Pathogenesis and treatment of multiple sclerosis (MS)

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Citation

A Pithadia, S Jain, A Navale. *Pathogenesis and treatment of multiple sclerosis (MS)*. The Internet Journal of Neurology. 2008 Volume 10 Number 2.

Abstract

Multiple sclerosis is a chronic inflammatory disease of the nervous system in which a T-cell-mediated inflammatory process is associated with destruction of myelin sheaths. In present review, the main clinical aspects and the basic features of the MS (Multiple sclerosis) with diagnosis, including the new McDonald criteria and the treatment approach to MS are discussed. The pathophysiology of multiple sclerosis is reviewed, with emphasis on the axonal conduction properties underlying the production of symptoms and the course of the disease. Various demyelination patterns and their correlation with the disease types have been discussed. Finally, a brief description of the available treatments is discussed. In addition to this, newer targets for the treatment of MS are also reviewed.

INTRODUCTION

Multiple sclerosis (MS) is a chronic, potentially debilitating disease that affects central nervous system, which is made up of brain and spinal cord. Multiple sclerosis is widely believed to be an autoimmune disease, a condition in which immune system attacks components of body. In multiple sclerosis, the body mistakenly directs antibodies and white blood cells against proteins in the myelin sheath, a fatty substance that insulates nerve fibers in brain and spinal cord. This results in inflammation and injury to the sheath and ultimately to the nerves that it surrounds. The result may be multiple areas of scarring (sclerosis). Eventually, this damage can slow or block the nerve signals that control muscle coordination, strength, sensation and vision.

EPIDEMIOLOGY

MS is the one of the leading causes of neurological disability in young adults, second only to traumatic accidents [1] . Certain factors are highly correlated with the risk of developing MS. The disease is usually diagnosed in patients between ages 20 and 45 years [1,2,3,4] . Only 5% of people diagnosed with MS are younger than 10 or older than 50 [4] . More women are afflicted than men, at a ratio of 2:1. Yet, men are usually diagnosed at a later age and are more likely to develop the progressive form of the disease. In addition, people who live farther away from the equator are more at risk. Ethnic differences in prevalence also exist: MS more frequently affects whites of Scandinavian ancestry than other ethnic groups [2] . MS occurs in relatives of patients more often than in the general population. Multiple sclerosis affects an estimated 300,000 patients in the United States (US) and probably more than 1 million patients around the world — including twice as many women as men. Most patients experience their first signs or symptoms between ages 20 and 40.Multiple sclerosis is unpredictable and varies in severity. In some patients, multiple sclerosis is a mild illness, but it can lead to permanent disability in others. Treatments can modify the course of the disease and relieve symptoms.

ETIOLOGY

The exact causes of MS are not known. Most experts agree that MS is probably caused from an altered immune system, an environmental exposure (i.e., infectious agent), or both. Evidence showing that the immune system has a major role in the pathogenesis of MS is overwhelming [4,5] . Based on this theory, MS results from an autoimmune attack against self-myelin or self-oligodendrocyte antigens by macrophages, killer T cells, lymphokines and/or antibodies when they cross into the brain [2] .

Other research suggests that environmental exposures may promote MS, possibly due to one or more viruses [6] . These viruses include measles, mumps, rubella, varicella and Epstein-Barr and may be involved in the pathogenesis of MS in several ways [7] .(1) Transient or persistent infection outside the central nervous system (CNS) may activate autoreactive T cells. (2) Alternatively, transient CNS infection may initiate a cascade of events that fosters autoimmunity. (3) Recurrent CNS infections may precipitate repeated

inflammation and demyelination, or (4) persistent CNS viral infection may incite inflammatory reactions detrimental to oligodendrocytes or directly injure them. However, to date, no infectious agent has been identified as a causal agent in MS [8,9].

PATHOPHYSIOLOGY

A special subset of lymphocytes, called T helper cells, specifically Th1 and Th17, play a key role in the development of MS. Under normal circumstances, these lymphocytes can distinguish between self and non-self. However, in MS, these cells recognize healthy parts of the central nervous system as foreign and attack them as if they were an invading virus, triggering inflammatory processes and stimulating other immune cells and soluble factors like cytokines and antibodies. Recently other type of immune cells, B Cells, have been also implicated in the pathogenesis of MS and in the degeneration of the axons [10,11].

Normally, there is a tight barrier between the blood and brain, called the blood-brain barrier (BBB), built up of endothelial cells lining the blood vessel walls. It should prevent the passage of antibodies through it, but in MS it does not work. For unknown reasons leaks appear in the blood-brain barrier [12]. These leaks, in turn, cause a number of other damaging effects such as swelling, activation of macrophagesand more activation of cytokines and other destructive proteins such as matrix metalloproteinases. The final result is destruction of myelin, called demyelination. Whether BBB dysfunction is the cause or the consequence of MS is still disputed,because activated T-Cells can cross a healthy BBB when they express adhesion proteins [13]. A deficiency of uric acid has been implicated in this process. Uric acid added in physiological concentrations (i.e. achieving normal concentrations) is therapeutic in MS by preventing the breakdown of the blood brain barrier through inactivation of peroxynitrite [14,15]. The axons themselves can also be damaged by the attacks. Often, the brain is able to compensate for some of this damage, due to an ability called neuroplasticity. MS symptoms develop as the cumulative result of multiple lesions in the brain and spinal cord. This is why symptoms can vary greatly between different individuals, depending on where their lesions occur.

Repair processes, called remyelination, also play an important role in MS. Remyelination is one of the reasons why, especially in early phases of the disease, symptoms tend to decrease or disappear temporarily. Nevertheless, nerve damage and irreversible loss of neurons occur early in MS. Proton magnetic resonance spectroscopy has shown that there is widespread neuronal loss even at the onset of MS, largely unrelated to inflammation [16].

The oligodendrocytes that originally formed a myelin sheath cannot completely rebuild a destroyed myelin sheath. However, the central nervous system can recruit oligodendrocyte stem cells capable of proliferation and migration and differentiation into mature myelinating oligodendrocytes. The newly-formed myelin sheaths are thinner and often not as effective as the original ones. Repeated attacks lead to successively fewer effective remyelinations, until a scar-like plaque is built up around the damaged axons. Under laboratory conditions, stem cells are quite capable of proliferating and differentiating into remyelinating oligodendrocytes; it is therefore suspected that inflammatory conditions or axonal damage somehow inhibit stem cell proliferation and differentiation in affected areas [17,18,19].

BLOOD-BRAIN BARRIER DISRUPTION

A healthy blood-brain barrier shouldn't allow T-cells to enter the nervous system. Therefore BBB disruption has always been considered one of the early problems in the MS lesions [20]. Recently it has been found that this happens even in non-enhancing lesion [21,22] and it has been found with iron oxide nanoparticles how macrophages produce the BBB disruption [23]. Abnormal tight junctions are present in both secondary progressive MS (SPMS) and Primary Progressive (PPMS). They appear in active white matter lesions and in normal apperaring gray matter (NAGM) in SPMS. They persist in inactive lesions, particularly in PPMS. Apart from that, activated T-Cells can cross a healthy BBB when they express adhesion proteins . In particular, one of these adhesion proteins involved is ALCAM (Activated Leukocyte Cell Adhesion Molecule), also called CD166and is under study as therapeutic target. Other protein also involved is CXCL12 [24].

SPINAL CORD DAMAGE

Cervical spinal cord has been found to be affected by MS even without attacksand damage correlates with disability. In Relapsing-remitting MS (RRMS), cervical spinal cord activity is enhanced, to compensate for the damage of other tissues [25]. Spinal cord presents grey matter lesions, that can be confirmed post-mortem and by high field magnetic resonance imaging (MRI). Spinal cord grey matter lesions may be detected on MRI more readily than gray matter (GM) lesions in the brain, making the cord a promising site

to study the grey matter demyelination.

RETINA AND OPTIC NERVE DAMAGE

There is axonal loss in the retina and optic nerve, which can be meassured by Optical coherence tomography or by Scanning laser polarimetry. This measure can be used to predict disease activity. Optical coherence tomography (OCT) is an optical signal acquisition and processing method allowing extremely high-quality, micrometre-resolution, three-dimensional images from within optical scattering media (e.g., biological tissue) to be obtained. In distinction with other optical methods, OCT, an interferometric technique, is able to penetrate significantly deeper into the scattering medium, for example ~3× deeper than its nearest competitor, Confocal microscopy. Depending on the use of high-brightness and wide-spectrum light sources such as superluminescent diodes or ultrashort pulse lasers, OCT has achieved sub-micrometre resolution (with very wide-spectrum sources emitting over a ~100 nm wavelength range) [26] . It is one of a class of optical tomographic techniques. Scanning laser polarimetry is the use of polarised light to measure the thickness of the retinal nerve fiber layer as part of a glaucoma workups [27] .

BRAIN TISSUES ABNORMALITIES

Brain normal tissues (Normal appearing white matter, NAWM and normal appearing grey matter, NAGM) show several abnormalities . It has been found that grey matter injury correlates with disability [28] and that there is high oxidative stress in lesions, even in the old ones [29] . Water diffusivity is higher in all NAWM regions, deep gray matter regionsand some cortical gray matter region of MS patients than normal controls [30] Cortical lesions also appear. They are more frequent in men than in women. These lesions can partly explain cognitive deficits. It is known that two parameters of the cortical lesions, fractional anisotropy (FA) and mean diffusivity (MD), are higher in patients than in controls [31] .There is decreased perfusion which does not appear to be secondary to axonal loss. The reduced perfusion of the NAWM in MS might be caused by a widespread astrocyte dysfunction, possibly related to a deficiency in astrocytic beta(2)-adrenergic receptors and a reduced formation of cAMP (cyclic andenosine monophosphate), resulting in a reduced uptake of K(+) at the nodes of Ranvier and a reduced release of K(+) in the perivascular spaces [32,33] .

LESION DISTRIBUTION

Using high field MRI system, with several variants several areas show lesionsand can be spacially clasified in infratentorial, callosal, juxtacortical, periventricularand other white matter area [34] . Other authors simplify this in three regions: intracortical, mixed gray-white matterand juxtacortical [35] . Others classify them as hippocampal, corticaland WM lesions [36] and finally, others give seven areas: intracortical, mixed white matter-gray matter, juxtacortical, deep gray matter, periventricular white matter, deep white matter and infratentorial lesions [37] .

Post-mortem authopsy reveal that gray matter demyelination occurs in the motor cortex, cingulate gyrus, cerebellum, thalamus and spinal cord [38] . Cortical lesions have been observed specially in people with SPMS but they also appear in RRMS and clinically isolated syndrome. They are more frequent in men than in women [39] and they can partly explain cognitive deficits.

Post-mortem studies over NAWM and NAGM areas show several biochemical alterations, like increased protein carbonylation and high levels of Glial fibrillary acidic protein (GFAP), which in NAGM areas comes together with higher than normal concentration of protein carbonyls, suggesting reduced levels of antioxidants and the presence of small lesion [40] . The amount of interneuronal Parvalbumin is lower than normal in brain's motor cortex area [41] . Citrullination appears in SPMS. It seems that a defect of sphingolipid metabolism modifies the properties of normal appearing white matter [42] .

NEURAL AND AXONAL DAMAGE

The axons of the neurons are damaged probably by B-Cells [43] , though currently no relationship has been established with the relapses or the attacks [44] . A relationship between neural damage and N-Acetyl-Aspartate concentration has been establishedand this could lead to new methods for early MS diagnostic through magnetic resonance spectroscopy [45] . Axonal degeneration at CNS can be estimated by N-acetylaspartate to creatine (NAA/Cr) ratio, both measured by with proton magnetic resonance spectroscopy.

BLOOD AND CSF (CEREBROSPINAL FLUID) ABNORMALITIES

It is known that glutamate is present at higher levels in CSF during relapses [46] compared to healthy subjects and to MS patients before relapses. Also a specific MS protein has been found in CSF, chromogranin A, possibly related to axonal degeneration. It appears together with clusterin and complement C3, markers of complement-mediated inflammatory reactions [47] . Also Fibroblast growth factor-2

appears higher at CSF [48] .

Blood serum also shows abnormalities. Creatine and Uric acid levels are lower than normal, at least in women [49] . Ex vivo CD4(+) T cells isolated from the circulation show a wrong T cell immunoglobulin (TIM-3) (Immunoregulation) behavior [50] and relapses are associated with CD8(+) T Cells [51] . Platelets are known to have abnormal high levels.MS patients are also known to be CD46 defectiveand this leads to Interleukin 10 deficiency, being this involved in the inflammatory reactions [52] . Levels of IL-2, IL-10 (Interleukins) and GM-CSF are lower in MS females than normal. IL6 is higher instead. These findings do not apply to men [53] .Varicella-zoster virus remains have been found in CSF of patients during relapses, but this particles are virtually absent during remissions [54] . Plasma Cells in the cerebrospinal fluid of MS patients could also be to blame, because they have been found to produce myelin-specific antibodies.Finally, B cells in CSF appearand they correlate with early brain inflammation [55] .

DEMYELINATION PATTERNS

Also known as Lassmann patterns [56] , it is believed that they may correlate with differences in disease type and prognosisand perhaps with different responses to treatment. This report suggests that there may be several types of MS with different immune-related causesand that MS may be a family of several diseases.

The four identified patterns are :

PATTERN I

The scar presents T-cells and macrophages around blood vessels, with preservation of oligodendrocytes, but no signs of complement system activation.

PATTERN II

The scar presents T-cells and macrophages around blood vessels, with preservation of oligodendrocytes, as before, but also signs of complement system activation can be found [57] .

PATTERN III

The scars are diffuse with inflammation, distal oligodendrogliopathy and microglial activation. There is also loss of myelin associated glycoprotein (MAG). The scars do not surround the blood vesselsand in fact, a rim of preserved myelin appears around the vessels. There is evidence of partial remyelinization and oligodendrocyte apoptosis.

PATTERN IV

The scar presents sharp borders and oligodendrocyte degeneration, with a rim of normal appearing white matter. There is a lack of oligodendrocytes in the center of the scar. There is no complement activation or MAG loss [58] . All the cases with PPMS (primary progressive) had pattern IV (oligodendrocyte degeneration) in the original study and nobody with RRMS was found with this pattern. Balo concentric sclerosis lesions have been classified as pattern III (distal oligodendrogliopathy). Balo concentric sclerosis is a demyelinating disease similar to standard Multiple sclerosis, but with the particularity that the demyelinated tissues form concentric layers. Scientists used to believe that the prognosis was similar to Marburg multiple sclerosis, but now they know that patients can survive, or even have spontaneous remission and asymptomatic cases [59] . Neuromyelitis optica was associated with pattern II (complement mediated demyelination), though they show a perivascular distribution, at difference from MS pattern II lesions. This produces an inflammation of the optic nerve (optic neuritis) and the spinal cord (myelitis). Although inflammation may also affect the brain, the lesions are different from those observed in the related condition multiple sclerosis. Spinal cord lesions lead to varying degrees of weakness or paralysis in the legs or arms, loss of sensationand/or bladder and bowel dysfunction [60] . The researchers are attempting this with magnetic resonance images to confirm their initial findings of different patterns of immune pathology and any evidence of possible disease “sub-types” of underlying pathologies.

SYMPTOMS

Signs and symptoms of multiple sclerosis vary widely, depending on the location of affected nerve fibers. Multiple sclerosis symptoms may include numbness or weakness in one or more limbs, which typically occurs on one side of body at a time or the bottom half of body, partial or complete loss of vision, usually in one eye at a time, often with pain during eye movement, double vision or blurring of vision, tingling or pain in parts of body, electric-shock sensations that occur with certain head movements, tremor, lack of coordination or unsteady gait, fatigue and dizziness [61] .

In some cases, patients with multiple sclerosis may also develop muscle stiffness or spasticity, slurred speech, paralysis, or problems with bladder, bowel or sexual function. A period of disease activity (exacerbation) may be triggered by a viral infection, such as a cold or flu, or by

changes in the immune system during the first six months following a pregnancy [62] .

Multiple sclerosis relapses are often unpredictable, occurring without warning and without obvious inciting factors. Some attacks, however, are preceded by common triggers. Relapses occur more frequently during spring and summer. Infections such as the common cold, influenza, or gastroenteritis increase the risk of relapse [63] . Stress may also trigger an attack. Pregnancy may affect susceptibility to relapse, offering protection during the last trimester, for instance. During the first few months after delivery, however, the risk of relapse is increased. Overall, pregnancy does not seem to influence long-term disability. Many potential triggers have been examined and found not to influence MS relapse rates. There is no evidence that vaccination for influenza, hepatitis B, varicella, tetanus, or tuberculosis increases risk of relapse. Physical trauma does not trigger relapses. Exposure to higher than usual ambient temperatures can exacerbate extant symptoms, an effect known as Uhthoff's phenomenon [64] .

TESTS AND DIAGNOSIS

Multiple sclerosis can be difficult to diagnose. Many other conditions may produce symptoms similar to multiple sclerosis, but with a different prognosis and treatment. There are no specific tests for multiple sclerosis. Ultimately, the diagnosis relies on a determination that the clinical symptoms, radiological studies and laboratory studies suggest MS and that no other condition provides a better explanation for them.

Neurological examination. This examination systematically tests various parts of nervous system, including reflexes, muscle strength, muscle tone and sensations of pain, heat, touch and vibration. Observation of gait, posture, coordination and balance and asking questions to help determine the clarity of thinking, judgment and memory (The McDonald Criteria) [65] .

Magnetic resonance imaging (MRI) scans. The cylinder-shaped MRI scanner creates tissue-slice images on a computer from data generated by a powerful magnetic field and radio waves. This imaging technique may reveal MS lesions, which are caused by myelin loss. An intravenous dye, gadolinium, will highlight “active” lesions that have developed within the past two months and this may help doctors know whether the MS is in an active phase, even if no symptoms are present indicating an attack of MS. Newer MRI techniques can provide even greater detail about the degree of nerve fiber injury or permanent myelin loss and recovery [66] .

Spinal tap (lumbar puncture). In this procedure, a small sample of cerebrospinal fluid from within spinal canal is removed for laboratory analysis. This sample can show abnormalities associated with multiple sclerosis, such as abnormal levels of white blood cells or proteins. This procedure can also help rule out viral infections and other conditions that can cause neurological symptoms similar to those of MS [67] .

Evoked potential test. This test measures the electrical signals sent by brain in response to stimuli. An evoked potential test may use visual stimuli or electrical stimuli, in which short electrical impulses are applied to legs or arms [68] .

Peripheral blood tests may be helpful in excluding other disease processes. Testing frequently includes determination of the vitamin B12 level, thyroid-stimulating hormone level, erythrocyte sedimentation rate and anti-nuclear antibody titers, as well as a test for Lyme disease and a test for syphilis (rapid plasma reagin test).

TREATMENTS AND DRUGS

MEDICATIONS FOR RELAPSING MS

IMMUNOTHERAPY

As evidence of immune system involvement in the development of MS has grown, trials of various new treatments to alter or suppress immune response are being conducted. Most of these therapies are, at this time, still considered experimental. Results of recent clinical trials have shown that immunosuppressive agents and techniques can positively (if temporarily) affect the course of MS; however, toxic side effects often preclude their widespread use. In addition, generalized immunosuppression leaves the patient open to a variety of viral, bacterial and fungal infections. The following chemotherapeutic agents used to treat relapsing/remitting and secondary/progressive MS are azathioprine, cyclophosphamide , cyclosporine and methotrexate [69] .

Over the years, MS investigators have studied a number of immunosuppressant treatments. One such treatment, Mitoxantrone is the drug of choice for the treatment of advanced or chronic MS. Mitoxantrone may cause serious side effects, such as heart damage, after long-term use, so it's typically not used for longer than two to three years. And it's

typically reserved for people with severe attacks or rapidly advancing disease who do not respond to other treatments.

A phase-III, randomized, placebo-controlled, multicenter trial found that mitoxantrone, an anthracenedione antineoplastic agent, reduced the number of treated MS relapses by 67 percent and slowed progression on the Expanded Disability Status Scale, Ambulation Index and MRI measures of disease activity. Mitoxantrone is recommended for use in patients with worsening forms of MS [70] .

Close monitoring is critical for anyone on this medication. Other therapies being studied are cyclosporine, cyclophosphamide, methotrexate, azathioprine and total lymphoid irradiation (a process whereby the MS patient's lymph nodes are irradiated with x-rays in small doses over a few weeks to destroy lymphoid tissue, which is actively involved in tissue destruction in autoimmune diseases). Inconclusive and/or contradictory results of these trials, combined with the therapies' potentially dangerous side effects, dictate that further research is necessary to determine what, if any, role they should play in the management of MS [71] .

Another potential treatment for MS is monoclonal antibodies, which are identical, laboratory-produced antibodies that are highly specific for a single antigen. One monoclonal antibody, natalizumab, was shown in clinical trials to significantly reduce the frequency of attacks in patients with relapsing forms of MS Natalizumab, an anti-alpha4-integrin antibody, binds to T-cell surface receptors to prevent migration from the circulation into the brain tissue. Common side effects of treatment with natalizumab may include, headache, tiredness, minor infections, such as a urinary tract infection, stomachache, joint pain, diarrhea. More serious side effects of natalizumab may include, allergic reaction to the shot, serious infections, such as pneumonia, serious and life-threatening disease called progressive multifocal leukoencephalopathy (PML) [72,73] .

Bone marrow transplantation (a procedure in which bone marrow from a healthy donor is infused into patients who have undergone drug or radiation therapy to suppress their immune system so they will not reject the donated marrow) and injections of venom from honey bees are also being studied. Each of these therapies carries the risk of potentially severe side effects [74] .

BETA INTERFERONS

Interferon beta-1b and interferon beta-1a are genetically engineered copies of proteins that occur naturally in body. They help to fight viral infection and regulate immune system. These medications reduce flare-ups of multiple sclerosis Beta interferons are not used in combination with one another; only one of these medications is used at a time. Beta interferons do not reverse damage and have not been proved to significantly alter long-term development of permanent disability. Some patients develop antibodies to beta interferons, which may make them less effective. Other patients can't tolerate the side effects, which may include symptoms similar to those of the flu (influenza). Generally beta interferons are recommend for patients who have more than one attack of MS a year and for those who do not recover well from flare-ups. The treatment may also be used for patients who have a significant buildup of new lesions as seen on an MRI scan, even when there may not be major new symptoms of disease activity [75,76] .

Side effects of treatment with interferon beta-1a and interferon beta-1b may include flu-like symptoms (such as fatigue, chills, fever and muscle aches) for 1 to 2 days after an injection. These symptoms, which can be debilitating for some people, often stop after 2 to 3 months of treatment. Taking a pain reliever such as ibuprofen or acetaminophen just before and after each injection may help reduce these symptoms [77] . Redness, swelling or tenderness at the injection site. Depression, anxiety, confusion and eating and sleeping disturbance are not very common and may be related as much to MS as to the treatment.

GLATIRAMER

Glatiramer works by blocking immune system's attack on myelin. Glatiramer acetate (GA) (Copolymer-1) is a polypeptide-based therapy approved for the treatment of relapsing-remitting multiple sclerosis. GA treatment is believed to promote development of Th2-polarized GA-reactive CD4+ T-cells, which may dampen neighboring inflammation within the central nervous system. Recent reports indicate that the deficiency in CD4+CD25+FoxP3+ regulatory T-cells in multiple sclerosis is restored by GA treatment. GA also exerts immunomodulatory activity on antigen presenting cells, which participate in innate immune responses. These new findings represent a plausible explanation for GA-mediated T-cell immune modulation and may provide useful insight for the development of new and more effective treatment options for multiple sclerosis. Side effects may include flushing and shortness of breath after

injection. Side effects of glatiramer acetate may include pain, redness, or swelling at the injection site (this occurs in most people), flushing, c hest pain, rapid heartbeat and shortness of breath, anxiety and tightness in the throat. These side effects are rarely serious and usually go away on their own shortly after the injection [78,79].

MEDICATIONS FOR PROGRESSIVE MS

Some medications may relieve symptoms of progressive MS. They include:

CORTICOSTEROIDS

Methylprednisolone plays an important role in the current treatment of multiple sclerosis (MS), particularly in the acute phase of relapse. It acts in various ways to decrease the inflammatory cycle including: dampening the inflammatory cytokine cascade, inhibiting the activation of T cells, decreasing the extravasation of immune cells into the central nervous system, facilitating the apoptosis of activated immune cells and indirectly decreasing the cytotoxic effects of nitric oxide and tumor necrosis factor alpha. This paper reviews the most recent observations on these mechanisms both to understand the disease mechanism and its treatment. As more becomes known about these mechanisms, it may become possible to design treatment regimes that are more specific towards both the individual and the disease state [80].

Short courses of oral or intravenous corticosteroids are found to reduce inflammation in nerve tissue and to shorten the duration of flare-ups. Prolonged use of these medications, however, may cause side effects, such as osteoporosis and high blood pressure (hypertension) and the benefit of long-term therapy in multiple sclerosis isn't established. Corticosteroids are usually well tolerated. Side effects include the following, heart failure, high blood pressure (hypertension), high blood sugar levels (hyperglycemia), high or low levels of sodium in the blood (hyper- or hyponatremia), increased risk for infection, low level of potassium in the blood (hypokalemia), personality changes (e.g., mood swings), stomach ulcer, swelling (edema) caused by fluid retention [81,82].

SYMPTOMATIC THERAPIES FOR MULTIPLE SCLEROSIS

As given in following table indicating symptoms, their therapy and possible adverse effects [83,84,85].

Figure 1

Symptom	Therapy and possible adverse effects
Spasticity	Baclofen , 10 to 40 mg three times daily; in high doses, can cause weakness and fatigue Tizanidine , 2 to 8 mg three times daily; in high doses, can cause weakness and fatigue Gabapentin , 300 to 900 mg three or four times daily; in high doses, causes fatigue
Pain and paroxysmal disorders	Gabapentin, 300 to 900 mg three or four times daily; in high doses, causes fatigue Carbamazepine , 100 to 600 mg three times daily; in high doses, causes rash and neurologic side effects; requires monitoring of complete blood count and liver function Amitriptyline , 10 to 150 mg per day at bedtime
Bladder urgency	Oxybutynin , 5 mg once daily to 20 mg per day in divided doses; causes dry mouth and can exacerbate glaucoma or worsen urinary retention Tolterodine , 2 to 4 mg twice daily; causes dry mouth and can exacerbate glaucoma or worsen urinary retention (these side effects occur less often than with oxybutynin)
Depression	selective serotonin reuptake inhibitor (SSRIs) preferred because of activating properties; can have sexual side effects Alternatives to SSRIs when sexual side effects occur: extended-release venlafaxine 75 to 225 mg per day, or sustained-release bupropion , 150 mg per day to 150 mg twice daily
Fatigue	Amantadine , 100 mg twice daily; can cause rash, edema and anticholinergic effects Modafinil , 100 to 200 mg given in the morning; can cause jittery sensation and palpitations SSRIs, can have sexual side effects

NEWER TARGETS FOR THE TREATMENT OF MS

THERAPIES TARGETING AN ANTIGEN

Trials of a synthetic form of myelin basic protein, called copolymer I, were successful, for the treatmernt of relapsing-remitting MS. Copolymer I, unlike so many drugs tested for the treatment of MS, has few side effects and studies indicate that the agent can reduce the relapse rate by almost one third. In addition, patients given copolymer I is more likely to show neurological improvement than those given a placebo [86].

Investigators are also looking at the possibility of developing an MS vaccine. Myelin-attacking T cells were removed, inactivated and injected back into animals with experimental allergic encephalomyelitis (EAE). This procedure results in destruction of the immune system cells that were attacking myelin basic protein. In a couple of small trials scientists have tested a similar vaccine in humans. The product was well-tolerated and had no side effects, but the studies were too small to establish efficacy. Patients with progressive forms of MS did not appear to benefit, although relapsing-remitting patients showed some neurologic improvement and had fewer relapses and reduced numbers of lesions in one study [87].

THERAPY TO IMPROVE NERVE IMPULSE CONDUCTION.

Because the transmission of electrochemical messages between the brain and body is disrupted in MS, medications to improve the conduction of nerve impulses are being investigated. Since demyelinated nerves show abnormalities of potassium activity, scientists are studying drugs that block the channels through which potassium moves, thereby restoring conduction of the nerve impulse. In several small experimental trials, derivatives of a drug called aminopyridine temporarily improved vision, coordination and strength when given to MS patients who suffered from both visual symptoms and heightened sensitivity to temperature. Possible side effects of these therapies include paresthesias (tingling sensations), dizziness and seizures [88].

REMYELINATION

Some studies focus on strategies to reverse the damage to myelin and oligodendrocytes (the cells that make and maintain myelin in the central nervous system), both of which are destroyed during MS attacks. Scientists now know that oligodendrocytes may proliferate and form new myelin after an attack. Therefore, there is a great deal of interest in agents that may stimulate this reaction. To learn more about the process, investigators are looking at how drugs used in MS trials affect remyelination [89].

OTHER APPROACHES

PHYSICAL AND OCCUPATIONAL THERAPY

A physical or occupational therapist can teach strengthening exercises and show how to use devices that can ease the performance of daily tasks. Therapists can assist in finding optimal mobility assistance devices such as canes, wheelchairs and motorized scooters. These devices and exercises can help preserve independence. Individual or group therapy may help cope with multiple sclerosis and relieve emotional stress [90].

PLASMA EXCHANGE (PLASMAPHERESIS).

Plasma exchange may help restore neurological function in patients with sudden severe attacks of MS-related disability who do not respond to high doses of steroid treatment. This procedure involves removing some of blood and mechanically separating the blood cells from the fluid (plasma). Blood cells then are mixed with a replacement solution, typically albumin, or a synthetic fluid with properties like plasma. The solution with blood is then returned to body. Replacing plasma may dilute the activity of the destructive factors in immune system, including antibodies that attack myelin and help to recover [91,92].

DIET

Many patients have tried to implicate diet as a cause of or treatment for MS. Some physicians have advocated a diet low in saturated fats; others have suggested increasing the patient's intake of linoleic acid, a polyunsaturated fat, via supplements of sunflower seed, safflower, or evening primrose oils. Other proposed dietary “remedies” include megavitamin therapy, including increased intake of vitamins B12 or C; various liquid diets; and sucrose-, tobacco-, or gluten-free diets. To date, clinical studies have not been able to confirm benefits from dietary changes; in the absence of any evidence that diet therapy is effective; patients are best advised to eat a balanced, wholesome diet.

The use of supplements as regular therapy must begin at an early stage of the disease and as quickly as possible once a diagnosis has been made.

The antioxidant abilities of the nutrients such as the vitamins C and E are extremely effective in treating some of the symptoms of MS-these vitamins slow down the damage done to nervous tissues. Nervous structure and functioning is maintained by the vitamin B complex, along with supplemental doses of extra vitamin B12 and folic acid-these supplements will shield the nerves from the worst damages caused by free radicals. The use of these supplements is supported by the results seen in certain scientific studies, which indicate that patients with MS patients tend to have low levels of the vitamin B12 and some of them seem to have problems processing it in the body [93,94].

HERBS FOR MS

GINKGO

Ginkgo biloba comes from one of the oldest tree species and has been used in China for medicinal purposes for thousands of years. There is some limited evidence to support ginkgo's ability to improve cognitive function among older people with mild to moderate dementia. Preliminary studies suggest that ginkgo may also improve memory or concentration among people with MS. Ginkgo is an antioxidant. It also inhibits a substance known as platelet activating factor (PAF). By inhibiting PAF, ginkgo can cause a decrease in the activity of certain immune cells. These activities provide theoretical support for the use of ginkgo to treat MS. Ginkgo has been studied in both the animal model of MS and in people with MS Ginkgo may inhibit blood clotting and

therefore should be avoided by people with bleeding disorders, those who take blood-thinning medications and those undergoing surgery. In all cases, regular ginkgo use should be reported to all health-care providers.

ECHINACEA

Echinacea is a flowering plant native to North America and a member of the daisy (Asteraceae) family. Of the three species available, the best studied is Echinacea purpurea. Echinacea is generally used to treat the common cold. Because viral respiratory infections may be linked to exacerbations or acute attacks of MS, treating colds or trying to prevent them with Echinacea is an appealing strategy.

VALERIAN

The unpleasant-smelling root of a flower called valerian is sometimes used as a sleep aid. (It is also sometimes used in root beer!) People with MS may have difficulty sleeping and difficulties with sleep may contribute to MS related fatigue. Thus, a sleep aid may be very useful to some people with MS. A few well-designed trials not involving people with MS show that valerian can decrease the amount of time required to fall asleep without residual feelings in the morning.

ASIAN GINSENG

Asian ginseng, also known as Panax ginseng, has been used for centuries by the Chinese and Indians for its supposed ability to enhance physical performance and resistance to stress and aging. An herb that increases energy and strength would be of great use to people with MS who sometimes suffer from debilitating fatigue. Although some evidence suggests ginseng might be safe in people with MS, other experiments raise the possibility that ginseng may stimulate the immune system in ways that may be detrimental to people with MS.

Black currant (Ribes nigrum). Black currant oil contains a compound known as gamma-linolenic acid (GLA) that is thought to be useful in treating MS.

Blueberry (Vaccinium, various species). These berries contain compounds known as oligomeric procyanidins (OPCs). The biochemistry of OPCs is complicated, but there is good evidence to show that they help prevent the breakdown of certain tissues, such as the myelin sheaths that surround the nerve fibers. OPCs also have anti-inflammatory activity that might help relieve MS symptoms. This sounds like a good reason to eat more blueberries.

Pineapple (Ananas comosus). Pineapple contains enzymes, pancreatin and bromelain, that break up protein molecules. Besides being anti-inflammatories, these enzymes have been shown to help reduce the level of circulating immune complexes (CICs). High levels of CICs occur in a number of autoimmune diseases, including MS.

CONCLUSION

The past few years ,there has increasing improvement in the development of laboratory and imaging approaches to study MS, leading to a better understanding of the pathophysiology and genesis of the MS. The introduction of interferon beta and glatiramer acetate has shown to be effective in modifying the course of relapsing-remitting multiple sclerosis. Ongoing research on MS will identify appropriate molecular targets of intervention and novel diagnostics and, more importantly, will enable the development of new and more effective as well as cost effective therapies.

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