechanism responsible for MS to be appeared can be summarized into two reasons: (1) the immune system destructed the myelin sheath, and (2) failure of the myelin-producing cells to produce new sheathes [13]. The two above mentioned two reasons include numerous genetics and environmental factors *e.g.* heredity, pollution, microbial and viral infections [11,14,15]. The MS is diagnosed depending on the present patient status and the medical check-up investigations.

There are endogenous repair mechanisms to improve from MS disease early phases and these repair mechanisms contains inside local factors control these mechanisms. The natural killer (NK) cells are quickly moved to the organs defined by auto-immunity and NK increasing numbers when inflammatory case occurs. The NK cells are recalled in the brain subventricular zone during the progressive type of MS in both humans and MS animal model. These NK cells are establish very close sub-ventricular zone neural stem cells (NSCs) so consequently the cells begin to secret interleukin-15 and maintain the NK cells function. Furthermore, the NK cells decrease the functional capability of NSCs following MS inflammation so neurorepair is found due to communication of both NK and NSCs cells [16]. There are different types of upper limb rehabilitation can be found in MS incidence and a training program is run directed toward the upper limbs improve limb function and structure but cannot effect on the upper limb capability and performance in MS patients [17].

There is no treatment for MS until now. All the MS treatments try to attempt to improve the neuronal function following MS occurs and stop any progress of the disease [11]. The use of MS treatments in the early stage of MS can induce adverse side effects and can be ineffective at all. The treatments with good results are observed in teenager women where MS appears early with relapsing type with few neurons damaged [18]. MS decreases life with an average 5–10 years than other healthy ones [10,19]. There are many treatments and diagnostic procedures of MS are in the process of development.

2. MS symptoms

MS is an autoimmune disease affecting principally the central nervous system (brain and spinal cord) that cause nerve sheath demyelination followed by axon damage and consequently paralysis [20]. There are many and distinguished lesions found in the lower urinary tract as pronounced symptoms in MS patients [21]. On the other hand, MS is a major important reason of disability of a neurological origin in the young adults where depression is the most observed psychiatric disorder in MS [22]. Central and peripheral auditory disturbances are always appeared in MS [23]. On the other hand, the typical optic neuritis is usually the presenting symptom of MS [24]. The sleep disorder, exhaustion, and pain interfering are among other symptoms associated with MS [25].

MS symptoms depend on the specific nerve attack in the central nervous system and may lead finally to loss of sensitivity in sensation such as muscle weakness, weak reflexes, muscle spasm, difficult in move; miss-coordination and unbalance with others; problem in speech, optic problem, feeling tired, acute or chronic pain, and bladder and bowel difficulties. Depression is always associated with MS due to variable mood of MS patients. In addition to, thinking and emotional problems are also observed in MS. There are many factors increasing MS disease symptoms *e.g.* viral infections such as cold, influenza, and gastrointestinal problems. Females are more sensitive to MS than males especially during 3 months after baby birth. Other factors do not effect on MS to be found such as vaccination, breast feeding, and physical status [10,25,26]. The expanded disability status scale (EDSS) is a well-known test of MS-associated disability, in addition to, other clinical investigations [27,28]. Stress also is a main cause of MS [29]. Figure 1 reveals MS main symptoms [30].

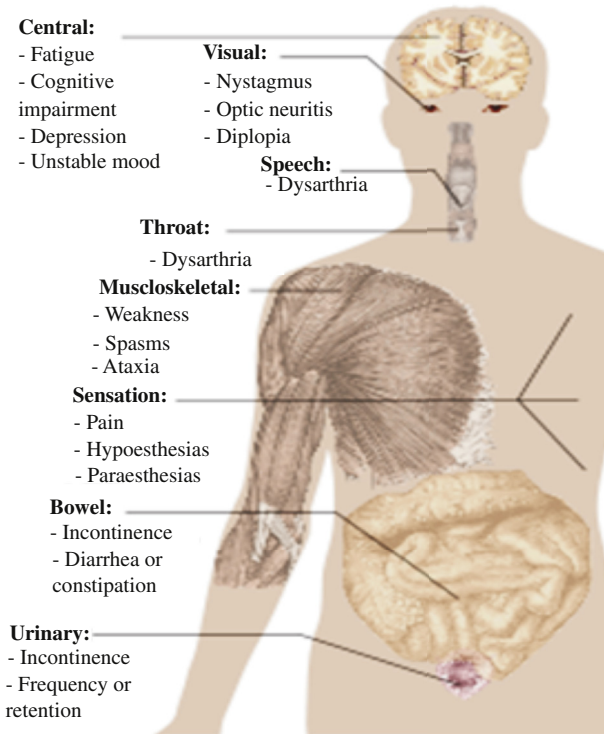

Figure 1. MS main symptoms [30].
https://en.m.wikipedia.org/wiki/Multiple_sclerosis

3. MS causes

Up to date, there are no reasons for MS incidence, however, there is a combination of environmental and hereditary factors including pollution, viral and bacterial infections, and stress may be included. There are many factors may be responsible for MS and these factors can be summarized into: microbial, viral and other infections.

3.1. Microbial infection

The infection with microbes has been associated in the main processes of introducing and increasing the incidence of MS [34]. MS can be induced by many microbes [11], where moving from one place to another increase microbial infection to induce MS [14,15].

The infectious disease (paratuberculosis) mainly affects wild and domestic ruminants. This disease induced by *Mycobacterium avium paratuberculosis* (MAP), where MAP correlated to MS incidence. The MAP DNA was found in 4/7 (57.14%) goat, and in 14/25 (56%) sheep cheese using qPCR. In goat, MAP produced type S strain of MAP, and this MAP occurs in quantities ranged from 1.8×10^4 to 6×10^4 MAP cells/g of cheese. In this study, 56.57% and 66.60% of cheese tested showed positive results for MAP and these can lead to increased incidence of MS in human [35].

The mechanism of MS induction can be related to hygiene hypothesis and prevalence hypothesis. The hygiene hypothesis assuming that microbial infection in early life is protective but MS responses later to the early infection at the later person life [10], while the prevalence hypothesis proposed that MS is due to infection factors found in the region where a high proportion of MS patients were recorded among population [14,15,36]. The results obtained from MS patients support the hygiene hypothesis other than the prevalence hypothesis [14,15].

3.2. Viral infection

Three evidences supported viral infection in MS: (1) presence of oligoclonal bands in the central nervous system fluid in MS patients; (2) many viruses related to human demyelination encephalomyelitis; (3) viral infection induced demyelination in animals also [37]. The lymphocytic choriomeningitis virus is the virus responsible for MS symptoms. The spreading of is depending on MS concentration in the temperate zone, higher occurrence away from the equator, and increased occurrence in proximity to regions of highest MS rate, on the other hand, there is no data about person-to-person transmission in MS incidence [7].

3.3. Other infections

MS can be induced also by smoking and stress [14,15,38]. Environmental toxins may be also induced MS especially exposure to solvents [38,39]. Contaminated diet and hormonal intake may be related to MS [14,15]. Gout disease is not reported in MS patients with lower uric acid levels in MS which suggested a protective role of uric acid in MS [40]. MS can be also induced through the dysregulation in the neurovisceral incorporation of cardiovascular tone which can lead to many MS-associated clinical symptoms. The MS neurodegenerative and inflammatory progresses are disturbed and can lead to the appearances of cardiovascular autonomic nervous system dysfunction [41].

4. MS geography

MS is wide spread in the populations found in North Europe and this related to lack of vitamin D due to decrease of sunlight exposure so the child born in May in North Europe has more resist to MS than the same child born in November [14,15,42,43]. This explained that the MS is presently the most common, and a growing, main reason of neurological disability in young adults in the Western world. The relation between vitamin D and MS incidence are affected by a rise of MS incidence, a month of birth effect, a relation of vitamin D with MS-associated genes and this lead to a fact that high vitamin D levels associated with a reduced MS risk [44]. There is a relation between places of birth and MS so if the person travels to MS high risk region before 15 years old increase his sensitivity to MS attack than the same person travel after 15 years old [10,38]. In 2010, MS patients was 2–2.5 million (30 MS/100000) all over the world with rates varying according to different regions as follow [3], in Africa, MS rates less than 0.5/100000; in South East Asia, MS rates 2.8/100000; in USA MS rates 8.3/100000; in Europe MS rates 80/100000 and MS rates increase to 200/100000 in Northern European countries [5,14,15,38].

MS symptoms usually occurs in late twenties and early thirties patients but it can in child and older patients over 50 years of age [3,5]. In child and youth patients, MS occurs in females twice than males but in older patients above 50 years old, MS appears equal in both males and females [45]. It explained the geographical spreading of MS and its higher ratio incidence in the northern places in Tehran, Iran and this may be correlated to higher socioeconomic status of this places [46]. Macroscopic and microscopic methods are used to determine the occurrence and incidence of MS. Most studies have focused on prevalent cases of MS but studies of MS variation are more related for MS causes understanding. There are 30 and 26 regions are detected MS incidence in Manitoba, Canada; where three methods of detection are used: (1) the circular spatial scan statistic, (2) the flexible spatial scan statistic, and the Bayesian disease mapping (BYM) where the BYM method is the most effective method than circular spatial scan statistic and flexible spatial scan statistic methods; where BYM method can at the same time detect the geographical differences and MS disease control [47]. In another study, the German statutory health insurance reported 200000 identified with MS in Germany in 2014. MS incidence is higher than expected where ≈49% of all MS patients taken MS-specific drug treatments. MS patients live in the east taken an average 30 daily doses per year less than MS patients live in the western part. There are a regional difference found in MS incidence and drug treatments [48].

The MS spreading in England is recorded by General Practice Research Database where the MS percentage increased annually by 2.4% however the MS equal to 285.8/100000 in females and 113.1/100000 in males in 2010 although the British government planned to decrease MS attacks to be 11.52/100000/year in females and 4.84/100000/year in males by 2010. Females recorded 72% of MS incidence and males equal to 71% of MS incidence. The highest MS incidence percentage occurs in Scotland in the UK where 126669 MS patients are recoded in the UK in 2010 (203.4/100000 population) [49]. Figure 2 shows MS disability-adjusted life year for MS/100000 inhabitants in 2004.

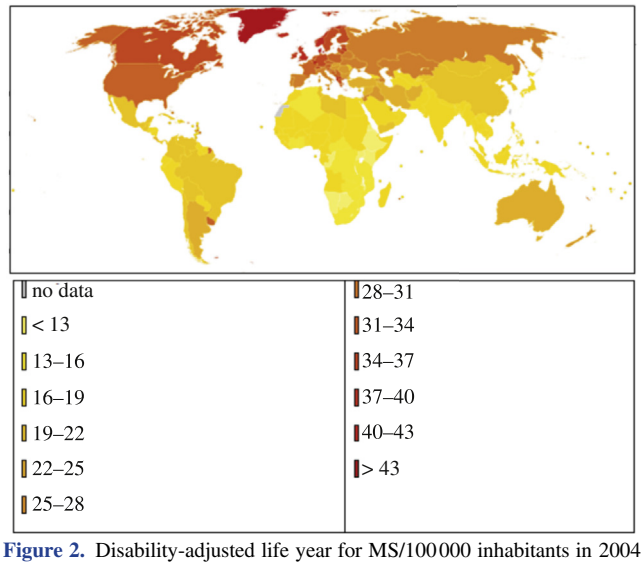

Figure 2. Disability-adjusted life year for MS/100000 inhabitants in 2004 (Data from Death estimates for 2004 by cause for WHO Member States (Persons, all ages), Multiple sclerosis world map. https://en.m.wikipedia.org/wiki/Multiple_sclerosis

5. MS biomarkers

Many laboratory markers play an important role for MS diagnosis such as: nitric oxide, interleukin-6, nitric oxide synthase, fetuin-A and osteopontin. Proteins represent nerve cell injury *e.g.* N-acetylaspartate and neurofilaments are also include for MS markers [50]. Moreover, interleukin-4, ferritincarbonyl protein, interleukin-10, interferon-γ, interleukin-17, tumor necrosis factor-α (TNF-α), plasma lipid hydroperoxides are among MS biomarkers used [51]. The magnetic resonance imaging (MRI) and positron emission tomography techniques can be also used as MS markers [52], but MRI technique facing many problems when apply in clinical application such as: magnetization transfer, double-inversion recovery sequences, functional magnetic resonance imaging and diffusion tensor [53]. On the other hand, there are other techniques are under development such as: (1) technique measure inflammatory markers, nerve dysfunction, and macrophages levels, (2) technique measure iron excretion from the body, and (3) technique measure cerebral perfusion [53] in MS patients (4) radioactive tracers technique measure change in cortical pathology, apoptosis, remylienation process and brain inflammation [54], and (5) technique measure antibodies against potassium channel are under advanced [55]. Figure 3 exhibits MRI technique as MS marker [31].

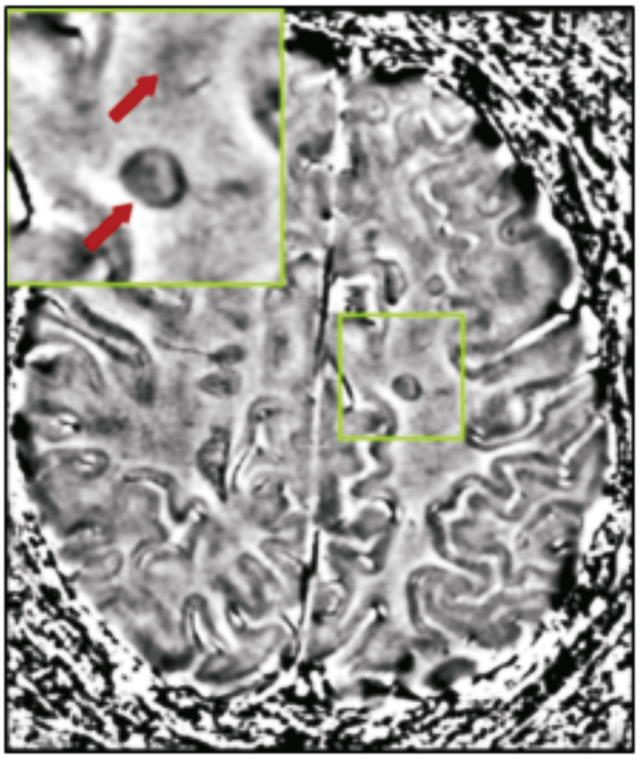

Figure 3. MRI technique showing an iron deposit in a white matter lesion (inside green box in the middle of the image [31].
https://en.m.wikipedia.org/wiki/Multiple_sclerosis

6. MS diagnosis

MS diagnosis related to patients' symptoms, MRI and laboratory results [56], but MS can only diagnosed in late phase [10,57]. The most known MS diagnosis is McDonald criteria which combined laboratory, clinical and radiology reports of lesions at different times in different body areas [3], in addition to, Schumacher and Poser criteria which the oldest known one [58]. The cerebrospinal fluid analysis, physical patients' characters, and MRI are the most common diagnostic method. MRI of the brain and spinal cord reveals the demyelination area in MS where gadolinium injected intravenously to discriminate the lesions areas [59,60]. MS associated inflammation can be detected by cerebrospinal fluid investigation where immunoglobulin G tests are done where immunoglobulin G inflammation marker occurs in 85% of MS patients [59,61]. MS is always associated with visual and sensory disturbances so optic and sensory clinical investigations are important diagnosis in MS symptoms [62].

7. MS genetics

MS is not a genetic disease although there a lot of genetic changes are responsible for MS symptoms [63]. MS increases among the family of MS patient [11], however, MS rate increases to 30% in identical twins while the rate 5% in non-identical twins [10,64]. MS risk equal to 10 times higher than normal in child in the case of both father and mother is affected [5]. MS occurs when human leukocyte antigen (HLA) system related genes are changed in chromosome 6 [10]. HLA system related genes in chromosome 6 are related to other autoimmune disease *e.g.* diabetes type I. The recent hereditary researches proved that at least twelve genes outside HLA in chromosome 6 are related to MS [65]. Pharmacogenetic-related studies have been developed to treat MS, however, interferon-β and glatiramer acetate showed the most successively, long-action and safety drugs used in the therapy of MS all over the world [66,67]. The omics technique and researches with microRNAs have been done for discovering the change in protein structure related with molecular mechanisms of MS so many biomarkers can be developed and used in MS diagnosis. The proteomic researches are preceding for detection of MS biomarkers found in the biofluids due to different physiological processes occurred in MS incidence. The microRNAs are very important complementary biomarkers correlated to cellular damage occurring in MS patients [68].

The higher MS relapse incidence is recorded during warmer months in different regions of the world so MS incidence is correlated into cytokines secretion in different seasons. The production of cytokines (interleukin-10, interleukin-6, and TNF-α) are recorded in spring season and the cytokines secretion increases from spring to summer particularly TNF-α and these observations can help us in understanding the higher MS-clinical activity [69].

Exogenous retroviruses are invaded into human cells so they become part of human DNA and spreading over many generations and transformed into human endogenous retroviruses (HERVs). The HERVs are silenced or expressed at low-levels, but in some physiological disturbances circumstances such as MS, HERVs expression becoming than normal cases. There are three HERV are correlated to MS: (1) HERV-H, (2) HERV-K, and (3) HERV-W. The MS-associated retrovirus protein envelop (MSRV) from HERV-W is the strongest one in the initiation of MS among the three above mentioned retroviruses [70]. The MSRV performs two functions: (1) MSRV expression in the peripheral immune cells, and (2) MSRV expression in monocytes and microglia in central nervous system lesions in MS patients, so it increases toll-like receptor 4 which stimulates cytokines secretion, declines myelin protein expression,

and destroyed oligodendrocyte precursors [70]. Figure 4 reveals HLA region of chromosome 6 [32].

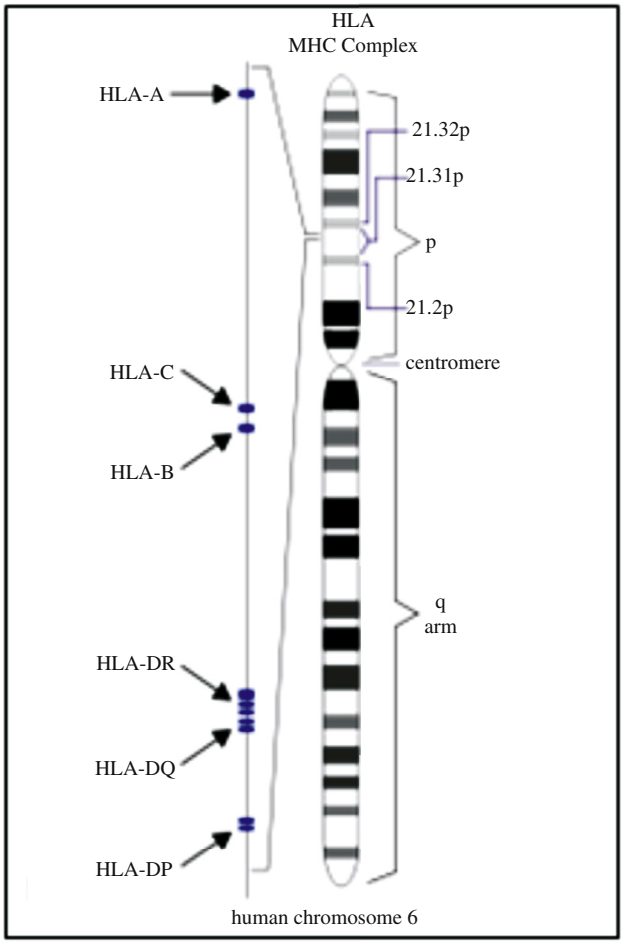

Figure 4. HLA region of chromosome 6. Changes in this area increase MS probability [32].
https://en.m.wikipedia.org/wiki/Multiple_sclerosis

8. MS physiology

The patients with MS have a physiological disturbances which lead to many of physical, mental and clinical disorders such as (1) deterioration of body composition (changes in fat and bone mass), (2) increased risk for diseases such as coronary artery heart disease, non-insulin dependent diabetes mellitus, lipid metabolism abnormalities, and osteoporotic fractures in these patients. MS immobility leads to a changing pattern of loading in the paralyzed areas, and secondary alteration in tissue structure. However, bone and soft tissue changes in these patients are usually reported so the treating physicians must increase the awareness of MS patients with respect to bone, bone and fat loss, and their consequences aiming to obtain measures to prevent bone and soft tissue loss in these patients [71].

The physiology of MS is monitored by activation of immune-inflammatory, oxidative and nitrosative stress pathways. These pathways include interleukin (IL)-1β, IL-4, IL-6, and IL-10; peroxides; nitric oxide metabolites (NOx); albumin; ferritin; C-reactive protein; and TNF-β and gadolinium-enhanced MRI scan [72]. In a study comprises MS patients with depression ($n = 42$) and MS patients without depression (n = 108) and normal healthy (n = 249). MS incapacity is measured using EDSS while depression in MS is evaluated using depressive subscale of the Hospital Anxiety and Depression Scale in addition to the above mentioned biochemical parameters. There are an increase in IL-6 and decrease in IL-4 and albumin beside gastrointestinal disorders and disease development in MS patients with depression compared to MS patients without depression, in addition, there is no relation between depression in MS patients and oldness, body weight index, MS form, gender, MS persist, and nicotine addiction, in the contrary, MS with depression is related to MS development, peripheral inflammation, optical and gastrointestinal disorders compared to MS patients without depression [72].

The neuroactive steroids control and communicate the physiology of the central and peripheral nervous system. They exert neuroprotective effects and represent interesting and promising trends for the therapeutic plans in MS disorders. The sex variances in the neuroactive steroids levels are identified not only under physiological conditions but are also detected in a sex-dependent way in different physiological variations in MS. The neuroprotective effects of neuroactive steroids, communicate with the sex variation to control the neuroactive steroids levels and this concept represents the basic to discover and produce a specific neuroactive steroids used in neuroprotective treatments [73].

The depression scores in MS patients were inversely correlated with: (1) the activity in the subgenual cingulate cortex; (2) the functional connectivity between the hippocampus, orbitofrontal cortex and the dorsolateral prefrontal cortex, and (3) the functional connectivity between the amygdala and dorsolateral prefrontal cortex. So the individual variation in depression in MS patients is significantly correlated with altered regional activity and functional connectivity shapes within the limbic system [74].

There are a relation between antiphospholipid antibodies and MS where three non-classic antiphospholipid antibodies are dominant in MS patients compared to healthy control ones. These antibodies contain immunoglobulin M and immunoglobulin G (IgG) against phosphatidylserine-β2GPI (PS-B2), IgG prothrombin complex (PT–PT) and immunoglobulin M prothrombin (PT). The good results obtained from different antiphospholipid antibodies are PS-B2 IgG and PT–PT IgG. All other antiphospholipid antibodies did not show any difference between the MS patients and healthy control groups so consequently a relation has been found between certain non-classic antiphospholipid antibodies and MS incidence [75]. Tobacco smoke induced changes in blood brain barrier physiology and function and so caused major destruction on blood brain barrier mechanisms such anti-inflammatory and immunity pathways [76].

The mechanism responsible for initiation of lesion in MS still undistinguishable, where there are two distinguished neuropathological results have been found as an early physiological process of MS: (1) microgalial nodules, and (2) newly forming lesions. Both microgalial nodules and newly forming lesions do not contain T cell infiltration or demyelination [77]. There are small number of aggregated macrophages/microglia due to damaged axons were reported in microgalial nodules result but the oligodendrocyte apoptosis is the pronounced characteristic step in the formation of new lesions. Both microgalial nodules and newly forming lesions are mutually and synergistically cooperate to induce MS [77].

The helper 1 cells, Th17, and regulatory T cells (T_{reg}) are produced by cytokines secreted in MS incidence. Many genes'

mutations and expression are changed by interferon-β 1b where 19 different genes in relapses-remitting MS are changed before and at 6, 12, 24, and 36 months of interferon treatments. All kind of microRNA is changed during the interferon therapy where higher interleukin-12Rβ2 mRNA levels were correlated with decrease risk of MS relapse [78]. Figure 5 shows physiological sequences of MS incidence [33].

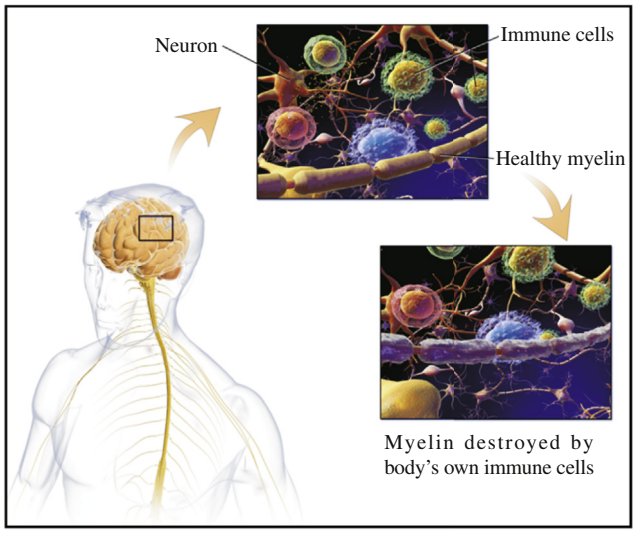

Figure 5. Physiological sequences of MS incidence [33]. https://en.m.wikipedia.org/wiki/Multiple_sclerosis

MS is including two main steps: (1) myelin sheath destruction and formation of lesions in the central nervous system (brain and spinal cord), (2) inflammation. The two steps are synergistically communicate together to destroy the neuron tissue and lead to MS [10]. In the other side, MS is an immune disease that appears due to collaboration of person hereditary and environmental factors [11]. Destruction of neuron tissues is occurred due to attacks from individual own immune system [10].

8.1. Myelin sheath destruction and formation of lesions

MS name means many injuries that found inside the nervous system and these lesions occurred in the white matter inside the visual neuron, basal ganglia, brain stem, and spinal cord. The lesions may be found in the white matter tracts very near to the lateral ventricles [10]. The white matter cells transfer neural signals from grey matter area where information is collected into the whole body, on the other hand, there is no lesions formed in the peripheral nervous system [11].

Oligodendrocytes (cells create and maintain myelin sheath of the neuron that transfers neural signals) are destroyed in MS [10], so consequently the destruction of myelin sheath have lead finally to break of the nerve axon. The destruction of myelin sheath lead to no electrical signals transfer [11], and a repair process is occurred in MS early phase this process named remyelination but oligodendrocytes in MS advances cannot rebuild the cells of myelin sheath and many lesions increases in the central nervous system and finally remyelination process is ineffective and many lesions appear covering damaged axon of the neuron [79]. The resulting lesions are responsible for MS symptoms [10]. There is an increase in astrocytes number synergistically with the increase of lesions number, where astrocytes accomplish many biochemical processes that maintain the endothelial cells the form the blood–brain barrier, facilitate the nutrients transfer to the nervous tissue, support the maintains of ion balance, and an important role in repair process of brain and spinal cord [80].

8.2. Inflammation

Inflammation occurs simultaneously with the demyelination process where T cells of the immune system causes inflammation [10], however, T cells direct into the brain through interruption in the blood brain barrier where T cells consider myelin sheath as a foreign body and began to attack it and these cells named "autoreactive lymphocytes" [11].

Demyelin of neuron sheath stimulates inflammatory processes to be activated and consequently immune cells begin to release more cytokines and antibodies which causes more damage of blood brain barrier and leading to activation of macrophages and more activation of cytokines and other destructive proteins [11]. Inflammatory processes decrease the information transfer in the central nervous system through: (1) cytokines and antibodies released halt neurotransmitters produced by directed attack neuron, (2) cytokines and antibodies produced increase destruction of myelin sheath, and (3) increase cytokines and antibodies in the body lead to axon damage totally [10]. The cytokines are important causes in the initiation of many immune refluxes. The interleukin-21 represents one of the major immune factors, inducing many immune refluxes by affecting on many immune cells. The interleukin-21 caused increased in autoimmunity through different mechanisms, such as improvement and increased of helper T-17 and follicular helper T (T_{FH}) cells, initiation of NK cells, increasing B-cell differentiation and antibody excretion and decreased of regulatory T (T_{reg}) cells. Furthermore, interleukin-21 has been induced of autoimmunity process to be increased when treatment of MS patients with alemtuzumab has occurred [81].

The inflammatory and apoptotic processes found in MS patients at the peripheral and central nervous system levels play an important role in MS symptoms. There are a link between MS phenomena and inflammatory and apoptotic processes occurring in either the periphery or in the central nervous system in MS [82].

9. MS types

Four types of MS can be distinguished depending on MS duration and future MS progression; this MS classification is important for treatment which is determined by US National MS Society [8]. However, International MS panel in 2013 added another two types: (1) clinically isolated syndrome, and (2) radiologically isolated syndrome, but the four types are still the main basic types [83], as follows: relapsing-remitting; primary progressive; secondary progressive, and progressive relapsing.

9.1. Relapsing-remitting type

Relapsing-remitting type refers to unobservable relapses staying for months or years of silent remission without any MS symptoms. MS signs observed are resolved and this type named benign MS with low disability [84], but in 40% cases of this type, the disease is developed to MS [10,57], and this type named malignant MS with high disability [85]. Benign MS named clinically isolated syndrome where demyelination found without any MS symptoms [10,86], but 30%–70% of clinically isolated syndrome developed into MS [86].

9.2. Primary progressive type

Primary progressive type includes progression of MS disability and slight improvement of MS symptoms [8]. The relapsing-remitting type (10%–20%) developed into the primary progressive type [45,56]. The relapsing-remitting type takes nearly 10 years to convert into the primary progressive type [10].

9.3. Secondary progressive type

The patients with relapsing-remitting MS (65%) developed into secondary progressive MS with progressive neurological decrease without any remission [8,10]. This type has observable relapses and slight remission [8], but the time spend from relapsing-remitting MS to be secondary progressive MS nearly 19 years [87].

9.4. Progressive relapsing type

Progressive relapsing type includes persons who have a stable neurological decrease and in the same time have also obvious MS attacks. This type is the lowest common type of MS types [8].

10. MS treatments

10.1. Relapsing-remitting MS

In 2014, nine treatments have been accepted by governing organizations for relapsing-remitting MS type: (1) interferon β-1a, (2) interferon β-1b, (3) mitoxantrone, (4) natalizumab, (5) glatiramer acetate, (6) fingolimod (7) dimethyl fumarate, (8) teriflunomide, and (9) alemtuzumab.

The interferons and glatiramer acetate are the best treatments used now [56], and both are effectively equal in decreasing MS relapses by 30% [64]. However, both of them are safe for longer therapy and MS improvement [88,89]. On the other hand, natalizumab decreases MS relapses more efficient than interferons and glatiramer acetate but natalizumab has side effects so it is used in MS patients who do not gave good results with other treatments [56] or with MS advances disease [64]. Mitoxantrone due to its side effects was used in MS patients who do not gave better results with other treatments and can be used following interferons, glatiramer acetate and natalizumab [56]. The disruption of natalizumab treatment in MS patients can be followed by disease reactivation [90]. Clinically isolated syndrome patients are treated with interferons showed declines in MS progression to clinical MS [10,91]. The interferons and glatiramer acetate equally effective in both children and adults [92]. There are newly discovered treatments *e.g.* teriflunomide, fingolimod, and dimethyl fumarate but their uses are limited [93].

A mixture of chimerism and allogeneic donors is used to treat the relapse type of MS and autoimmune disorders in equal manner in both animals' models and humans however the reverse of autoimmunity is associated with a pronounced decrease in autoreactivity of $CD4^+$ T cells among host-type $CD4^+$ T cells in the spleen and lymph nodes [94]. On the other hand, intravenous methylprednisolone pulse therapy for MS patients showed a better results in decreasing MS symptoms following 1st, 2nd, and 3rd clinical courses but recorded ineffectively following 4th and 5th clinical courses of MS treatments [95].

The myelin-derived altered peptide ligands treatments prevent and improve MS-associated optic neuritis. The altered peptide ligand declines pain hypersensitivity and neuroinflammation which cure the vision and this results revealed the role of neuroimmune treatments in MS neuropathic pain and the visual disturbance resolves in 95% of MS cases [24,96]. Other oral MS treatments are under examination such as laquinimod and ozanimod where laquinimod was produced in 2012 and represents the third phase III of MS treatments [97]. Moreover, PEGylated form of interferon-β-1a also gave a good results in MS treatment [98].

A new treatments represents monoclonal antibodies *e.g.* ocrelizumab, rituximab and ofatumumab are under investigation [99], but with adaptable infection as side effects of these treatments, for example progressive multifocal leukoencephalopathy appears after natalizumab treatment [52]. The intravenous injection of methylprednisolone (at higher doses) accelerates visual neuritis treatment in MS patients but the MS patients with visual neuritis can be later back to MS symptoms [24].

10.2. Progressive MS

There is no treatment until now which can improve the primary and secondary progressive type of MS [56]. However, the only treatment used is mitoxantrone for progressive MS [100]. Mitoxantrone is used carefully due to its side effects and this treatment can slowing MS progression and decreasing MS relapse during two years period [101,102].

10.3. Treatments side effects

A lot of MS treatments side effects are recorded. Irritation is the most common and pronounced one following subcutaneous injections (90%) and intramuscular injections (33%) with interferon and glatiramer acetate. A detectible hollow site in the same place of injection due to breakdown of the adipose tissue in injection place, this process is known as lipoatrophy [103]. On the other side, interferons cause flu-like symptoms [104], while glatiramer acetate produces heart palpitations, chest tightness, flushing, and anxiety, its duration less than 30 min [105]. Liver damage from interferons injections [106], which occurs in low cases, moreover, infertility, systolic dysfunction (12%), and acute myeloid leukemia (0.8%) from mitoxantrone [102,107], and progressive multifocal leukoencephalopathy found after natalizumab injections [57,108].

The fingolimod treatments induces heart rate decline, hypertension, macular edema, increases liver enzymes or a decrease in lymphocyte levels [93]. On the other hand, the teriflunomide treatments produce fatigue, hair loss, headaches, limb pain, nausea, hepatic failure and fetal incomplete development [109,110]. The side effects of dimethyl fumarate are gastrointestinal problems and flushing [93]. Furthermore, dimethyl fumarate causes a decrease in the white blood cell count [99,110].

All the above mentioned treatments improve some MS but cannot stop the MS progressive disease [111]. There is a low confirmation for the efficacy of person therapeutic agents [112,113]. The exercise and psychology therapy gave good results in MS patients [114,115], and psychology therapy specially is effective in this matter [116].

10.4. Complementary treatments

Fifty percent of MS patients could be use complementary treatments [117], due to lack of any side effect but the efficiency of these treatments are weak [117,118]. These treatments include several types: vitamin D, Yoga, medicinal plants, oxygen therapy, acupuncture and reflexology [117,119–122]. The percentage of MS females patients using complementary treatments are higher than males patients however these females have a long MS history, more disable, in-satisfaction with MS health programs [117].

A cannabidiol ointment obtained from *Cannabis sativa* is used from MS treatment where daily treatment of cannabidiol ointment exerts neuroprotective effects in MS animal model. The ointment declines MS-clinical symptoms by improving hind limbs paralysis, as well as, recovering of MS histological score *e.g.* lymphocytic infiltration and neural demyelination in the spinal cord tissues. In addition, cannabidiol ointment can neutralize MS-associated damaged release of CD_4 and CD_8 T cells pro-inflammatory cytokines and other inflammatory biomarkers, oxidative damage, and apoptosis (caspase 3) [123]. Another study was carried-out used hemp seeds and primrose oils gave good results in the treatment of clinical symptoms in relapsing-remitting MS patients where both hemp seeds and primrose oils improving MS disease risk and progression specially MS patients with hereditary-related disease [124].

The melatonin administration which a natural hormone secreted by pineal gland to MS animals' model and humans in such a physiological dose revealed a protective action. Melatonin can be also used for MS treatments in MS animals' models and in the future can be apply into clinical practice [125].

On the other side, low-level laser therapy (LLLT) has been used in clinically treatment of inflammation due to its tissue healing and repair procedures. The LLLT has the ability to reduce the clinical symptoms in MS animals' model and in the same time delayed the MS incidence, moreover, prevented the MS-associated weight loss. These good results of LLLT associated with the down-regulation of nitric oxide levels in the central nervous system but in the same time LLLT unsuccessful in inhibiting lipid peroxidation and ameliorates the antioxidant defense in MS animals' model. Furthermore, the histology reveals that LLLT blocked neuroinflammation through a decline of inflammatory cells in the central nervous system, particularly lymphocytes, and stopping the demyelination in the spinal cord in MS animals' model so LLLT is a good therapeutic agent to treat MS patients [126].

A telemedicine meditation was also used for MS treatments including assessments of quality of life, anxiety, and depression level, moreover, assessments of mindfulness level, quality of sleep and fatigue level will be considered secondary outcome measures [127]. In the same direction, susceptibility weighted imaging is a new imaging technique where the imaging very high sensitive to hemorrhagic constituents, however, the sensitivity of this imaging provide to detect microvasculature with high precision inside the veins with highly accurate detection, susceptible grade and continues observing of MS progression. Furthermore, this imaging can observe any change in blood flow and vascular defects. This imaging can define the small lesions, axon damage, the exact place of these lesions which can be of more beneficial for MS treatments [128].

MS patients are characteristic by muscle softness and exhaustion due to the decrease of MS normal daily life activity. MS treatments increase and improve the MS muscle strength through practicing exercise, where exercise improves different aspects of MS patients such as: motor and cognitive functions, exhaustion, and life mode and activity. The exercise diminishes the MS-related complications such as: muscle strength, functional capability, timed up and go test, and MS-related EDSS test [129].

The protein gelsolin is the protein No. 4 among most rich body protein in the human body. In MS animals' model, gelsolin protein decreases in the blood while its concentration increased in the animals' brain. On the other hand, the recombinant human form of gelsolin protein decreased extracellular actin and myeloperoxidase activity in the brain which lead to decrease in MS disease activity and lowest clinical symptoms which suggest the beneficial therapeutic role of gelsolin in MS [130].

Another new trend of MS treatment is developed in the last decade such as stem cell therapy but still in the early steps [131]. The administration of skin-derived mesenchymal stem cells (MSCs) is able to alleviate the clinical score of MS animal model by inhibiting the differentiation of Th17 cells where the TNF-α is a critical cytokine for promoting Th17 cell differentiation. The activated skin-derived MSCs produced high amount of soluble TNF receptor 1, which neutralized TNF-α and inhibited Th17 cell polarization [132]. The efficacy of MSCs-based therapy for MS likely depends on the number of cells that home to inflamed tissues and on the controlled production of paracrine and immunomodulatory factors. The treatment with MSCs exhibited a superior therapeutic function over native (unmodified) MSCs, evidenced by significantly improved myelination and decreased lymphocytes infiltration into the white matter of the spinal cord, so MSCs could potentially be utilized to increase the effectiveness of MSC-based therapy for MS [133].

11. Conclusions

MS is a complex disease which characterized by a wide phenotypic variability where genetic and environmental factors communicate to induce MS. The changes in HLA system related genes in chromosome 6 induced MS symptoms. The physiological pattern of MS includes two main steps: (1) myelin sheath destruction and formation of lesions in the central nervous system, (2) inflammation. The relapsing-remitting, primary progressive, secondary progressive, and progressive relapsing are the four principal types of MS. The interferons and glatiramer acetate are the main treatments for relapsing-remitting MS type while mitoxantrone is the treatment for progressive MS type. Vitamin D, Yoga, medicinal plants, oxygen therapy, acupuncture and reflexology are complementary treatments used.

Multi-drug therapy is recommended and need future investigations where two or more drugs with similar or different mechanisms of action and is known as a more efficient way to provide good ways for new drugs delivery. In the other way, a combination of drug–drug, drug–nutraceutical, and drug–gene can provide a good source for MS discovering new treatments.

On the other hand, the future efforts would be well value targeting the researches correlated with pharmacogenetic, as it is very important in MS diagnosis and treatments to determine the patients' genetic background to define the specific and accurate treatments for MS patients so more researches are needed in this direction in the future.

There is an urgent need to connect MS behavior into physical activity and exercise training especially those with progressive

MS where the application of a specific time table program for a physical exercise play a vital role in increasing physical activity and exercise to promote the MS treatments.

Conflict of interest statement

I declare that I have no conflict of interest.

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