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Corrigendum to '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 causes nerve sheath demyelination, followed by axon damage and paralysis. MS symptoms include muscle weakness, weak reflexes, muscle spasm, difficulties in movement and unbalance. Many factors may be responsible for MS: microorganism, virus, smoking, stress, environmental toxins, contaminated diet and gout. MS is widely spread in the population in North Europe and this is 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 (not transferred from parents into next generations) but MS appears when leukocyte antigen system-related genes are changed in human chromosome 6. The physiology of MS patients is controlled by numbers of biological processes such as activation of immune-inflammatory, oxidative and nitrosative stress pathways. MS includes 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 with many side effects. Complementary treatments are also used in MS treatments such as vitamin D, Yoga, medicinal plants, oxygen therapy, acupuncture and reflexology.

1. Introduction

Scientist Jean-Martin Charcot was the first one who had discovered the disease in 1868 [1]. It is the most famous and pronounced autoimmune disease that attacks the central nervous system [2]. According to World Health Organization reports in 2008, 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 deaths in 1990 [4]. MS attacks people from age 20–50 years old and the records shows that females' attacks are double than males' attacks [5,6]. Disseminated sclerosis and encephalomyelitis disseminate are two alternative names of MS. MS is an autoimmune disease induced by external and environmental factors that initiate genetic changes such as virus-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, sociodemographic factors restrictions, declined employment state, and decreased educational level [9]. The MS symptoms may disappear completely, however, the permanent neurological problems happen when the disease advances [8]. MS symptoms occur when the nerve cells myelin sheath in the central nervous system (brain and spinal cord) start to be injured and consequently damaged. MS is associated with many symptoms and these include: physical, mental, and sometimes psychiatric disturbances [10–12], due to the neural

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damage which blocks the communication among different parts of the nervous system.

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

Recovery from organ-specific autoimmune diseases in early phases relies on mobilization of endogenous repair mechanisms and local factors that control them. The natural killer (NK) cells are quickly moved to the organs aimed by autoimmunity and the number of NK cells are increased when inflammatory case occurs. The NK cells are recalled in the brain subventricular zone in the progressive type of MS in both human and animal models. These NK cells are established very close to subventricular zone neural stem cells (NSCs), 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 neuro repair is found due to communication of both NK and NSCs cells [16]. Different types of disability (unmovable) of the upper limb can be found in MS incidence and a training program is proposed and directed toward the upper limbs to improve the limb function and structure in MS but it has no observable effect on the upper limb capability and performance in MS patients with advanced types [17].

All the MS treatments try to improve the neuronal function following MS occurrence and stop the progress of the disease [11]. The use of treatments in MS can induce adverse side effects. The long-term treatments with good results are observed in MS teenager women with relapsing type that have few neurons damaged [18]. MS decreases life span with an average of 5–10 years than other healthy ones [10,19]. 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]. Many distinguished lesions are found in the lower urinary tract as pronounced symptoms in MS patients [21]. On the other hand, MS is a major reason for human disability of neurological origin in the young adults where depression is the most observed psychiatric disorder [22]. Central and peripheral auditory disturbances always appear in MS [23]. On the other hand, the typical optic neuritis is usually the presenting symptom of MS [24]. Sleep disorder, exhaustion, and pain are other symptoms associated with MS [25].

MS symptoms depend on the specific nerve attack in the central nervous system and may finally lead to loss of sensitivity in sensation such as muscle weakness, weak reflexes, muscle spasm, difficulties in movement; problems in coordination and balance; problem in speech, optic problem, tired feeling, acute or chronic pain, and bladder and bowel difficulties. Depression is always associated with MS due to variable mood of MS patients. In addition, thinking and emotional problems are also observed in MS. There are many factors that increase MS disease symptoms *e.g.* viral infections such as cold, influenza, and gastrointestinal problems. Females are more sensitive to MS than males especially during the first three months after baby birth. Other factors do not play a role in MS reappearance 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 is also a main cause of MS [29]. Figure 1 reveals MS main symptoms [30].

3. MS causes

Up to date, the reasons for MS incidence have not been found. However, a combination of external and environmental factors that initiate genetic changes include pollution, stress as well as viral and bacterial infections. 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 [31]. MS can be induced by many microbes [11], and moving from one place to another increases microbial infection to induce MS [14,15].

The infectious disease, paratuberculosis, mainly affects wild and domestic ruminants. This disease is induced by *Mycobacterium avium paratuberculosis* (MAP), where MAP correlated to MS incidence. The MAP DNA was found in 4/7 (57.14%) goats, and in 14/25 (56%) sheep cheese using qPCR. In goat, MAP produced type S strain of MAP, and this MAP occured in quantities ranging 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 [32].

The mechanisms of MS induction include hygiene hypothesis and prevalence hypothesis. The hygiene hypothesis assumes that microbial infection occurs in early life but human can be

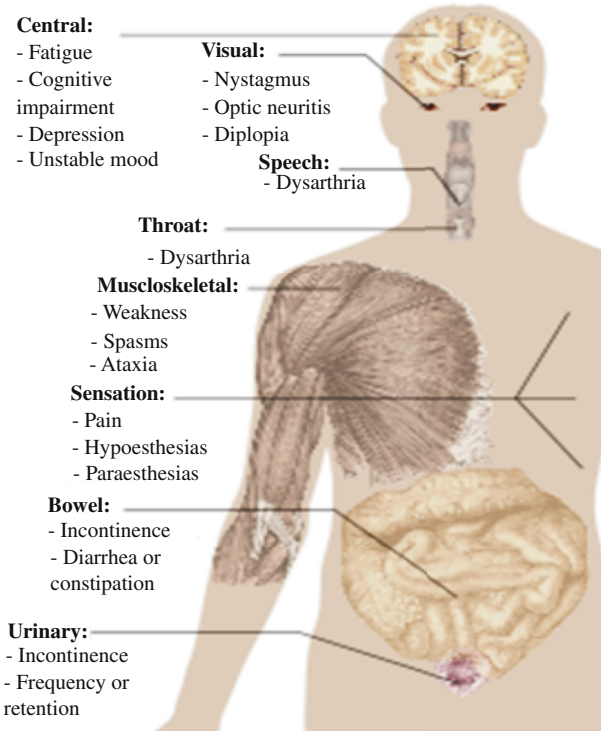

Figure 1. MS main symptoms [30]. https://en.m.wikipedia.org/wiki/Multiple_sclerosis.

protected from MS at this time. However, the human body response later at 50–60 years age to this early life infection and MS occurs [10], while the prevalence hypothesis proposes that MS is due to infection factors found in the region where a high proportion of MS patients are recorded among population [14,15,33]. The results obtained from MS patients supported the hygiene hypothesis other than the prevalence hypothesis [14,15].

3.2. Viral infection

Three evidences supported viral infection in MS: (1) oligoclonal bands were present in the central nervous system fluid in MS patients; (2) many viruses were related to human demyelination encephalomyelitis; (3) viral infection also induced demyelination in animals [34]. The lymphocytic choriomeningitis virus is responsible for MS symptoms. The lymphocytic choriomeningitis virus depends on MS cases in the temperate zone where more virus was found outside the equator region, and virus increases in regions with highest MS cases, on the other hand, there is no data on person-to-person transmission in MS incidence [7].

3.3. Other factors

MS can also be induced by smoking and stress [14,15,35]. Environmental toxins may also induce MS, especially when exposed to solvents [35,36]. Contaminated diet and hormonal intake may be related to MS [14,15]. Gout is not associated with MS patients, and MS cases had lower uric acid levels, which suggested a protective role of uric acid in MS [37]. MS can also be induced through disturbances in the neurovisceral integration of cardiovascular tone which can lead to many MS-associated clinical symptoms. Consequently, MS neurodegeneration occurs and inflammatory progresses are also increased and can lead to the appearances of cardiovascular autonomic nervous system dysfunction [38].

4. MS geography

MS is widely spread in the populations in North Europe and this is related to lack of vitamin D due to decrease of sunlight exposure. So children born in May in North Europe have more resistance to MS than children born in November [14,15,39,40]. 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 is inversely proportional where high vitamin D levels is associated with reduced MS risk [41]. The sensitivity to MS incidence is increased in a person below 15 years old who travels to MS high region than the same person above 15 years old who travels to the same MS high region [10,35]. In 2010, the number of 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 rate was less than 0.5/100000; in South East Asia, MS rate was 2.8/100000; in USA MS rate was 8.3/100000; in Europe MS rate was 80/100000 and MS rate increased to 200/100000 in Northern European countries [5,14,15,35].

MS symptoms usually occur in late twenties and early thirties patients, but it can also occur in child and older patients above 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 males and females [42]. A study described 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 these places [43]. 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 variations are more related to understanding MS causes. Three methods of detection were 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. BYM method can at the same time detect the geographical differences and MS disease control [44]. In another study, the German statutory health insurance reported 200000 MS cases in Germany in 2014. MS incidence was higher than expected and about 49% of all MS patients took MS-specific drug treatments. MS patients live in the east took an average of 30 daily doses per year, which was less than MS patients live in the western part did. There was a regional difference in MS incidence and drug treatments [45].

The MS spreading in England is recorded by General Practice Research Database where the MS percentage increased annually by 2.4%. 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 the level of 11.52/100000/year in females and 4.84/100000/year in males by 2010. MS was recorded in 72% of females and 71% of males. The highest MS incidence percentage occurred in Scotland in the UK where 126669 MS patients were recoded in the UK in 2010 (203.4/100000 population) [46]. Figure 2 shows MS disability-adjusted life year for MS/100000 inhabitants in 2004.

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. The roles of proteins indicative of neuronal, axonal, and glial loss such as N-acetylaspartate, 14-3-3 proteins, tau and neurofilaments are under investigation as

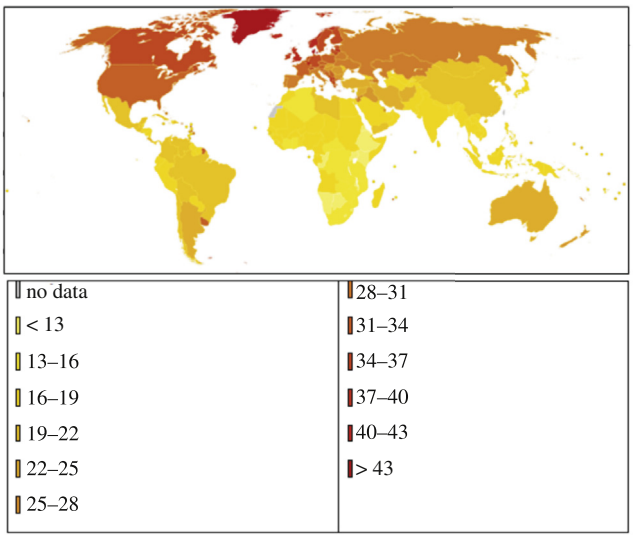

Figure 2. Disability-adjusted life year for MS/100000 inhabitants in 2004 (Data from Death estimates for 2004 by cause for WHO Member States (Persons, all ages), Multiple sclerosis world map. https://en.m.wikipedia.org/wiki/Multiple_sclerosis.

proteins affecting remyelination and regeneration [47]. 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 [48]. The magnetic resonance imaging (MRI) and positron emission tomography techniques can also be used MS technique descriptive tools [49], but MRI technique has many problems when used in clinical application such as magnetization transfer, double-inversion recovery sequences, functional magnetic resonance imaging and diffusion tensor [50]. On the other hand, other techniques are under development such as (1) techniques that measure inflammatory markers, nerve dysfunction, and macrophages levels; (2) techniques that measure iron excretion from the body; (3) techniques that measure cerebral perfusion [50] in MS patients; (4) radioactive tracers technique that measures change in cortical pathology, apoptosis, remyelination process and brain inflammation [51], and (5) techniques that measure antibodies against potassium channel [52]. Figure 3 exhibits MRI technique as MS marker [53].

6. MS diagnosis

MS diagnosis is related to patients' symptoms, MRI and laboratory results [54], but MS can only be diagnosed in the late phase [10,55]. The most known diagnosis method of MS is McDonald criteria which combined laboratory, clinical and radiology reports of lesions at different times in different body areas [3]. In addition, Schumacher and Poser criteria were the oldest known ones [56]. The cerebrospinal fluid analysis, patients' physical characters, and MRI are the most common diagnostic methods. MRI of the brain and spinal cord reveals the demyelination area in MS where gadolinium was injected intravenously to discriminate the lesions areas [57,58]. MS associated inflammation can be detected by cerebrospinal fluid investigation where immunoglobulin G tests are done and immunoglobulin G inflammation marker occurs in 85% of MS patients [57,59]. MS is always associated with visual and sensory disturbances, so optic and sensory clinical investigations are important diagnosis in MS symptoms [60].

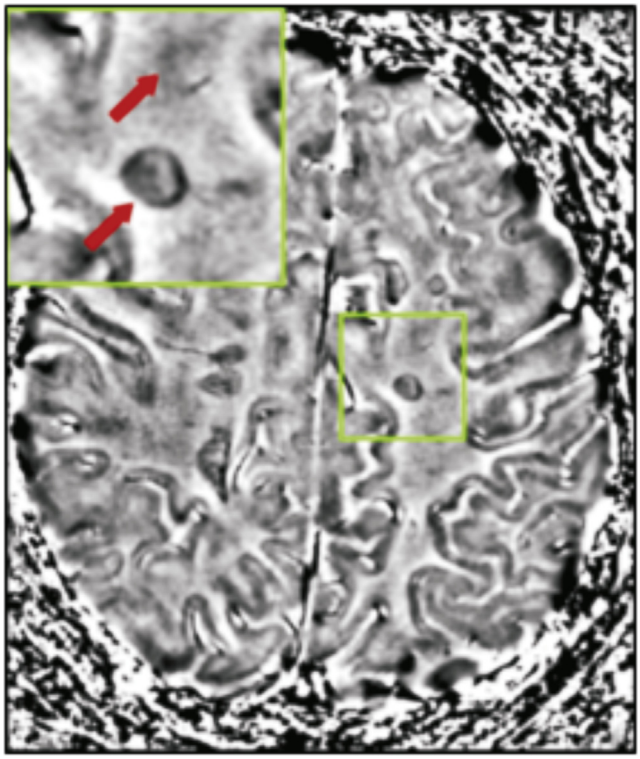

Figure 3. MRI technique showing an iron deposit in a white matter lesion (inside green box in the middle of the image [53]. https://en.m.wikipedia.org/wiki/Multiple_sclerosis.

7. MS genetics

MS is not a genetic disease although a lot of genetic changes are responsible for MS symptoms [61]. MS incidence increases among the family of MS patients [11]. However, MS rate is about 30% in identical twins and 5% in non-identical twins [10,62]. MS risk is 10 times higher in child if both father and mother are 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 diseases *e.g.* diabetes type I. The recent hereditary researches proved that at least twelve genes outside HLA in chromosome 6 were related to MS [63]. Pharmacogenetic-related studies have been developed to treat MS. Interferon-β and glatiramer acetate were showed to be the most successful, long-acting and safe drugs used in the therapy of MS all over the world [64,65]. The omics technique and researches with microRNAs have been done for discovering the change in protein structure related to 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 occurring in MS incidence. The microRNAs are very important complementary biomarkers correlated to cellular damage occurring in MS patients [66].

Higher MS relapse incidence is recorded during warmer months in different regions of the world. MS incidence is correlated to cytokines secretion in different seasons. The production of cytokines (interleukin-10, interleukin-6, and TNF-α) is recorded in spring season and the cytokines secretion increases from spring to summer, particularly TNF-α. These observations can help us to understand the higher MS-clinical activity [67].

Exogenous retroviruses invade into human cells so they become a part of human DNA and spread over many generations and transform 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 become higher. Three HERVs 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 [68]. 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 destroys oligodendrocyte precursors [68]. Figure 4 reveals HLA region of chromosome 6 [69].

8. MS physiology

The patients with MS have physiological disturbances which are accompanied with many physical, mental and clinical

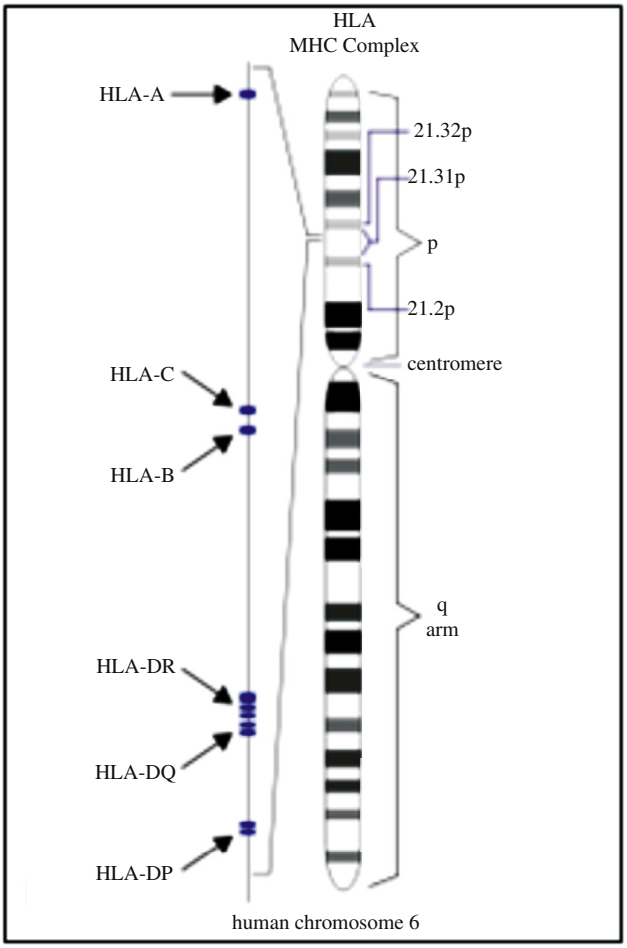

Figure 4. HLA region of chromosome 6. Changes in this area increase MS probability [69]. https://en.m.wikipedia.org/wiki/Multiple_sclerosis.

disorders such as changes in fat and bone mass, and increased risk for diseases such as coronary artery heart disease, non-insulin dependent diabetes mellitus, lipid metabolism abnormalities, and osteoporotic fractures. MS disability (unmovable) causes a changing pattern of muscle tissue shape in the paralyzed areas, and secondary alteration in tissue structure. However, bone and soft tissue changes in these patients are usually reported, thus 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 [70].

The physiology of MS patients is controlled by numbers of biological processes such as 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 [71]. In a study which comprised MS patients with depression (n = 42) and MS patients without depression (n = 108) and normal healthy (n = 249), MS incapacity was measured using EDSS while depression in MS was evaluated using depressive subscale of the Hospital Anxiety and Depression Scale in addition to the above mentioned biochemical parameters. There were 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 was no relationship between depression in MS patients and oldness, body weight index, MS form, gender, MS persistence, and nicotine addiction; in the contrary, MS with depression was related to MS development, peripheral inflammation, optical and gastrointestinal disorders compared to MS patients without depression [71].

Neuroactive steroids regulate the physiology of the central and peripheral nervous system, exert neuroprotective effects and represent interesting and promising trends for the therapeutic plans in MS disorders. Sex differences in their levels are detected not only under physiological conditions but are also modified in a sex-dependent way in different pathological alterations. Sex differences play a role in MS incidence, symptomatology and/or neurodegenerative outcome. The neuroprotective actions of neuroactive steroids, together with the sex specific regulation of its levels provide the strategy of sex-specific neuroprotective therapies [72].

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 connective forms within the limbic system [73].

There is 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 positive results according to Bonferroni correction 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 [74]. Tobacco smoke induced changes in blood brain barrier physiology and function and caused major destruction on blood brain barrier mechanisms such as anti-inflammatory and immunity pathways [75].

The mechanism responsible for initiation of lesion in MS is still undistinguishable; 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 [76]. There are small number of aggregated macrophages/microglia due to damaged axons reported in microgalial nodules but the oligodendrocyte apoptosis is the pronounced characteristic step in the formation of new lesions. Both microgalial nodules and newly forming lesions mutually and synergistically cooperate to induce MS [76].

The helper 1 cells, Th17, and regulatory T cells (T_{reg}) are produced by cytokines secreted in MS patients. Many gene 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 kinds of microRNA are changed during the interferon therapy where higher interleukin-12Rβ2 mRNA levels were correlated with decreased risk of MS relapse [77]. Figure 5 shows physiological sequences of MS incidence [78].

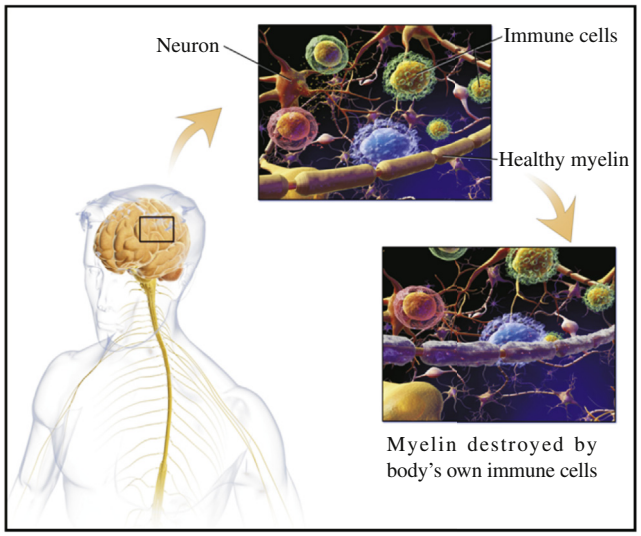

Figure 5. Physiological sequences of MS incidence [78]. https://en.m.wikipedia.org/wiki/Multiple_sclerosis.

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

8.1. Myelin sheath destruction and formation of lesions

MS means many injuries that are 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 that 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 causes no electrical signals transfer [11], and a repair process occurred in MS early phase; this process named remyelination but oligodendrocytes in MS advanced types cannot rebuild the cells of myelin sheath and many lesions increase 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 that form the blood–brain barrier, facilitate the nutrients transfer to the nervous tissue, support the maintaining of ion balance, and play 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 cause inflammation [10]. However, T cells enter into the brain through interruption in the blood brain barrier where T cells consider myelin sheath as a foreign body and begin to attack it and these cells are named "autoreactive lymphocytes" [11].

Demyelin of neuron sheath stimulates activation of inflammatory processes and consequently immune cells begin to release more cytokines and antibodies which cause 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 signals in the neurons (information transfer in the central nervous system) by the following 3 successive steps: (1)Inflammation increases secretion of cytokines and antibodies which stop neural secretion of neurotransmitters that transfer data from one neuron to another, (2) cytokines and antibodies also increased destruction of myelin sheath of the neuron throughout the whole human body, and (3) cytokines and antibodies consequently lead to neural axon damage of the body [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 increase in autoimmunity through different mechanisms, such as improvement and increase of helper T-17 and follicular helper T (TFH) cells, initiation of NK cells, increasing B-cell differentiation and antibody excretion and decrease of regulatory T (T_{reg}) cells. Furthermore, interleukin-21 has increased autoimmunity process 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 play an important role in MS symptoms. There is 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

The US National MS Society determined four MS types and these types depend on MS duration time and future development of MS disease symptoms [8], but International MS panel in 2013 added another two: (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

Unobservable relapses type stay 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 rate [84], but in 40% cases of this type, the disease is developed to MS [10,55], and this type named malignant MS with high disability rate [85]. Benign MS named clinically isolated syndrome where demyelination is 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 [42,54]. 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 for progressing from relapsing-remitting MS to secondary progressive MS is nearly 19 years [87].

9.4. Progressive relapsing type

Patients with progressive relapsing type have a steady and prolonged neurological damage and in the same time have also obvious MS symptoms. 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 [54], and both are equally effective in decreasing MS relapses by 30% [62]. Both of them are safe for longer therapy and MS improvement [88,89]. On the other hand, natalizumab decreases MS relapses more efficiently than interferons and glatiramer acetate, but natalizumab has side effects, so it is used in MS patients who do not give good results with other treatments [54] or with MS advanced (complicated) disease [62]. Mitoxantrone due to its side effects was used in MS patients who do not give better results with other treatments and can be used following interferons, glatiramer acetate and natalizumab [54]. The disruption of natalizumab treatment in MS patients can be followed by disease reappearance [90]. Clinically isolated syndrome patients treated with interferons showed declines in MS progression to clinical MS [10,91]. The interferons and glatiramer acetate are 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 neuro-inflammation which cure the vision, and this results revealed the role of neuroimmune treatments in MS neuropathic pain and the visual disturbance is resolved 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].

There are three new treatments using monoclonal antibodies such as ocrelizumab, rituximab and ofatumumab, but these treatments are under investigation [99]. On the other hand, there are some side effects of the treatments using monoclonal antibodies. For example, progressive multifocal leukoencephalopathy occurred after natalizumab treatment [49]. High-dosed intravenous methylprednisolone therapy speeds the recovery of optic neuritis but does not improve the final outcome. The risk that a patient with optic neuritis will later develop MS can be assessed with an MRI scan of the brain [24].

10.2. Progressive MS

No treatment until now can improve the primary and secondary progressive type of MS [54]. However, the only treatment used is mitoxantrone for progressive MS [100]. Mitoxantrone is used carefully due to its side effects and this treatment can slow MS progression and decrease 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 hand, interferons cause flu-like symptoms [104], while glatiramer acetate causes heart palpitations, chest tightness, flushing, and anxiety, with duration less than 30 min [105]. Liver damage due to interferons injections [106] occurs in few cases; moreover, infertility, systolic dysfunction (12%), and acute myeloid leukemia (0.8%) due to mitoxantrone [102,107], and progressive multifocal leukoencephalopathy were found after natalizumab injections [55,108].

The fingolimod treatments induce heart rate decline, hypertension, macular edema, increase liver enzymes or decrease lymphocyte levels [93]. On the other hand, the teriflunomide treatments result in 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 symptoms [111]. There is little confirmation for the efficacy of these therapeutic agents in MS patient [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 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 female patients using complementary treatments is higher than male patients; however these females have a long MS history [117].

A cannabidiol ointment obtained from *Cannabis sativa* is used for 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 MS histological score *e.g.* lymphocytic infiltration and neural demyelination in the spinal cord tissues. In addition, cannabidiol ointment can neutralize MS-associated neural damage, reducing release of CD_4 and CD_8 T cells and expression of the main pro-inflammatory cytokines and other inflammatory biomarkers, oxidative damage, and apoptosis (caspase 3) [123]. Another study carried out using 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 in MS patients with hereditary-related disease [124].

The melatonin administration in 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 applied 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 delay the MS incidence, and moreover, prevent the MS-associated weight loss. These good results of LLLT are associated with the down-regulation of nitric oxide levels in the central nervous system but in the same time LLLT is unsuccessful in inhibiting lipid peroxidation and ameliorating 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 as secondary outcome measures [127]. Susceptibility weighted imaging is a new imaging technique where the imaging has high sensitivity to hemorrhagic constituents. This imaging has a sensitivity to detect microvasculature inside the veins with high precision. This imaging can observe different MS progressive symptoms. This technique is called Multiple Sclerosis Functional Composite (MSFC). MSFC is a new clinical outcome measure for future MS trials. MSFC consists of timed tests of walking, arm function, and cognitive function. 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 more beneficial for MS treatments [128].

MS patients are characteristic by muscle softness and exhaustion due to the decrease of normal and daily life activity. MS treatments improve the MS muscle strength through practicing exercise; 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 which are detected by the following tests: muscle strength test, functional capability test, timed up and go test, and MS-related Expanded Disability Status Scale (EDSS) test [129].

The protein gelsolin is the fourth most rich body protein in the human body. In MS animals' model, gelsolin protein decreased in the blood while its concentration increased in the animals' brain. On the other hand, the recombinant human extracellular antibody of gelsolin protein (injected form) decreased extracellular actin and myeloperoxidase activity in the brain which lead to decrease in MS progressive or advanced types 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 experimental autoimmune encephalomyelitis in MS animal model by inhibiting the differentiation of Th17 cells. 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 depends on the number of cells that are placed or injected 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 is characterized by a wide phenotypic variability where external and environmental factors work together to induce human genetic changes that cause 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 principle types of MS. The interferons and glatiramer acetate are the main treatments of relapsing-remitting MS type while mitoxantrone 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 needs future investigations. Two or more drugs with similar or different mechanisms of action are 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 valuable 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.

The physical activity and exercise training programs of MS patients are needed to improve the clinical and physical features of MS patients, especially those with progressive MS where the application of a specific time table program for a physical exercise plays 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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