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Review Paper

Utility of Magnetic Resonance Imaging in Multiple Sclerosis: A Comprehensive Review of Diagnostic and Prognostic Applications

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ABSTRACT:
Multiple Sclerosis (MS) is the most commonly occurring disease that is a non-traumatic disease to affect the young generation. The occurrence of multiple sclerosis is rapidly increasing on a worldwide scale. The main cause of multiple sclerosis is thought to be compound gene-environment relations. Various things play a huge part in the development of this disease are- low vitamin D, smoking, childhood obesity, and some infections. As and when changes in the diagnostic criteria and methods occur, we can diagnose multiple sclerosis very early in the disease trajectory. Along with this, there has been an exponential increase in the number, risk, and efficacy of the cure of multiple sclerosis. We are now in a place where we can diagnose pre-symptomatic MS. MS affects the CNS and is an inflammatory disease that occurs most commonly in people of age 20-40 years. MRI has played a very important role in revolutionizing the diagnostic accuracy of multiple sclerosis in adults, and because of that it is now being used extensively to evaluate the efficacy of immune-modulatory therapies. The diagnosis of multiple sclerosis is based on the history of demyelination of the central nervous system and physical signs and symptoms that are seen upon examination. The diagnosis of MS is confirmed by evaluation through MRI. Currently, MRI is the most reliable and widely accepted biomarker for the evaluation of multiple sclerosis.

Keywords: Multiple Sclerosis, Demyelination, Myelin sheath, Magnetic Resonance Imaging, demyelinating diseases.

INTRODUCTION:

HISTORY OF MULTIPLE SCLEROSI:

MS is a disease that usually disables the brain along with the spinal cord. French professor Jean Cruveilhier and British professor Robert Carswell, who taught pathologic anatomy and showed the disease's different clinical features, never thought of the condition as a distinct disease. "A remarkable lesion of the spinal cord accompanied by atrophy," was how Carswell described the wounds after discovering them. A Swiss doctor named Georg Eduard Rindfleisch observed that the inflammations around the blood arteries were dispersed throughout the lesions later in 1863. (Compston, 1988) (Lassmann, 2005)

ANATOMY OF HUMAN BRAIN:

The human brain is a roughly 1.45kg organ that performs amazing functions like interpreting information that comes from the external world and embodies the main essence of the mind along with the soul. The brain is protected within the skull, and it has 3 parts, namely- cerebrum, cerebellum, and brainstem. (*Neuroimaging Genetics: Principles and Practices - Google Books*, no date)

Cerebrum: Both the hemispheres of the brain are located in cerebrum, which is biggest part of brain. It carries out a variety of higher order tasks. (*The Science & Psychology of Music Performance: Creative Strategies for ... - Google Books*, no date)

Cerebellum: It is found below the cerebral cortex. Its major job is to keep the posture and equilibrium while coordinating all the muscle movements. (Nashner, Shumway-Cook and Marin, 1983)

Brainstem: The cerebellum and brainstem are connected to the spinal cord by this area, which serves as a relay hub. Along with breathing, heart rate, body temperature, wake and sleep cycles, vomiting, and swallowing are just a few of the automatic processes it undertakes. (Nowinski, 2011)

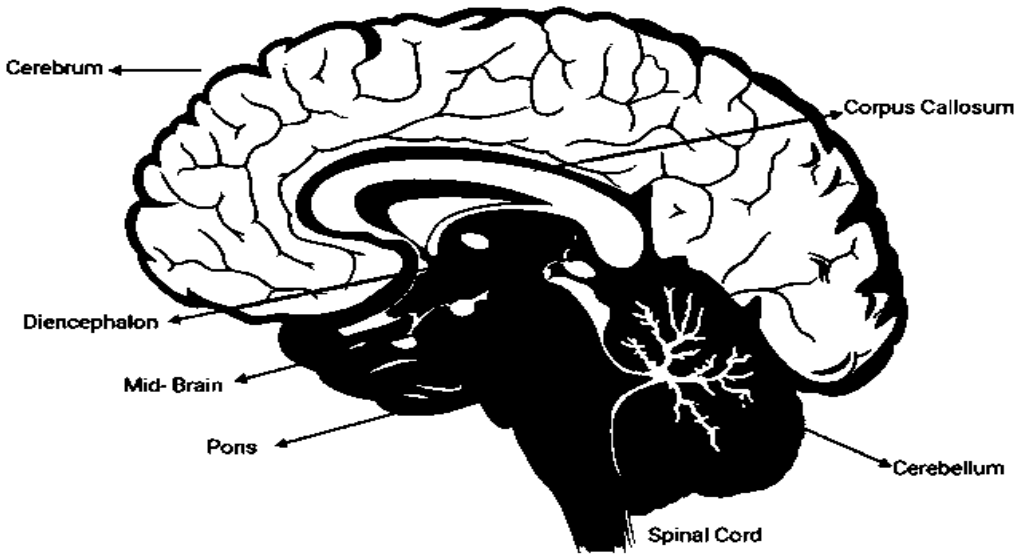


Fig1. Parts of the brain

Left brain and the right brain: Left as well as the right hemispheres of the brain's cerebrum is the two divisions. The network of fibers known as corpus callosum which connects them and carries all the messages from one side of the brain to the other side. Control over the opposing side of the body is exercised by each hemisphere. (Sperry, 1975)

Lobes of the brain: The brain's hemispheres are divided into several lobes by discrete fissures. There are four lobes in each hemisphere of the brain: parietal, frontal, occipital, and temporal. It is possible to further separate each lobe into regions with distinct functions. (Standring and Gray, 2008)

ANATOMY OF THE HUMAN SPINAL CORD:

There are 33 separate bones that make up the human spine. The body's primary support structure is the spinal cord. We can stand straight, stoop down, and turn around thanks to it. (Maton, 1993)

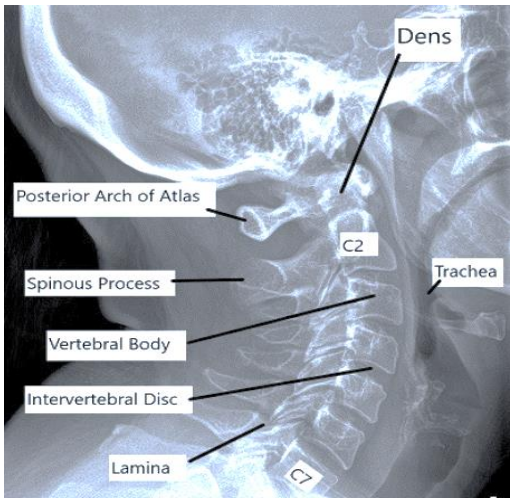


Fig2. Cervical Spine anatomy (Sharda Hospital)

3.1 Spinal Curves: When the spine is seen from the lateral aspect, it is viewed as an S-shaped curved organ. The neck or the cervical spine region along with the lower back or the lumbar region has a gentle concave cure, whereas the upper back or thoracic region has a slight concave curve. These curves of the spine function as shock absorbers, help in maintaining balance and allow a wide range of movements along the spinal column. (Guertin, 2012)

Vertebrae: The vertebrae are the 33 separate spinal column bones that fit together to form the spine. These are separated into the cervical, lumbar, thoracic, sacral, and coccyx areas.

A. Cervical (neck region) – The cervical spine supports the weight of the head as its primary

function. The cervical vertebrae are seven in number.

B. Thoracic (upper back area) - The DL spine's major function is supporting the rib cage and safeguarding the important organs including the heart and lungs.

C. Lumbar (lower back area) - The lumbar spine's main function is to support the weight of the entire body. The first lumbar vertebra, L1, is among the five.

D. Sacrum: The sacrum connects the hip bones to the spine and serves as its main purpose. There are five fused sacral vertebrae in total.

E. Coccyx region - the four fused bones of the coccyx region, often known as the tailbone, serve as attachment points for the pelvic floor's ligaments and muscles**.** (Saladin, 2012)

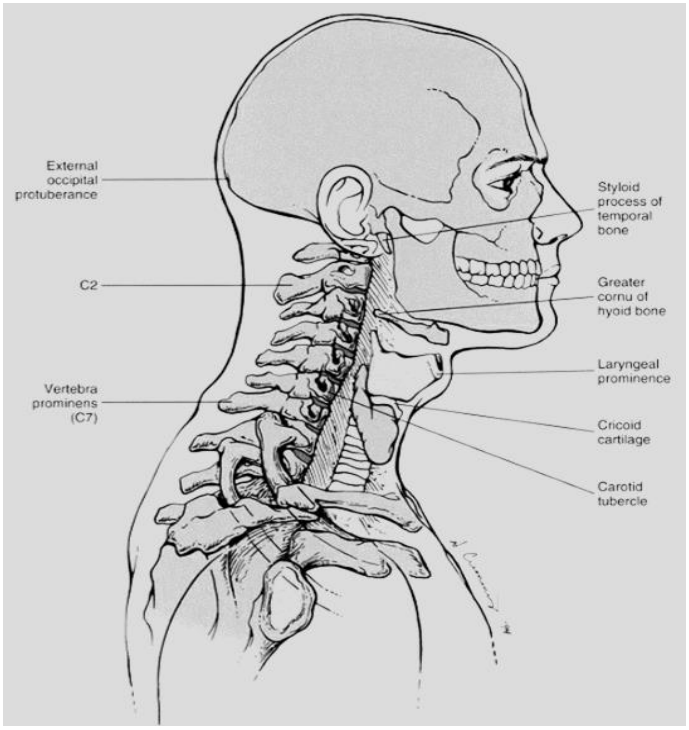


Fig 3. Cervical Spinal Cord (Cramer and Darby, 2013)

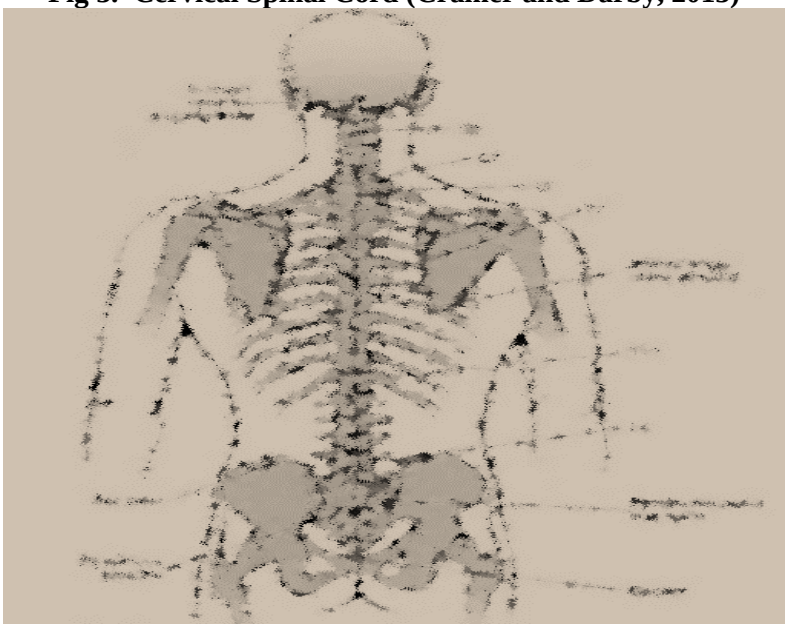


Fig 4. Anatomy of Spinal Cord including cervical, lumbar and thoracic spine (Cramer and Darby, 2013)

MULTIPLE SCLEROSIS:

In multiple sclerosis, the myelin layer or the protective sheath which Communication problems amongst the brain and the remaining body result from the immune system attacking the membrane that surrounds the nerve fibres. Sclerosis is the pathological hardening of tissues, mainly because of the overgrowth of fibrous tissue; or it can be caused due to increase in interstitial tissue also. Multiple sclerosis causes damage to the nerve fibres of the CNS. As time passes MS can lead to problems in vision, weakness of the muscles, loss in balance or numbness. Several drug therapies can be used to slow the disease's progress as they can limit nerve damage. MS is inflammatory, chronic and an autoimmune neurological disease of the CNS. The axons in the CNS are attacked by multiple sclerosis, which in turn destroys the myelin sheath along with the axons to varying degrees. The course with which the multiple sclerosis attacks the myelin is very unpredictable and varied. MS is diagnosed based on evidence and clinical findings from the ancillary tests, including MRI, and CSF examination. MS is mainly present in people from age group of 20 to 45 years of age, and sometimes it can be visible in people in their childhood or late middle age. (Rudick *et al.*, 1997)

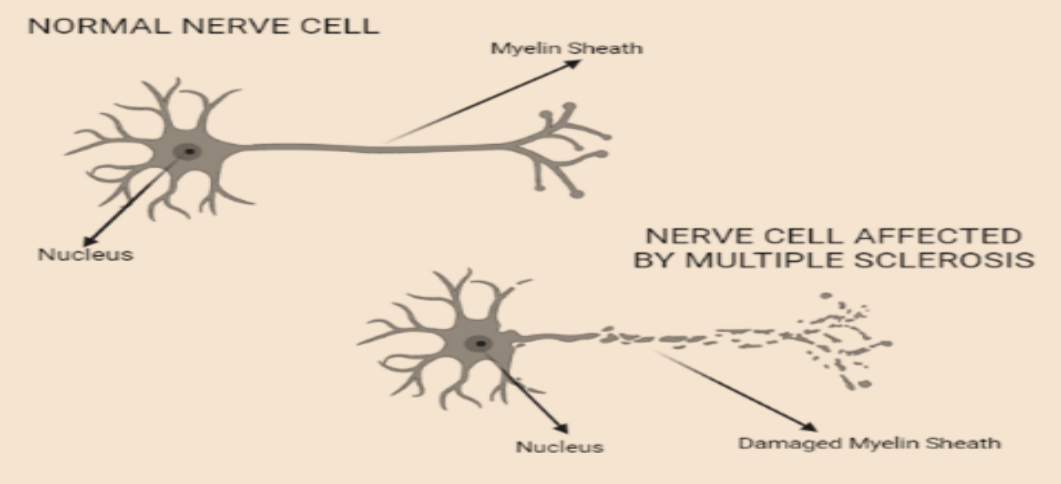


Fig 5. Nerve cell affected by multiple sclerosis

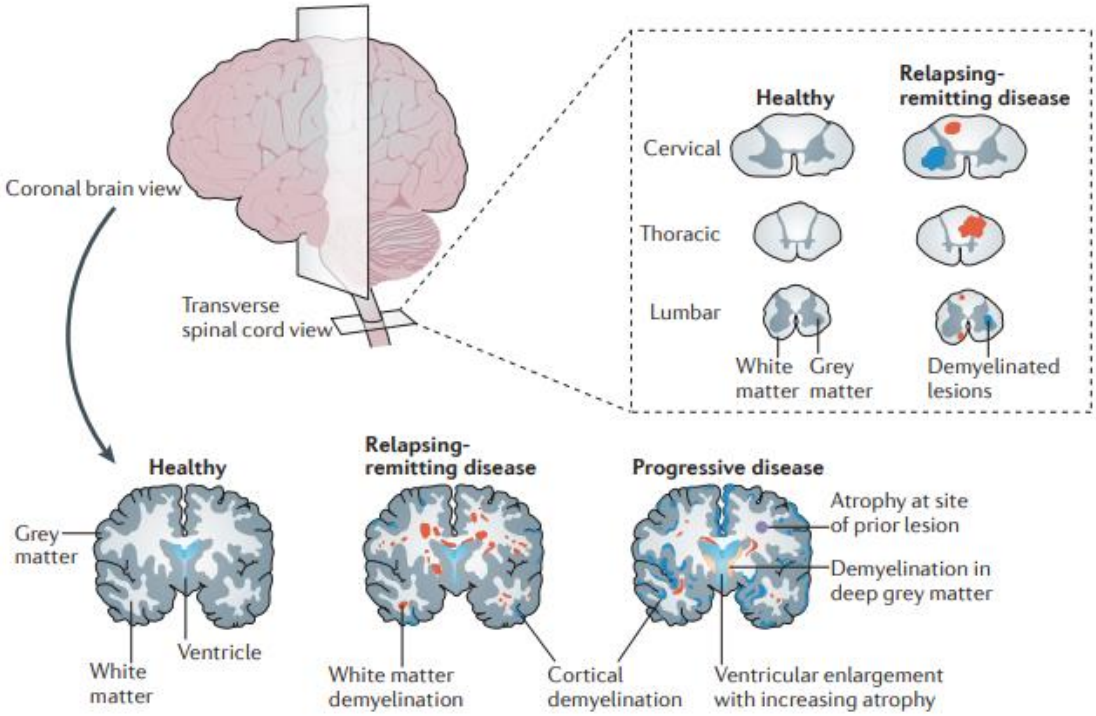


Fig 6. Pathology of Multiple Sclerosis (Dendrou, Fugger and Friese, 2015)

CAUSES OF MULTIPLE SCLEROSIS:

The main reason behind occurrence of MS is not known, but it is thought that it is usually caused due to a mixture of genetic factors and environmental factors which include various agents. (Milo and Kahana, 2009)(Milo and Kahana, 2009)

Infectious Agents- Various types of microbes have been suggested as the cause of multiple sclerosis. One of the theories holds that a broad microbial infection aids or accelerates the development of the disease, and that the geography of the individual has a substantial impact on the course of the disease's development. According to the hygiene hypothesis, early life exposure to some infectious agents can guard against them later in life, and any subsequent contact with these agents causes sickness. According to the widely accepted theory, the probability of contracting the disease is increased by any early exposure to the infectious agent is commonly found. (Pugliatti *et al.*, 2008)

Genetics- Although multiple sclerosis is not a sort of hereditary disease, the risk increases if it was common in earlier generations. Microglial cells have a higher prevalence of some disease-related genes. The likelihood of contracting the disease increases with degree of relatedness. MS is allegedly more common in certain ethnic groups compared to others. (Skene and Grant, 2016)

Geography- Though there are few exceptions, multiple sclerosis is more likely to affect those who are living further away from the equator. These mentioned exceptions which are ethnic groups like the Amerindians, Sami, Canadian, New Zealand Mori, Hutterites, and Canada's Inuit who have a substantially reduced chance of contracting MS and also reside far from the equator. It is still unclear what causes this spatial pattern to be valuable. (Alonso and Hernán, 2008)

Other- an independent risk factor for multiple sclerosis includes smoking. Stress is also considered as a huge risk factor. Along with occupational exposures and toxic substances which mainly include organic solvents multiple sclerosis is often associated. Many other risk factors are the diet of an individual, their hormonal intake as well as childhood obesity. (Hedström *et al.*, 2018)

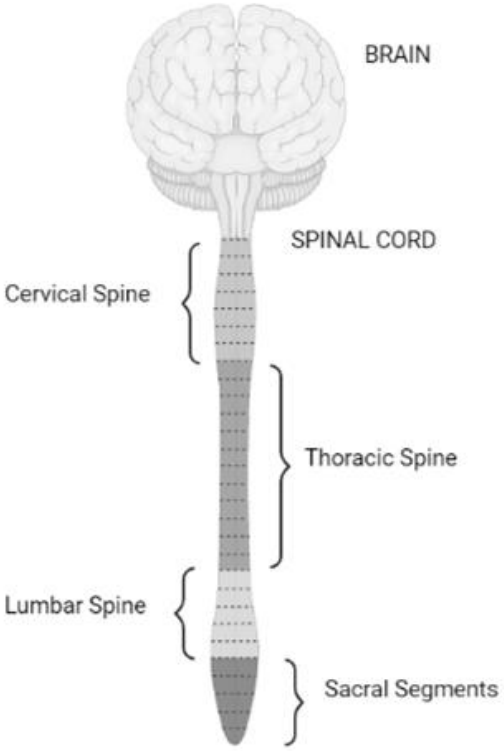


Fig7. Central Nervous System

PATHOPHYSIOLOGY OF MS:

The expansion of lesions on the CNS, swelling, and the degeneration of the neurons' myelin layers are the three basic traits or aspects of MS. These features combine in a difficult way to start the breakdown of nerve tissues, which then causes the disease's signs and symptoms. The category of immune-mediated illnesses, which include multiple sclerosis, results from a complicated interaction between a person's genetics and environment. It is thought that the person's own immune system is what

harms the neurological system. (Cantuti-Castelvetri *et al*., 2018)

Lesions: The lesions which develop in the neurological system are known as multiple sclerosis. The white matter, which is present in the brain stem, basal ganglia, spinal cord, and optic nerve, is typically affected by these injuries. These white matter cells' primary job is to transmit messages between bodily regions with grey matter and the remainder of the brain. Rarely is the Peripheral Nervous System involved in this illness. (Chari, 2007)

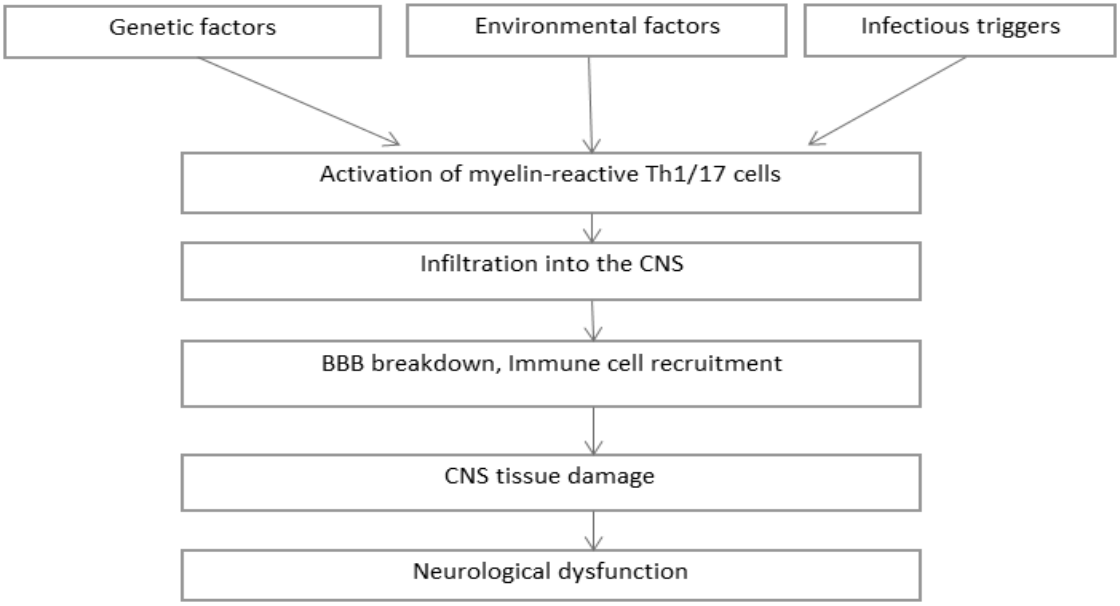


Fig 8. Pathophysiology of MS

Inflammation: Inflammation is another symptom of multiple sclerosis besides demyelination. T-cells are lymphocytes that play a highly crucial function in the body's defences and are what induce inflammation. When the blood-brain barrier (BBB) is breached, these T-cells can enter the brain. The T-cells assault the myelin sheath because they perceive it as a foreign object, which results in demyelination. (Compston and Coles, 2002)

Blood-brain barrier: The BBB is a crucial component of the capillary network which blocks T-cell entry into the brain. After a viral or bacterial infection, the BBB may eventually become permeable to T-cells. The T-cells may still be imprisoned inside the brain even after the BBB repairs itself, which often happens after the infection has subsided. Gadolinium-enhanced MRI is used to view the BBB collapse since the metal cannot traverse a healthy blood-brain barrier. (Huang, Hussain and Chang, 2021).

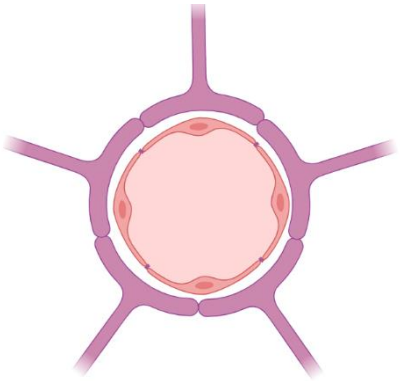


Fig 9. Cross-section of Blood-brain barrier.

The course of the disease is grouped into 4 major categories by Neurologists, namely:

1. **Relapsing-remitting multiple sclerosis:** It is a collective type of MS which affects almost 85% of total Multiple Sclerosis patients. Relapses or exacerbations of the symptoms are used to diagnose it, followed by intervals of remission.
2. **Secondary progressive MS:** In some patients it may develop along with relapsing-remitting disease. In many patients, to delay such progression, treatment with disease-modifying agents helps a lot.
3. **Primary progressive MS:** It affects 10% of the total multiple sclerosis patients. Its symptoms keep on worsening from its outcome. The medications that are typically used to treat the condition are not very effective against this type of MS.
4. **Progressive-relapsing MS:** Less than 5% of MS patients have this extremely unusual type of the disease. In this form, there are no remissions seen. Starting off, it progresses gradually with occasional flare-ups of progressively worsened symptoms over time. (Dobson and Giovannoni, 2019)

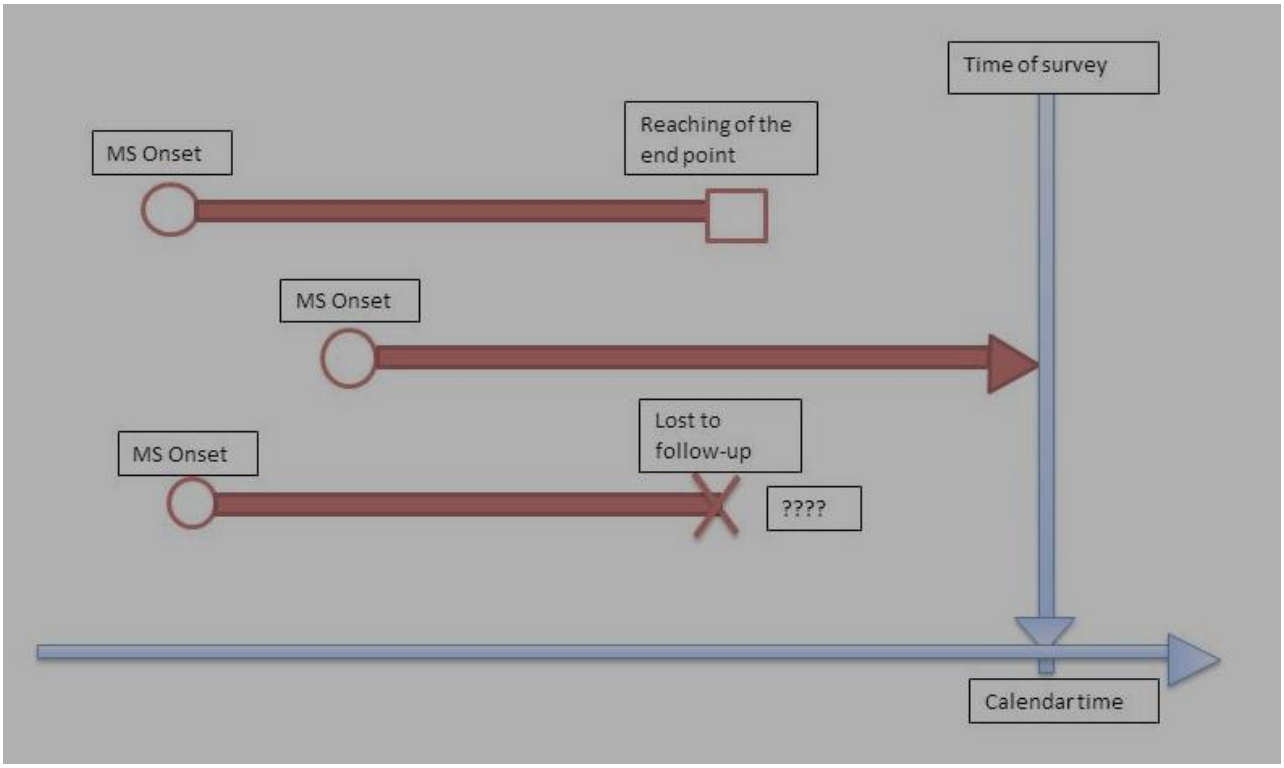


Fig 10. Course of Multiple Sclerosis.

DIAGNOSIS OF MULTIPLE SCLEROSIS:

Multiple sclerosis has no test for diagnosis. The diagnosis is done on the evidence of:

1. **SPACE DISSEMINATION CRITERION:** Two or more distinct lesions, such as white matter plaques or scars, must be present in the CNS's white matter.
2. **TIME DISSEMINATION CRITERION:** A minimum of 2 different episodes in the disease course.
3. **INFLAMMATORY CRITERION:** Analysis of the Cerebro-spinal fluid determines the chronic inflammation of the Central Nervous System. (Brownlee *et al.*, no date)

The physician does the following to diagnose multiple sclerosis:

Finding evidence of damage in minimum 2 different areas of the CNS, which include the optic nerve, spinal cord, and the brain. Determining that damaged areas develop 1 month apart from one another. All the other kinds of diagnostic possibilities should be excluded. The symptoms should last for more than a day, i.e., 24 hours. A magnetic resonance imaging test should be performed. (Rudick *et al.*, 1997)

SIGNS AND SYMPTOMS OF MULTIPLE SCLEROSIS:

MS is an unpredictable disease, but here are some of its symptoms:

1. FATIGUE: Affects roughly 80% of people and can make it difficult to carry out daily tasks at home and at work. In a person who is otherwise healthy and active, it could be the most noticeable symptom.
2. NUMBNESS AND TINGLING: For those who are eventually diagnosed with MS, numbness and tingling of the face, body, or upper and lower extremities is frequently the initial symptom.
3. WEAKNESS: In MS, the deconditioning of inactive muscles or damage to the nerves that activate muscles cause weakness.
4. VERTIGO AND DIZZINESS: People with MS may experience vertigo, dizziness, or the sense that they or their surroundings are whirling.
5. SEXUAL PROBLEMS: Symptoms and injury to the central nervous system can both impair sexual responses.
6. PAIN: According to a study, "clinically significant pain" was experienced by 55% of MS patients at some point.
7. EMOTIONAL CHANGES: Neurological and immunological changes, as well as the strains of living with MS, can cause emotional changes.
8. DEPRESSION: Studies have shown that clinical depression, the most severe type, is one of the signs and symptoms of MS.
9. COGNITIVE CHANGES: This term describes a variety of high-level brain activities that are compromised in more than 50% of MS patients. (Oreja-Guevara *et al.*, 2019).

INVESTIGATION OF MULTIPLE SCLEROSIS:

NAME OF INVESTIGATION	FINDINGS
Cerebro-Spinal Fluid	• Myelin debris, oligoclonal bands, aberrant colloidal gold curve, raised IgG, minor mononuclear pleocytosis, and normal or slightly elevated protein.
BLOOD TESTINF FOR MS	• Antiphospholipid antibody syndrome, B-12 and folate levels, antinuclear antibody (ANA) titers, and women with unexplained miscarriages or a history of deep venous thrombosis must be investigated in individuals with evidence of blood dyscrasia. • Elevated ESR and elevated rheumatoid factor titers should be able to detect the presence of a vasculitis illness that may be mistaken MS.
MAGNETIC RESONANCE IMAGING	• MRI of CNS shows many plaques. • MRI shows multiple lesions with high T2 signal intensity. • Demyelinating lesions sometimes copy brain tumours because of the associated Edema and swelling.

CLINICAL SIGNIFICANCE:

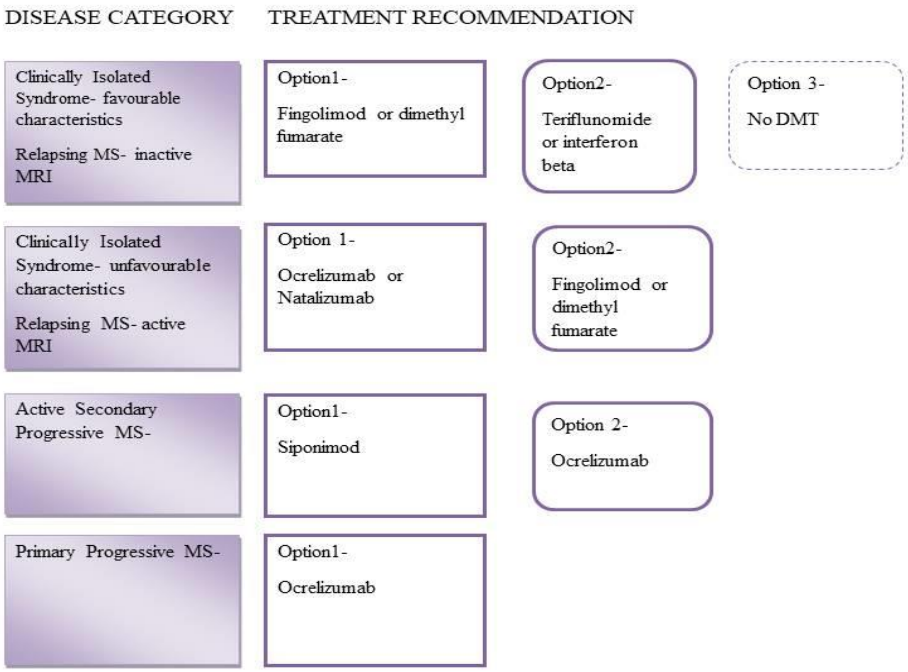
MS is a very commonly found autoimmune disease of CNS that causes demyelination. It has 2 main components, namely- inflammation and neurodegeneration, which is reasons for worsening. Recently formed multiple sclerosis theories are very effective in preventing attacks, and they are known to partially protect against progression. (Sospedra and Martin, 2005)

PATHOLOGIES UNDERLYING MULTIPLE SCLEROSIS PROGRESSION:

The various pathologies underlying multiple sclerosis are as follows:-

1. Classic MS Plaque: These are known with relapses, but these can also be seen for patients who don't get short attacks and progress gradually.
2. Meningeal B-cell Rich Follicle: These aggregate in meningeal region and are usually found within the deep sulci.
3. Enlarging Plaque: These lesions are because of gradual concentric expansion in the chronic plaques.
4. Diffuse White Matter Gliosis: Widespread astrogliosis and diffuse microglial inflammation in the white matter of the CNS, together with diminished density of the myelin and continuing axonal injury.
5. Atrophy related to age: Is age related neurodegeneration. (Popescu, Pirko and Lucchinetti, 2013)

An algorithm for disease-modifying therapies used for MS:



DRUGS FOR MS:

NAME OF THE DRUG	COMPANY THAT PRODUCES DRUGS	DESCRIPTION OF THE DRUG	THERAPEUTIC DOSAGE OF THE REQUIRED DRUG
Teriflunomide	Sanofi/ Genzyme	Immune modulator; active metabolite of leflunomide	7mg or 14mg once daily PO
BG-12	Biogen Idec	Immune modulator	240mg twice or three times daily PO
Alemtuzumab	Genzyme	CD52-targeted humanized monoclonal antibody	30mg/day three times per week for 12 weeks IV
Rituximab	Genentech	CD20-targeted chimeric murine/human monoclonal antibody	375 mg/m² IV
Ocrelizumab	Roche/Biogen	CD20- targeted humanized monoclonal antibody	600 mg or 2,000mg in two doses
Laquinimod	Active Biotech/ Teva	Synthetic small-molecule, anti-inflammatory agent	0.6mg once daily PO
Daclizumab	Roche	CD25-targeted humanized moclonal antibody	1.0mg/kg IV

In total there are 7 drugs used for MS:

1 LAQUINIMOD: Laquinimod is an orally active, anti-inflammatory agent, synthetic, small molecule which affects the immune system. The Th2 response increases the synthesis of the neuroprotective molecules. (Dobson and Giovannoni, 2019)
2 TERIFLUNOMIDE: Teriflunomide, the active metabolite of leflunomide, is a medication that modifies the immune system. It prevents the mitochondrial enzyme dihydro-orotate dehydrogenase (DHODH) from functioning, reversibly inhibiting the de novo synthesis of the pyrimidine. (Dobson and Giovannoni, 2019)
3 BG-12 (Dimethyl Fumarate): An experimental immune modulator that is given orally and is now in phase 3 of clinical research as a monotherapy for relapsing-remitting MS is called BG-12. In the ongoing CONFIRM (Comparator and an oral Fumarate in Relapsing-remitting MS) experiment, BG-12 is also being tested in individuals with relapsing-remitting MS. (Dobson and Giovannoni, 2019)
4 DACLIZUMAB (Zenapax): It is a humanised IgGI monoclonal antibody that has been immune-suppressively authorised by the FDA. The mechanism of action of this medicine is believed to involve preferential binding to and inhibition of the IL-2 receptor on activated T cells, which prevents the depletion of T cells. After a kidney transplant, daclizumab is approved as a component of an immunosuppressive regimen to avoid acute organ rejection. (Dobson and Giovannoni, 2019)
5 ALEMTUZUMAB (Campath): A humanised monoclonal antibody called alemtuzumab (Campath/Lemtrada, Genzyme/Sanofi) is designed to target the immune cell surface protein CD52, which is widely expressed. The medication can also have neuroprotective effects and removes lymphocyte populations from the bloodstream for a brief period of time. (Dobson and Giovannoni, 2019)
6 RITUXIMAB (Rituxan): Rituximab is a modified chimeric murine/human monoclonal IgG1 kappa antibody that is directed against the CD20 antigen, a hydrophobic transmembrane protein found on pre-B and mature B cells. Rituximab is sold under the brand name Rituxan by Genentech. The Fc domain of the rituximab medicine engages immune-effector activities to induce the B-cell lysis in vitro. (Dobson and Giovannoni, 2019)
7 OCRELIZUMAB: A humanised anti-CD20 monoclonal antibody called ocrelizumab (Roche/Biogen Idec) is used to attack mature B cells. It was created especially for the treatment of autoimmune conditions like MS, rheumatoid arthritis, and lupus erythematosus. Ocrelizumab's development by Roche for the treatment of lupus and rheumatoid arthritis was put on hold in March 2010 as a result of significant infections, some of which were fatal, occurring during clinical studies. (Dobson and Giovannoni, 2019)

CLINICAL FEATURES OF MS:

Multiple Sclerosis is a path which goes from being a lot of risk, to being asymptomatic, at prodromal stage or even symptomatic phases. MS is mostly suspected when the patient comes with CIS. This syndrome is either mono or poly symptomatic based on where the eloquent lesion is present. Multiple sclerosis can also have a relapse which usually develops Seba cutely over a time period of hours to days and reaches a plateau stage which lasts for several weeks before gradually recovering. Relapses even though can be treated they usually leave some damage behind. (Dobson and Giovannoni, 2019)

TREATMENT AND MANAGEMENT OF MULTIPLE SCLEROSIS:

Multiple Sclerosis treatment can be divided into 2 types that are:

disease modifying therapies and symptomatic treatments. These are used in various areas were the disease that affected and caused symptoms that are a cause of neurological dysfunction. (McGinley, Goldschmidt and Rae-Grant, 2021)

1 **Disease Modifying Therapies**: when the number along with rate of success of therapies have increased the attention to treat MS at an early stage so that long term disability can be prevented has also increased. A recent concept for the treatment of multiple sclerosis is NEDA, this has made us understood that clinical relapses are only a part of the bigger problem.
2 **Symptomatic Treatments**: these mean the pharmaceutical and physical therapies that are done in order to treat the symptoms that occur due to any damage to the central nervous system. These symptoms are not MS specific but rather treat the symptoms that arise due to MS. (Dobson and Giovannoni, 2019)
3 Magnetic Resonance Imaging modality is used in the evaluation or diagnosis of multiple sclerosis. MRI is a modality that used magnetic field instead of ionising radiation to produce images of the internal structures of the body. (Update *et al.*, no date)

MRI:

It is a method which is continuously evolving from the last 20 years which yields Magnetic Resonance systems

that have stronger static magnetic fields. MRI is usually defined as a 'safe' modality because, unlike all x ray modalities, ionizing radiation is not utilized here. On the other hand, there are hazards within the MR area that should be considered while performing any procedure. Many of the injuries reported are related to MR and some of the fatalities that occur are a result of failure in following the safety standards of MRI. (Kearney *et al.*, 2018)

Fig 11. MRI machine

MAIN MECHANISMS OF MRI:

There are 3 basic mechanisms of MRI system:

A. Strong static magnetic fields: Any device can be rotated, dislodged, moved, or even accelerated towards the magnetic bore.

B. Pulsed gradient magnetic fields: These are more weak as compared to the magnetic field. For various features of image acquisition encoding is done using time-varying magnetic fields.

C. Pulsed radiofrequency fields: The main effect produced by this is their thermos genic effect. Out of all the energy which is applied, some is absorbed by our body and then is further turned into heat. (Dill, 2008)

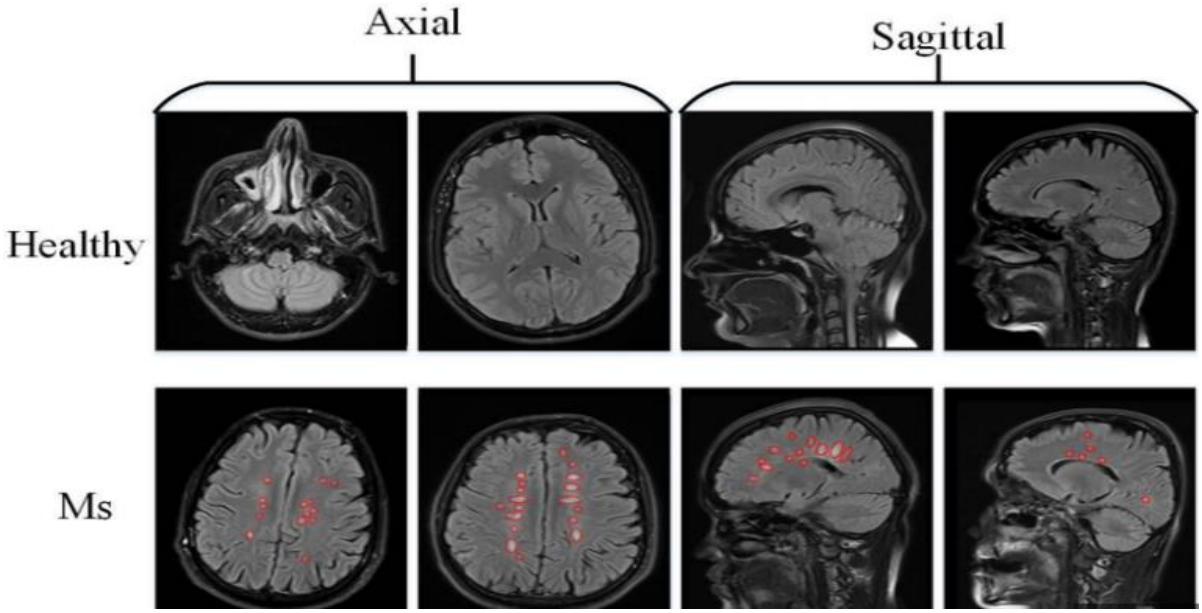


Fig 12. MRI of patient with and without MS.

MRI PERFORMED FOR MS PATIENTS TO EVALUATE:

All the patients that have symptoms similar to that of multiple sclerosis should undergo Magnetic Resonance Imaging of the brain as well as the spinal cord. MRI for multiple sclerosis helps to finalize the diagnosis by showing dissemination in time as well as in space.(Lassmann, 2005) MRI is also helpful as it excludes MS mimics when it is interpreted by a neuro radiologist. An MRI examination/imaging may help to rule in or rule out tethered cord syndrome, along with congenital malformations like syrinx and Chiari malformations. (Banwell *et al.*, 2007)

CONCLUSION:

Thanks to developments in our understanding of the origin and course of multiple sclerosis, treatment has advanced remarkably. Relapsing illness and focal brain inflammation have been brought under near-complete control as a result of the introduction of such potent medicines. Since none of the available treatments offer complete protection from the neurodegenerative aspects of MS, the effective treatment of progression remains an unmet need. The long-term course of this disease has reportedly been significantly improved during the era of treatment, according to all-natural history research. To acquire long-term efficacy and safety evidence for the medicines, all additional clinical and real-world evaluations are required. In order to establish evidence-based and individualized approaches to Multiple Sclerosis therapy and management, additional investigations of the usefulness of highly effective medicines for early treatment and early identification of patients who benefit most from treatment will also be crucial.

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