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A REVIEW ON CLINICAL MANAGEMENT OF MULTIPLE SCLEROSIS

***G. Balammal, G. Sangeetha, M. Sekar Babu, L. Mohan Krishna, G. Aruna**

*Krishna Teja Pharmacy College, Chadalawada Nagar, Renigunta Road,
Tirupati-517605, Andhra Pradesh, India.

ABSTRACT

Multiple sclerosis affects the ability of nerve cells in the brain and spinal cord to communicate with each other. Nerve cells communicate by sending electrical signals called action potentials down long fibers called axons, which are wrapped in an insulating substance called myelin. In Multiple sclerosis, the body own immune system attacks and damages the myelin. When myelin is lost, the axons can no longer effectively conduct signals. Multiple sclerosis is characterized by inflammation and demyelination of white matter in the brain and spinal cord. The myelin sheath influences the rate of nerve impulse conduct with transmission being more rapid in myelinated nerve fibers. In Multiple sclerosis, an auto immune response is evoked that causes the body to attack its own myelin. The disease is usually characterized by a relapsing remitting course in the early stages, with full or nearly full recovery initially. It is known from previous studies of the natural history of Multiple sclerosis, that a high frequency of clinical relapses over the first years is associated with an increased risk of later deterioration. Based on this observation and the inflammatory reactions described in Multiple sclerosis there are reasons to initiate treatment as early as possible to prevent axonal damage and irreversible damage.

Keywords: Multiple sclerosis, Clinical manifestations, Clinical management, Pathophysiology.

INTRODUCTION

A chronic degenerative disease of the central nervous system in which gradual destruction of myelin occurs in patches throughout the brain or spinal cord (or both), interfering with the nerve pathways and causing muscular weakness, loss of coordination and speech and visual disturbances. It occurs chiefly in young adults and is thought to be a defect in the immune system that may be of genetic or viral origin. Multiple sclerosis [MS] is an inflammatory demyelinating disease of the central nervous system of unknown origin, which is widely considered to be autoimmune in nature which the fatty myelin sheaths around the axons of the brain and spinal cord are damaged, leading to demyelination and scarring as well as a broad spectrum of signs and symptoms [1].

MS affects the ability of nerve cells in the brain and spinal cord to communicate with each other. Nerve cells communicate by sending electrical signals called action potentials down long fibers called axons, which are wrapped in an insulating substance called myelin. In MS, the body own immune system attacks and damages the myelin. When myelin is lost, the axons can no longer effectively conduct signals.

MS is characterized by inflammation and demyelination of white matter in the brain and spinal cord. The myelin sheath influences the rate of nerve impulse conduct with transmission being more rapid in myelinated nerve fibers. In MS, an auto immune response is evoked that causes the body to attack its own myelin. The disease is usually characterized by a relapsing remitting course in the early stages, with full or nearly full recovery initially. In the early stages there may be little damage to axons. Over time the disease enters an irreversible progressive phase of neurological deficit. Acute relapses are caused by inflammatory demyelination, while disease progression is thought to result from axonal loss. Each relapses causes further loss of nervous tissue and progression dysfunction. In some class cases there may be chronic progression without remission or acute disease rapidly leading to death.

Corresponding Author:- **G. Balammal** Email:- bala.hospira@gmail.com

The signs and symptoms of multiple sclerosis depend on where the plaques are formed and differ greatly between patients. Common problems include weakness affecting the arms and legs, spasticity, UN co-ordinated speech, tremor, altered sensation, including paraesthesia and a feeling of burning, tearing and numbness in the limbs, trunk and face. Other problems include urinary incontinence, constipation, abnormal eye movements, optic neuritis (pain in one eye followed by visual disturbances and rarely partial blindness), cognitive impairment, depression and sexual dysfunction. Exposure to excessive heat (bathing in hot water) and exercise commonly accentuates symptoms. Symptoms worsen with age, reflecting the ongoing nature of the disease [2].

There is no known cure for MS. Treatments attempt to return function after an attack, prevent new attacks, and prevent disability. MS medications can have adverse effects or be poorly tolerated, and many patients pursue alternative treatments, despite the lack of supporting scientific study. The prognosis is difficult to predict; it depends on the subtype of the disease, the individual patient's disease characteristics, the initial symptoms and the degree of disability the person experiences as time advances. Life expectancy of patients is nearly the same as that of the unaffected population.

Multiple sclerosis (MS) though rare in Asia, is the commonest progressive neurological disease in the temperate climates. There are approximately 2,50,000 to 3,50,000 people in United States of America with MS with the prevalence being approximately 100 cases per 1,00,000 population and approximately 80,000 people in United Kingdom with the prevalence being approximately 130 cases per 1,00,000 population. The onset of MS usually occurs between 20 and 50 years of age, with a peak a 30 years. MS is more common in women than men by a ratio 2:1. Multiple sclerosis is rare between the equator and latitudes 30^{o}- 35^{o} north and south. The prevalence of MS increases proportionally with increased distance from the equator. There is no satisfactory explanation of this phenomenon, although certain variables have been researched [3].

These include environmental factors, such as climate, humidity, hours of daily sunshine, levels of hygiene (and hence resistance to certain viruses) and even consumption of cow's milk. Interestingly, if a person moves further away from the equator, for instance from Africa to the United Kingdom before a certain age (thought to be between 5 and 15 years), the relative risk of developing MS increases and a move closer to the equator results in a decreased risk. Genetic factors probably have an influence with certain combinations of genes being more prevalent in certain racial groups. The risk of an identical twin developing MS when the other twin already has it has been reported to be as great as one in three. It is thought a child with one parent having MS has a one percent greater risk of developing MS than a child with no such parent. MS occurs in all major racial groups but is most common in whites, less common in blacks and rare in Asians. MS is almost absent within the Eskimo population, New Zealand maoris and Australian aborigines. Virus infection by slow growing viruses has been suggested but so far none have been identified [4].

Types of MS

MS is a diverse disease. No two patients are the same and each will experience different combinations of symptoms with differing severity. There are four general types of MS: benign multiple sclerosis; relapsing-remitting multiple sclerosis (RRMS); primary progressive multiple sclerosis (PPMS); and secondary progressive multiple sclerosis (SPMS). A minority of patients will have benign multiple sclerosis, a form of MS that is not disabling. The majority (80%) of patients will have RRMS in which episodes of increased disability occur at a random and for an unpredictable period, with a subtle course in between. At a later stage, the majority of patients will enter SPMS, accumulating varying degree of disability overtime. About 10% of patients have no relapses but gradually progress overtime, usually becoming wheelchair dependent and this is PPMS [5].

1. Primary progression multiple sclerosis
2. Secondary chronic progression multiple sclerosis
3. Relapsing remitting multiple sclerosis
4. Benign multiple sclerosis

Primary Progression

Primary progressive describes the approximately 10% of individuals who never have remission after their initial MS symptoms Decline occurs continuously without clear attacks. Affects people who are older at disease onset.

Secondary chronic progression multiplesclerosis

The 80% of those with initial relapsing-remitting MS, who then begin to have neurological decline between their acute attacks without any definite periods of remission. This decline may include more severe neurological symptoms, worsening cognitive function, or other deficits.

Relapsing remitting multiple sclerosis

85% to 90% of individuals with MS. Unpredictable attacks (relapses) lasting 24 hours or more followed by Periods of months to years of improvement (remission) with no new signs of disease activity .The period between attacks may shrink Symptoms become more severe [5].

Benign multiple sclerosis

10-20% of people have a "Benign"type of MS, Symptoms progress very little over the course of their lives.Return to normal between attacks

EPIDEMIOLOGY

Multiple sclerosis (MS) was first described in 1868by Jean-Martin Charcot. Affects mainly Caucasians (N. Europe) Most common neurodegenerative disease of young adults (1 per 400).Average age at onset 28(f)/30(m) years. Female: male ratio = 2:1 Chronic illness with cumulative disability Treatment expensive (>US$10,000).

Two main measures are used in epidemiological studies: incidence and prevalence. Incidence is the number of new cases per unit of person–time at risk (usually number of new cases per thousand person–years); while prevalence is the total number of cases of the disease in the population at a given time. Prevalence is known to depend not only on incidence, but also on survival rate and migrations of affected people. MS has a prevalence that ranges between 2 and 150 per 100,000 depending on the country or specific population (Rosati G, 2001) Studies on populational and geographical patterns of epidemiological measures have been very common in MS (Kurtzke JF, 1993) and have led to the proposal of different etiological (causal) theories [6].

MS usually appears in adults in their thirties but it can also appear in children. The primary progressive subtype is more common in people in their fifties. As with many autoimmune disorders, the disease is more common in women, and the trend may be increasing. In children, the sex ratio difference is higher, while in people over fifty, MS affects males and females almost equally. There is a north-to-south gradient in the northern hemisphere and a south-to-north gradient in the southern hemisphere, with MS being much less common in people living near the equator Climate, sunlight and intake of vitamin D have been investigated as possible causes of the disease that could explain this latitude gradient. However, there are important exceptions to the north-south pattern and changes in prevalence rates over time in general, this trend might be disappearing. This indicates that other factors such as environment or genetics have to be taken into account to explain the origin of MS. MS is also more common in regions with northern Europe populations. But even in regions where MS is common, some ethnic groups are at low risk of developing the disease, including the Samis, Turkmen, Amerindians, Canadian Hutterites, Africans, and New Zealand Māori.

Environmental factors during childhood may play an important role in the development of MS later in life. Several studies of migrants show that if migration occurs before the age of 15, the migrant acquires the new region's susceptibility to MS. If migration takes place after age 15, the migrant retains the susceptibility of his home country. However, the age–geographical risk for developing multiple sclerosis may span a larger timescale. A relationship between season of birth and MS has also been found which lends support to an association with sunlight and vitamin D [6].

Causes and etiology

Most likely MS occurs as a result of some combination of genetic, environmental and infectious factors. Epidemiological studies of MS have provided hints on possible causes for the disease. Theories try to combine the known data into plausible explanations, but none has proved definitive.

It is generally accepted that multiple sclerosis is an autoimmune disease, which means the body's immune system attacks certain parts of the body; in this case it is the myelin, the fatty sheath that surrounds and insulate nerve fibers in the central nervous system. Symptoms may be mild to severe and include fatigue, numbness of the face, trunk, or limbs, walking and balance problems, bladder and/or bowel incontinence, vision problems, pain, and cognitive dysfunction, among others. Multiple sclerosis is two to three times more common in women than in men [7].

The University at Buffalo researchers will be testing the possibility that a condition called chronic cerebrospinal venous insufficiency (CCSVI) is the cause of multiple sclerosis symptoms. CCSVI is characterized by narrowing of the primary veins outside the skull. The narrowing of the blood vessels inhibits the normal outflow of blood from the brain, resulting in changes in the blood flow patterns within the brain, ultimately damaging brain tissue and degeneration of nerve cells.

Genetic Factors

MS is not considered a hereditary disease. However, a number of genetic variations have been shown to increase the risk of developing the disease. The risk of acquiring MS is higher in relatives of a person with the disease than in the general population, especially in the case of siblings, parents, and children. The disease has an overall familial recurrence rate of 20%. In the case of monozygotic twins, concordance occurs only in about 35% of cases, while it goes down to around 5% in the case of siblings and even lower in half-siblings. This indicates susceptibility is partly polygenically driven. It seems to be more common in some ethnic groups than others [8].

Apart from familial studies, specific genes have been linked with MS. Differences in the human leukocyte antigen (HLA) system a group of genes inchromosome 6 that serves as the major histocompatibility complex (MHC) in humans increase the probability of suffering MS. The most consistent finding is the association between multiple sclerosis and alleles of the MHC defined as DR15 and DQ6.

Environmental Factors

Different environmental factors, both of infectious and non-infectious origin have been proposed as risk factors for MS. Although some are partly modifiable, only further research especially clinical trials will reveal whether their elimination can help prevent MS.

MS is more common in people who live farther from the equator, although many exceptions exist. Decreased sunlight exposure has been linked with a higher risk of MS. Decreased vitamin D production and intake has been the main biological mechanism used to explain the higher risk among those less exposed to sun.

Severe stress may also be a risk factor although evidence is weak. Smoking has also been shown to be an independent risk factor for developing MS. Association with occupational exposures and toxins mainly solvents has been evaluated, but no clear conclusions has been reached. Vaccinations were also considered as causal factors for the disease; however, most studies show no association between MS and vaccines. Several other possible risk factors, such as diet and hormone intake, have been investigated; however, more evidence is needed to confirm or refute their relation with the disease [9].

Gout occurs less than would statistically be expected in people with MS, and low levels of uric acid have been found in MS patients as compared to normal individuals. This led to the theory that uric acid protects against MS, although its exact importance remains unknown.

Infections

Many microbes have been proposed as potential infectious triggers of MS, but none has been substantiated. Genetic susceptibility can explain some of the geographic and epidemiological variations in MS incidence, like the high incidence of the disease among some families or the risk decline with genetic distance, but does not account for other phenomena, such as the changes in risk that occur with migration at an early age. An explanation for this epidemiological finding could be that some kind of infection, produced by a widespread microbe rather than a rare pathogen, is the origin of the disease. Different hypotheses have elaborated on the mechanism by which this may occur. The hygiene hypothesis proposes that exposure to several infectious agents early in life is protective against MS, the disease being a response to a later encounter with such agents. The prevalence hypothesis proposes that the disease is due to a pathogen more common in regions of high MS prevalence. This pathogen is very common, causing in most individuals an asymptomatic persistent infection. Only in a few cases, and after many years since the original infection, does it cause demyelination. The hygiene hypothesis has received more support than the prevalence hypothesis [10].

Evidence for viruses as a cause includes the presence of oligoclonal bands in the brain and cerebrospinal fluid of most patients, the association of several viruses with human demyelination encephalomyelitis, and induction of demyelination in animals through viral infection. Human herpes viruses are a candidate group of viruses linked to MS. Individuals who have never been infected by the Epstein-Barr virus have a reduced risk of having the disease, and those infected as young adults have a greater risk than those who had it at a younger age. Although some consider that this goes against the hygiene hypothesis, since the non-infected have probably experienced a more hygienic upbringing, others believe that there is no contradiction since it is a first encounter at a later moment with the causative virus that is the trigger for the disease. The diseases that have also been related with MS are measles, mumps and rubella [11].

PATHOPHYSIOLOGY

The pathogenic events in MS are not fully understood, but most research supports immunological involvement in which the myelin sheath surrounding the neuron is attacked by sensitized T-cells which trigger a non-specific inflammatory response, mediated by cytokines and other immune modulating substances. Demyelination may have either negative or positive effects on axonal conduction. Negative conduction abnormalities consist of slowed axonal conduction, variable conduction block that occurs in the presence of high - but not low - frequency trains of impulses. Helen T, David KL or complete conduction block. Positive conduction abnormalities include ectopic impulse generation, spontaneously or following mechanical stress, and abnormal “crosstalk” between demyelinated axons. Conduction block may account for the fluctuations in function that vary from hour to hour and from day to day in MS. Conduction of. Helen T, David KL nerve impulse is impaired due to edema at the perivascular cuff, causing compression of the axons. MS appears to be an autoimmune disease mediated at least in part by T lymphocytes. In the laboratory model experimental allergic encephalomyelitis (EAE), an autoimmune disease

resembling MS is induced by immunization with CNS antigens. Antigens that can elicit EAE are myelin basic protein (MBP), proteolipid protein, myelin oligodendrocyte glycoprotein and other myelin proteins or neural antigens [12]. The sequence of immunopathogenic events is as follows:

- Neural antigens are processed by antigen - presenting cells in regional lymphnodes and presented to T cells capable of recognizing them.
- Small number of sensitized memory T cells migrates to the CNS, where they are reactivated by antigen presented by macrophages or microglial cells.
- Proinflammatory cytokines, including interleukins (IL-1, IL-2, IL-6), tumor necrosis factor (TNF)α, RANTES, interferon (IFN)γ are secreted that enhance expression of adhesion molecules by vascular endothelium, alter the permeability of the blood brain barrier (BBB) and induce a second wave of inflammatory cell recruitment to the site. .
- Multiple effector mechanisms may contribute to the formation of lesions, including auto-antibodies, cytotoxicity mediated by T cells or natural killer cells and cytokine mediated injury to oligodendrocytes or myelin. The mutations resulting from chronic stimulation of MBP reactive T cells in vivo, appears to be specific for MS. Continuation of non-specific secondary inflammatory reaction with enlargement of existing lesions and further plaque formation produces the chronic phase of MS. The extent of axonal damage is controversial, but evidence that some axons may remain intact provides encouragement to research targeted at stimulating remyelination (Matthews WB & Mc Alpine's, 1991). Remyelination does occur to some extent, but obviously cannot keep pace with the rate of demyelination [13].

Autoimmunology

MS is currently believed to be an immune-mediated disorder mediated by a complex interaction of the individual's genetics and as yet unidentified environmental insults. Damage is believed to be caused by the patient's own immune system. The immune system attacks the nervous system, possibly as a result of exposure to a molecule with a similar structure to one of its own [14].

Lesions

The name *multiple sclerosis* refers to the scars (sclerosis – better known as plaques or lesions) that form in the nervous system. MS lesions most commonly involve white matter areas close to the ventricles of the cerebellum, brain stem, basal ganglia and spinal cord; and the optic nerve. The function of white matter cells is to carry signals between grey matter areas, where the processing is done, and the rest of the body. The peripheral nervous system is rarely involved.More specifically, MS destroys oligodendrocytes, the cells responsible for creating and maintaining a fatty layer known as the myelin sheath which helps the neurons carry electrical signals. MS results in a thinning or complete loss of myelin and, as the disease advances, the cutting (transection) of the neuron's extensions or axons. When the myelin is lost, a neuron can no longer effectively conduct electrical signals. A repair process, called remyelination, takes place in early phases of the disease, but the oligodendrocytes cannot completely rebuild the cell's myelin sheath. Repeated attacks lead to successively fewer effective remyelinations, until a scar-like plaque is built up around the damaged axons. Different lesion patterns have been described [15].

Inflammation

Apart from demyelination, the other pathologic hallmark of the disease is inflammation. According to a strictly immunological explanation of MS, the inflammatory process is caused by T cells, a kind of lymphocyte. Lymphocytes are cells that play an important role in the body's defenses. In MS, T cells gain entry into the brain via the previously described blood–brain barrier. Evidence from animal models also point to a role of B cells in addition to T cells in development of the disease [16].

The T cells recognize myelin as foreign and attack it as if it were an invading virus. This triggers inflammatory processes, stimulating other immune cells and soluble factors like cytokines and antibodies. Leaks form in the blood–brain barrier, which in turn cause a number of other damaging effects such as swelling, activation of macrophages, and more activation of cytokines and other destructive proteins.

CLINICAL MANIFESTATIONS

Signs and symptoms

Almost any neurologic deficit can occur in MS, but there are several signs and symptoms that are characteristic. None of these characteristic findings are pathognomonic, but their presence should suggest MS as a possible diagnosis, particularly in a young adult [17].

Optic neuritis (ON):

Optic neuritis is characterized by acute or subacute loss of vision usually in one but occasionally in both eyes. The visual loss evolves over a period of hours or days. Vision returns to normal within two months but may deteriorate in later years. Previous history of ON in a patient who develops a neurological illness will strongly support the diagnosis of MS.

Internuclearophthalmoplegia (INO):

INO results from lesion of medial longitudinal fasiculus. With unilateral lesion, there is restriction of adduction of the ipsilateral eye and the abducting eye

shows nystagmus. With bilateral lesion, on looking towards either side, the adduction would be impaired and abducting eye will show nystagmus. INO is usually an early warning sign of MS.

Acute transverse myelitis:

A spinal cord syndrome may be the presenting feature of MS. Incomplete transverse myelopathy is more frequent than complete transverse myelitis. The diagnosis usually becomes apparent after a second episode involving a different site in the CNS.

Cerebellar syndrome:

Cerebellar involvement results in ataxia. In advanced MS, cerebellar dysarthria (scanning speech) is common. In individual patients, the contribution of cerebellar involvement to specific symptoms may be difficult to define when motor and sensory deficits are also present [18].

Cognitive impairment:

Cognitive impairment is thought to affect 40-70% of MS patients and can be present even in the early stages of MS. Approximately one third of people with MS have some degree of memory loss. Other areas of cognitive function particularly affected in the MS patient include sustained attention, verbal fluency, conceptional reasoning and visuospatial perception. Dementia is said to be common in the latter stages of MS.

Temperature sensitivity:

Many MS patients are temperature sensitive. In hotter weather or during a period of raised body temperature, their MS symptoms worsen. Most frequently vision is affected and muscle weakness occurs.

Lhermitte sign:

It is a symptom rather than a sign. A tingling or electric like sensation down the back and legs is felt on flexing the neck. The symptom is non-specific but occurs more frequently in MS than in any other condition and may be the only indication of a lesion in the spinal cord and thus provides an important clue to the correct diagnosis [19].

Incontinence and constipation:

Urinary incontinence affects up to 90% of patients and usually occurs before major physical disability is apparent. It is perceived by many as the worst symptom of MS. Bladder problems are due to plaques in the spinal cord. If demyelination occurs in both controlling pathways, the bladder will neither store urine nor void properly, leading to urgency, frequency and nocturia. Constipation affects about 40% of people with MS. Bowel incontinence and urgency of defaecation also occur, with estimations of prevalence ranging from rarely15 to 52% [20].

Fatigue:

Fatigue is a common complaint in MS. Characteristics of fatigue include muscle weakness, co-ordination problems, ataxia, transient deafness, changes in taste or smell and numbness of the extremities [21].

Spasticity and tremor:

Spasticity occurs in up to 90% of MS patients and it can be painful and distressing. MS patients also often have disabling tremors. Spasticity and tremor lead to various nursing and general self-care problems, with feeding and personal hygiene.

Sexual dysfunction:

Sexual dysfunction is common among multiple sclerosis sufferers. However this is often inadequately dealt due to various misconceptions and stereotypes leading to poor or no patient counselling and a lack of research into the area [22].

DIAGNOSIS

Accurate diagnosis of multiple sclerosis is important not only to exclude other disorders and give prognosis but also for epidemiological studies and entering patients in multicentre clinical trials for therapy. The diagnosis of MS is usually made in a young adult with relapsing and remitting symptoms referable to different areas of CNS white matter. Diagnosis is more difficult in a patient with the recent onset of neurologic complaints or with a primary progressive clinical course. Examination reveals evidence of neurologic disease in the great majority of patients. The differential diagnosis of MS will vary depending on the specific clinical situation. Numerous diagnostic formulas have been proposed while they are useful; they cannot replace sound clinical judgment. The diagnosis of MS is made on the basis of the clinical signs and symptoms, with magnetic resonance imaging (MRI) and other laboratory tests playing a supportive role. All tests are non-specific and only provide supportive evidence for diagnosis.

Laboratory tests in MS

Magnetic resonance imaging (MRI): MRI is the single most useful laboratory tests in the diagnosis of MS have compared MRI and CT scans in patients with MS. They demonstrated that MRI not only picked up all the lesions seen on the CT scan, it revealed many more, particularly in the brain stem. The lesions also had more distinct margins. All patients had multiple lesions on MRI and many of these were periventricular and hence considered specific for MS by these authors have demonstrated that MRI evidence for disease activity is much more frequent than clinical evidence [23].

Electrophysiological tests:

- Visual evoked potentials (VEP) are most frequently employed in clinical practice. Since MS affects anterior optic pathways, VEP reveal abnormality in significant number of patients. In the series of 86% patients of MS who had no history of ON and had normal optic disc showed an abnormal VEP.

- Brainstem auditory evoked potentials (BAEP) have also been used in the diagnosis of MS. Sixty percent of patients without clinical signs of brainstem involvement showed abnormalities Of BAEP.

Diagnostic criteria:

1. Examination must reveal objective abnormalities of the CNS
2. Examination or history must implicate involvement of two or more areas of the CNS.
3. Age of onset between 15 and 60 years

4. Involvement must reflect predominantly disease of white matter long tracts, usually including
a. Pyramidal Pathways
b. Cerebellar pathways
c. Medial longitudinal fasciculus
d. Optic nerve
e. Posterior columns

5. The clinical pattern must consist of
a. Two or more separate episodes of worsening involving different sites of the CNS, each lasting at least 24 h and occurring at least one month apart or
b. Gradual or stepwise progression over at least 6 months if accompanied by increased CSF, IgG synthesis or two or more oligoclonal bands.

6. The patient's neurologic condition could not better be attributed to another disease. Laboratory testing that may be advisable In certain cases includes,
a. CSF analysis
b. MRI of the head or spine
c. Serum vitamin B12 level
d. Human T cell lymphotropic virus type I titer.
e. Erythrocyte sedimentation rate.
f. Rheumatoid factor, antinuclear, anti-DNA antibodies.
g. Serum VDRL
h. Angiotensin - converting enzyme (sarcoidosis)
i. Borrelia serology (Lyme disease).
j. Very long chain fatty acids (adrenoleukodystrophy) and
k. Serum or CSF lactate, muscle biopsy or mitochondrial DNA analysis.

Diagnostic categories:

1. Definite MS: All six criteria fulfilled.
2. Probable MS: All six criteria fulfilled except
a. Only one objective abnormality despite two symptomatic episodes or
b. Only one symptomatic episode despite two or more objective abnormalities.
3. At risk for MS: All six criteria fulfilled except only one symptomatic episode and one objective abnormality.

Other laboratory tests:

- The examination of cerebrospinal fluid (CSF) has been used to support the diagnosis of MS for a long time. The presence of myelin basic protein in the CSF of MS patient may be highly suggestive of activity of MS process but its absence does not rule out active disease.

- Presence of IgG oligoclonal band in the CSF has proved to be the most sensitive laboratory test in the diagnosis of MS and is not dependent on the activity of the disease and treatment received by the patient.

Disease biomarkers:

The variable clinical presentation of MS and the lack of diagnostic laboratory tests lead to delays in diagnosis and the impossibility of predicting diagnosis. New diagnostic methods are being investigated. These include work with anti-myelin antibodies, analysis of microarray gene expression and studies with serum and cerebrospinal fluid but none of them has yielded reliable positive results.

Currently there are no clinically established laboratory investigations available that can predict prognosis. However, several promising approaches have been proposed. Investigations on the prediction of evolution have centered on monitoring disease activity. Disease activation biomarkers include interleukin-6, nitric oxide and nitric oxide synthase, osteopontin, and fetuin-A. On the other hand since disease progression is the result of neurodegeneration the roles of proteins indicative of neuronal, axonal and glial loss such as neurofilaments, tau and N-acetyl aspartate are under investigation. A final investigative field is work with biomarkers that distinguish between medication responders and nonresponders [24].

CLINICAL MANAGEMENT

Pharmacological:

As of 2009, five disease-modifying treatments for MS have been approved by regulatory agencies of various countries. Interferon beta 1a (Trade names: *Avonex*, *CinnoVex*, *Reci Gen* and *Rebif*) and interferon beta-1b (U.S. trade name *Betaseron*, in Europe and Japan *Betaferon*). A third medication is glatiramer

acetate (*Copaxone*), a non-interferon, non-steroidal immunomodulator. The fourth medication, mitoxantrone, is an immunosuppressant also used in cancer chemotherapy. The fifth is natalizumab (marketed as *Tysabri*). The interferons and glatiramer acetate are delivered by frequent injections, varying from once-per-day for glatiramer acetate to once-per-week (but intra-muscular) for *Avonex*. Natalizumab and mitoxantrone are given by IV infusion at monthly intervals.

All five kinds of medications are modestly effective at decreasing the number of attacks in relapsing-remitting MS (RRMS) while the capacity of interferons and glatiramer acetate is more controversial. Studies of their long-term effects are still lacking. Comparisons between immunomodulators (all but mitoxantrone) show that the most effective is natalizumab, both in terms of relapse rate reduction and halting disability progression. Mitoxantrone may be the most effective of them all; however, it is generally not considered as a long-term therapy, as its use is limited by severe secondary effects. The earliest clinical presentation of RRMS is the clinically isolated syndrome (CIS). Treatment with interferons during an initial attack can decrease the chance that a patient will develop clinical MS.

Treatment of progressive MS is more difficult than relapsing-remitting MS. Mitoxantrone has shown positive effects in patients with secondary progressive and progressive relapsing courses. It is moderately effective in reducing the progression of the disease and the frequency of relapses in patients in short-term follow-up. No treatment has been proven to modify the course of primary progressive MS.

As with many medical treatments, these treatments have several adverse effects. One of the most common is irritation at the injection site for glatiramer acetate and the interferon treatments. Over time, a visible dent at the injection site, due to the local destruction of fat tissue, known as lipoatrophy, may develop. Interferons produce symptoms similar to influenza some patients taking glatiramer experience a post-injection reaction manifested by flushing, chest tightness, heart palpitations, breathlessness, and anxiety, which usually lasts less than thirty minutes. More dangerous but much less common are liver damage from interferons, severe cardiotoxicity, infertility, and acute myeloid leukaemia of mitoxantrone, and the putative link between natalizumab and some cases of progressive multifocal leukoencephalopathy [20,25].

NON PHARMACOLOGICAL

Acupuncture:

Acupuncture is the procedure of inserting and manipulating needles into various points on the body to relieve pain or for therapeutic purposes.

Aromatherapy:

Aromatherapy is a form of alternative medicine that uses volatile plant materials, known as essential oils, and other aromatic compounds for the purpose of altering a person's mind, mood, cognitive function or health. The effectiveness of aromatherapy is yet to be scientifically proven; however some evidence exists that essential oils may have therapeutic potential.

Cannabis (Marijuana):

Cannabis (Cán-na-bis) is a genus of flowering plants that includes three putative species, Cannabis sativa, Cannabis indica (Cannabis sativa information from NPGS/GRIN, 2008 and Cannabis ruderalis. These three taxa are indigenous to Central Asia, and South Asia (Marijuana and the Cannabinoids). Cannabis has long been used for fibre (hemp), for medicinal purposes, and as a recreational drug. Industrial hemp products are made from Cannabis plants selected to produce an abundance of fiber and minimal levels of THC (Δ^9-tetrahydrocannabinol), a psychoactive molecule that produces the "high" associated with marijuana. The psychoactive product consists of dried flowers and leaves of plants selected to produce high levels of THC. Various extracts including hashish and hash oil are also produced from the plant.

Chiropractic:

Chiropractic is a health care discipline and profession that emphasizes diagnosis, treatment and prevention of mechanical disorders of themusculoskeletal system, especially the spine, under the hypothesis that these disorders affect general health via the nervous system. It is generally categorized as complementary and alternative medicine (CAM).

Cold Immersion:

This may be taken for four seconds to 20 minutes at a temperature ranging from 100C to 23.80C. Before entering the bath, cold water should be poured on the patient's head, chest, and neck and the head should be protected with a cold moist towel. During the bath, the patient should vigorously rub his or her body. After the bath the body should be quickly dried and wrapped up in a blanket. If the climate is favorable, moderate exercise should be undertaken.

This bath helps to bring down fever. It also improves the skin when taken for five to 15 seconds after a prolonged hot bath, by exhilarating circulation and stimulating the nervous system.

Dietary Supplements:

The main role of multiple sclerosis diet is to enable people to manage common problems which include fatigue, incontinence and constipation and to help them avoid exacerbating other symptoms. Currently dietary regimens advertised as being beneficial or even curative for multiple sclerosis symptoms follow three basic hypotheses of the cause of multiple sclerosis: excess of or deficiency in a food, allergic reaction to a food and toxic effects of a food. So the general rules of a dietary therapy is: Eat a diet high in protein and anti-inflammatory oils (nuts, seeds, and cold-water fish); orange, yellow, and dark green vegetables; Whole grains - such as whole wheat, brown rice, oats and whole grain corn - provide a fiber boost to the carbohydrates in your diet Avoid food allergens such as wheat, dairy, eggs, soy, citrus, tomatoes, corn, chocolate, fish, and peanuts - eliminate these foods, then reintroduce one at a time, watching for reactions. Many individuals with multiple sclerosis are sensitive to foods that contain gluten. Eliminate refined foods, alcohol, caffeine, saturated fats (animal products), and additives (multiple sclerosis G and aspartame). Individuals with multiple sclerosis should follow the American Heart Association guidelines on fat intake.

Omega-6 and omega-3 essential fatty acids might slow the progress of the disease and reduce the severity and duration of relapses. It is suggested to havemega-6 oils (borage, evening primrose, black currant oils) 1,500 mg two to three times per day. Include zinc (30 mg per day) and selenium (200 mcg per day). As the diet may contain high levels of polyunsaturates, a good intake of vitamin E, vitamin B6, zinc and vitamin C is needed. Vitamin E is the main antioxidant that helps prevent peroxidation of polyunsaturates and vitamin C helps to protect vitamin E. Zinc and vitamin B6 are part of the enzyme delta-6-desaturase which is involved in conversion of linoleic acid (found in polyunsaturated fat and oils) to its longer chain derivatives. Alcohol inhibits the vital conversion process of essential fatty acids, increases the level of saturated fat in the blood and depletes the body's supply of valuable nutrients. So drink alcohol in moderation Smoking also depletes blood levels of vitamin C and can worsen the symptoms of the disease.

Herbal Medication:

Inflammation of nerve tissue is partly responsible for the breakdown of myelin in people with MS. When intravenous injections of a constituent of Ginkgo biloba, known as ginkgolide B, were given to people with multiple sclerosis for five days, 80% of them reportedly improved. This specialised treatment is experimental, and it is not known whether oral use of ginkgo extracts would have the same effect.

Green Tea is has potential in the treatment and prevention of neuro-degenerative diseases, such as MS. A major constituent of green tea is epigallocatechnin-3-gallate (or ECGG). This has been found to powerfully inhibit auto-reactive T cells (imuune cells that attack one's own tissue). Green tea, is derived from dried leaves of the Camellia Sinesis plant, came over from China between 4,000 and 5,000 years ago. Now green tea is popular both for its taste and many health benefits.

Homeotherapy:

Homoeopathy is a system of medicine which has a different approach to disease and remedy from that of conventional or Allopathic medicine. In the Allopathic approach, medicines are used that work against diseases and their symptoms. In Homoeopathy, the symptoms of an illness are viewed as a direct manifestation of the body's attempt to heal itself and a Homoeopathic substance is given that is capable of producing similar symptoms if given to a well person. In so doing, Homoeopathic attempts to stimulate the body's own natural healing capacity with Homoeopathic remedies acting as a trigger for the body's own healing forces.

Injection of Venom such as snake and bee:

Use of bee venom as medicine is a part of apitherapy, a discipline of alternative treatment that in addition to venom utilizes other bee products such as honey, pollen and royal jelly. Although there are claims that the treatment does work, the medical community is less confident in apitherapy. Apitherapy has been a popular form alternative medicine throughout history, with stories of Frank king Charlemagne treating himself with bee stings and a reference to the medicinal use of produced liquid appearing in the Koran.

Use Bee venom is purported to contain an anti-inflammation agent as well as amines, enzymes and peptides, all of which have medicinal properties to treat arthritis, back pain, eczema, herpes, multiple sclerosis, psoriasis and migraines, according to the American Cancer Society. While traditionally bee venom is injected by inducing live bees to sting the patient in the right area, it also can be taken as a cream, ointment or injection. The administration can cause inflammation, pain, redness, itchiness and swelling.

Massage:

Massage therapy can play an effective role in reducing both the symptoms of MS and the stress of daily life. For joint stiffness, massage increases blood circulation in muscles around joints, which creates more pliable tendons, ligaments, and other connective tissue. More pliable tissue means easier joint movement. The effects of massage can be enhanced by stretches and

exercises that maintain a joint's range of motion and flexibility between massage therapy sessions. For muscle weakness or atrophy, it's important to maintain the integrity of muscle tissue. Massage therapy improves the circulation of oxygenated, nutrient rich blood to muscles and other tissues.

For excess muscle tension or spasticity, many massage techniques reduce abnormal muscle tone; relieve pain, and increase circulation and muscle length to reduce spasm. Other massage strokes sedate the nervous system or local peripheral nerves, which temporarily reduces their exaggerated stimulation of muscle fibers.

Reflexology:

Reflexology is a therapeutic technique from traditional Chinese medicine in which pressure is applied to the feet (and sometimes hands) without using oils or creams.

Yoga:

Yoga stresses the need for stretching and breathing. This helps release tension, improves circulation as well as body awareness. Further, Yoga helps reduce fatigue in patients with multiple sclerosis. Yoga practice also helps harmonize the muscular and nervous systems. This results in more fluid movement and relief from muscle tension. As the patient's level of body awareness improves, he / she are able to recognize the first sign of stress on the system before it gets overwhelming.

For a patient suffering from multiple sclerosis, Yoga directly addresses 3 types of symptoms, viz. fatigue and heat intolerance, loss of coordination and numbness in limbs, and loss of flexibility and balance. Fatigue and heat intolerance seem to be the most limiting factors multiple sclerosis patients. To offset these constraints, patients have to learn to master their breathing and practise restorative postures such as Tadasana (Mountain Pose), Virabhadrasana I (Warrior Pose I) and Virabhadrasana II (Warrior Pose II), and Trikonasana (Triangle Pose).

Both techniques, together, help cool down the body and calm the nervous system. Simple breathing techniques of extending the exhale a bit longer than the inhale help calm the nervous system. Heat, stress, and tension can cause temporarily aggravate symptoms of multiple sclerosis. Hence, the pace of practice should be relaxed yet focused. Keep the body just short of sweating; this is very important [21,24].

CURRENT THERAPY

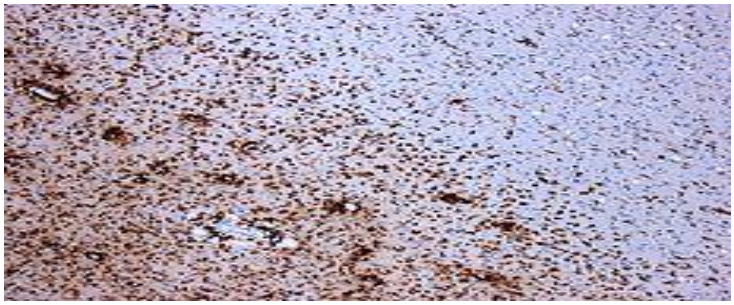
Interferon-beta (IFN) for Relapsing remitting MS

IFN is a naturally occurring cytokine with immunomodulatory and antiviral properties. There are several class I clinical trials showing a beneficial effect on relapse frequency in relapsing-remitting MS (for review see reference. The drugs are generally considered to reduce the relapse frequency by approximately 30%. The IFN β drugs have also been shown to have a substantial effect in reducing the numbers of new lesions and delaying the increase of total lesion load seen on brain MRI scans. The effect on long term disability and in secondary progressive MS, unless there are concomitant relapses, is less well studied and more uncertain. In some small studies of primary progressive MS, IFN β drugs have not been shown to be clinically useful. The most frequent side effects of IFN β are "flu-like symptoms" with muscle pain and fever or local injection-site reactions. If side effects occur at initiation of treatment, they usually subside or disappear after some weeks.

Glatiramer acetate (GA)

Glatiramer acetate is a polypeptide of 4 amino acids based on the composition of myelin basic protein. Several putative immunological mechanisms have been discussed including generation of GAreactive T helper 2 (anti-inflammatory) cells and a possible neuroprotective effect. GA has, in a class I study, been shown to reduce the relapse rate in relapsing- remitting MS by approximately 30%. Other studies have shown beneficial effects on MRI parameters. The most frequent side effects of GA are usually mild and include local injection site reactions with pain, but also more generalized or systemic reactions, including sweating, palpitations and shortness of breath [24,25].

Fig 1. The CD68 (monocytes) colored tissue shows several macrophages in the area of the lesion



CONCLUSION

It is known from previous studies of the natural history of MS, that a high frequency of clinical relapses over the first years is associated with an increased risk of later deterioration. Based on this observation and the inflammatory reactions described in MS there are reasons to initiate treatment as early as possible to prevent axonal damage and irreversible damage. There have been three large clinical trials performed to evaluate the effect of IFN β treatment after the first clinical isolated syndrome (CIS). Avonex and Betaferon have been registered for initiation of treatment after the first clinical event suggestive of MS.

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