# **Review On Multiple Sclerosis**

#### Jyotsna Jangra<sup>1\*</sup> and Tausif Khan<sup>2</sup>

<sup>1</sup>Department of Biotechnology, Amity University, Noida, Uttar Pradesh, India <sup>2</sup>Department of Microbiology, SGRR, Dehradun, Uttarakhand, India

#### **Review Article**

#### ABSTRACT

Received: 06/12/2016 Revised: 15/12/2016 Accepted: 23/12/2016

#### \*For Correspondence

Jyotsna Jangra, Department of Biotechnology, Amity University, Noida, Uttar Pradesh, India.

**Keywords:** Demyelination, Autoimmune, Type 1 diabetes, Multiple sclerosis, Inflammation

E-mail: jyotsna.jangra@gmail.com

Multiple sclerosis occurs when immune system targets the central nervous system. It affects the myelin sheath which leads to disruption in the signalling process. Damaged myelin forms scar tissue known as sclerosis and inflammation process will take place by T-cell and other antibodies and cytokines. Individual suffers with MS shows various signs and symptoms including neurological symptoms with visual, motor and sensory problems. MS is classified into: Relapsing-remitting MS which later on leads to secondary progressive and primary progressive MS and lastly progressive relapsing MS which is a rare one. There is no particular cure for MS but with the help of medication and therapies, progress of this disease can be reduced.

### INTRODUCTION

Multiple sclerosis is a disease that targets the central nervous system. MS attacks the myelin sheath which is an insulating coating around nerve cells (demyelination). It is acknowledged to be an "immune-mediated diseases" rather than "autoimmune" <sup>[1-6]</sup>. The name of the disease is because the damaged myelin forms scar tissue which is called as sclerosis. When any part of the myelin sheath got damaged, nerve impulses travelling to and from the brain and spinal cord are disrupted which causes wide range of symptoms which can include physical, mental and even psychiatric problems <sup>[7-11]</sup>. MS continues to progress in a patient, sometimes symptoms may disappear completely but the neurological problems often remains especially when the diseases progress.

Still the cause for MS is unknown, and it is believed that genetics and environmental factors are responsible such as infectious agents. MS is not a hereditary disease but still number of genetic variations is responsible for increasing the risk <sup>[12-16]</sup>. The strongest genetic factor which consider to cause MS is the (Human leukocyte antigen) HLA-DRB1\*1501 haplotype. However, this is only responsible to increase the risk up to 2 to 4 fold and is present in 20-30% of individual <sup>[17-22]</sup>. Patients can be responsible to increase the risk of MS in their relatives with 20-40% fold and monozygotic twins are more at risk than dizygotic twins. According to the geography, people who live farther from the equator are more prone to have this disease. Statistic has shown that more than 400,000 people in the United States and more than 2.5 million people all around the world are infected with this disease <sup>[23-27]</sup>. In the United States approximately 200 people or more than that are diagnosed because of this disease.

MS normally starts between the ages of 20 and 40 years and it is the main source of non-traumatic handicap in youthful grown-ups. Initial manifestations once in a while happen before age 10 years or after age 60 years. The strongest genetic factor which consider to cause MS is the (Human leukocyte antigen) HLA-DRB1\*1501 haplotype <sup>[28-33]</sup>. However, this is only responsible to increases the risk up to 2 to 4 fold and is present in 20-30% of individual. Patients can be responsible to increase the risk of MS in their relatives with 20-40% fold and monozygotic twins are more at risk than dizygotic twins <sup>[34-37]</sup>. Environmental factors which can be responsible for MS are sunlight and UV exposure, EBV that is Epstein-Barr virus, vitamin-D and other viruses or infective agents <sup>[38-47]</sup>. It is estimated that this diseases is twice as high in northern state where this range is between 110 to 140 cases per 100,000 rather than in southern state with 57 to 78 cases per 100,000 people. In colder climate, there are high chances of getting MS, where northern European people are at higher risk, Asian and Native Americans are at lowest risk of getting this disease <sup>[48-55]</sup>. Studies have shown that immigrants are tends to take on the risk level either high or low which depends upon the area to which they move.



Figure 1: Multiple sclerosis Statistics.

More than 2.3 million people are affected with this disease. Statistics have shown that ratio of women with disease is more than men that is 2:1. MS is not an inherited disease but parents or sibling with MS have 1-3% chances of developing it and in case of twins, risk develops to 30%. People with thyroid problems, inflammatory bowel diseases and type 1-Diabetes are slightly at higher risk of getting MS <sup>[56-64]</sup>. Some factors may increase the chances of having MS for example: age: MS can affect any person at any age but mostly people between the age of 15 to 60 affected more. Some viruses are also linked with MS like Epstein-Barr, a type of virus which is responsible for mononucleosis. Smoking can also be a factor which can cause MS <sup>[65-73]</sup>. According to some hypothesis, individuals who exposed to more sunlight and UV rays have a lower incidence of MS which fits to the latitude-based observations but sometimes exception exists. Increased uptake of Vitamin-D results in decreased MS incidence but exceptions are also there with Israeli-born individuals. EBV and MS are also correlated, if at an early age one's exposed to this virus has less chances of MS <sup>[74-78]</sup>.

#### Pathophysiology

During the progression of MS, there are three main characteristics which MS follows: formation of lesions in the central nervous system which are called as plaques second is the inflammation and third is the destruction of myelin sheaths of neurons. The scar which forms during this disease commonly known as plaque or lesions affects the white matter in the brain stem, optic nerve and spinal cord <sup>[79-84]</sup>. As MS progresses, there will be thinning or complete loss of myelin which results in the breakdown of the axons of neurons which leads to the point where a neuron can no longer conduct electrical signals <sup>[85-93]</sup>. In the initial stage of MS remyelination process will take place but oligodendrocytes are unable to rebuild the cell's myelin sheath. Formation of these scars is the origin of MS.

Blood-brain barrier is the crucial part of the capillary system which prevents the entry of T-cell into the CNS (Central Nervous System). This barrier can be broken down because of any infection by a virus or bacteria <sup>[94-97]</sup>. The inflammation part is carried out by T-cell, which gain entry into the brain via disruption of this blood-brain barrier. T-cell will recognize myelin as a foreign body and attack it <sup>[98-100]</sup>. This will start inflammatory processes, which triggers other immune cells like cytokines and antibodies to release. Person with MS can show multiple signs and symptoms <sup>[101-105]</sup>. Most common are any neurological symptoms with autonomic, motor, visual and sensory problems. Visual symptoms can involve: Optic neuritis, Diplopia and Nystagmus, Dysphagia (throat problem), Dysarthria (speech), fatigue, cognitive impairment, depression, anxiety and unstable mood <sup>[106-110]</sup>. Musculoskeletal problems can be weakness, spasms and ataxia, diarrhea or constipation, pain, paraesthesias, incontinence, frequency or retention (urinary problem).

Multiple sclerosis can be, Primary Progressive MS (PPMS), Relapsing-Remitting MS (RRMS), Secondary Progressive MS (SPMS) and Progressive Relapsing MS (PRMS) <sup>[111-115]</sup>. RRMS is the common MS type, they will experience new or worsening symptoms known as "relapses" which can last for days to weeks and sometimes month also, then slowly improve over a period of time. Symptoms may disappear with or without any treatment but these attacks can be repeated over several years <sup>[116-120]</sup>. Periods between these attacks are called as "remission". Some people after many years go on to develop this disease which finally leads to secondary progressive MS. In this type of MS, symptoms gradually worsen over time without obvious attacks. Around half of the people with RRMS will gradually develop SPMS <sup>[121-125]</sup>.

Primary progressive MS affects few of the individual with around 10-20%. In this MS, after the initial symptoms there is no remission and improvements. Progressive relapsing MS describes individuals which have a steady neurologic decline with clear superimposed attacks <sup>[126-131]</sup>. It is the least common type of MS. There is currently no

such cure for MS but there is number of treatments that can help to control the condition which depends upon the specific symptoms and difficulties a patient have. Relapses can be treated with short courses of steroid medication which can help to speed up the recovery <sup>[132-138]</sup>. Also there is treatment available to reduce the number of relapses with medication which is called as diseases-modifying therapies. However, many treatments have unacceptable side effects with some cost-prohibitive issue. McLaughlin mentioned in research about OGF treatment which is a regulatory pathway involving opioid growth factor. OGF therapy initiated at the time of disease presentation <sup>[139-145]</sup>. Treatments may help the individual to slow or reduce the overall worsening of disability of MS. Unfortunately apart from that there is no treatment for MS. There are currently 12 disease modifying medications available in the market which is approved by the U.S. Food and Drug Administration: teriflunomide (Aubagio), interferon beta-1a, beta-1b, glatiramer acetate (Coaxone), fingolimod (Gilenya), mitoxantrone (Novantrone), Dimethyl fumarate (Tecfidera), natalizumab (Tysabri), alemtuzumab (Lemtrada) <sup>[146-150]</sup>.

#### Role of Open Access Journals and Global Events In The Awareness Of MS

Now-a-days more number of people is being diagnosed with MS. There is now increased awareness of MS and better diagnostic tools are available for the treatment of MS. Open access journals are also played their role in increasing awareness, it provide a platform for the researchers to update their current knowledge about the MS to the people. More the awareness is less chances of having MS in a population. Journal of Multiple Sclerosis is one of the journal which provides latest research on MS. Along with that Journal of Neurological Disorder is another open access journal with highest impact factor. These open access platforms encourage the researchers from all parts irrespective to economical and geographical barriers to publish novel findings in their peer-reviewed journals. More or less these journals help to fills the gap between the academics, clinicians and other professionals. Brain disorders journal serves the International scientific community with its standard brain research publications. Neurophysiology Journal is a scientific journal that deals with the diagnosis and treatment of all categories of diseases involving central, peripheral and autonomous nervous system.

To improve the understanding about MS, scientific conferences drew attentions of the researchers where discussion and panel meetings help to disclose more specific knowledge about those diseases. Conferences like 10<sup>th</sup> International Conference on Neuroscience and Neurochemistry which is organized by Conference Series LLC where experts will discuss about this field. For more knowledge on MS, there are some more conferences like 11<sup>th</sup> World Congress on Neurology and Therapeutics, and 3<sup>rd</sup> International Conference on Neuroinfecticious Disorders.

### CONCLUSION

Multiple sclerosis is one of those diseases which continue to progress in the body with no cure at all. It is an immune-mediated disease which directly effects on the coordination between the electrical signal to and from the brain. FDA has approved some of the drugs which can help in reducing the progression of MS in the body and some therapies are also there for MS. Taking these medicines doesn't approve that MS is treatable because sometimes despite everything a patient and physician do, MS still continue to get worse in some patients. Despite all of these, drugs and therapies may enhance the quality of life.

### REFERENCES

- 1. Mohamadirizi S, et al. Eating disorders in a multiple sclerosis clinical population and its association with social anxiety. J Mult Scler. 2016;3:183.
- 2. Petrou P, et al. Clinical efficacy of plasma-exchange in patients with progressive forms of multiple sclerosis and NMO-spectrum disease. J Mult Scler. 2016:3;181.
- 3. Hunter SF, et al. The effects of fingolimod on T cells and the central nervous system in the pathogenesis of multiple sclerosis. J Mult Scler. 2016;3:180.
- 4. Okuda B, et al. Useless Hand Syndrome and Astereognosis in Multiple Sclerosis. J Mult Scler. 2015;2:159.
- 5. Capelle V, et al. Multiple sclerosis and work: an interpretative phenomenological analysis of the perspective of persons with early stage MS. J Mult Scler. 2015;2:158.
- Mekers WFT, et al. Introduction of planaria as a new model for multiple sclerosis research: evidence from behavioural differences in cuprizone treated planaria exposed to patterned magnetic fields. J Mult Scler. 2015;2:156.
- 7. Rima R, et al. A rare case of familial multiple sclerosis. J Neurol Disord. 2015;S1:006.

- 8. Mohamadirizi S, et al. The survey of obsessive-compulsive disorder symptoms in patients with multiple sclerosis and its association with eating attitudes. J Mult Scler. 2016;3:179.
- 9. Stratton CW, et al. A review of multiple sclerosis as an infectious syndrome. J Neurol Neurophysiol. 2016;7:400.
- 10. Navikas V and Link H. Review: cytokines and the pathogenesis of multiple sclerosis. J Neurosci Res. 1996;45:322-333.
- 11. Clifford DB, et al. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. Lancet Neurol. 2010;9:438-446.
- 12. McDonald WI, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International panel on the diagnosis of multiple sclerosis. Ann Neurol. 2001;50:121-127.
- 13. Tremlett HL and Oger J. Interrupted therapy: stopping and switching of the beta-interferons prescribed for MS. Neurology. 2003;61:551-554.
- 14. Dalgaard JZ, et al. Could multiple sclerosis develop due to Epstein Barr virus infections causing a time-delayed transcriptional-activation of human endogenous retroviruses?. Adv Tech Biol Med. 2015;4:191.
- 15. Diaz EPC, et al. The clinical and epidemiological spectrum of multiple sclerosis in Quito, Ecuador. J Neurol Disord. 2016;4:312.
- 16. Caprio MG, et al. Vascular disease in multiple sclerosis: a real thing?. J Blood Disord Transfus. 2016;7:370.
- 17. Nischala T, et al. Multiple sclerosis patients gets the most help from nurses. J Nurs Health Sci. 2016;2.
- 18. Meheroz H, et al. Comparison of the kurtkze expanded disability status scale and the functional independence measure: measures of multiple sclerosis related disability. Int J Phys Med Rehabil. 2015;3:285.
- 19. Gallien P, et al. Interest of botulinum toxin for treatment of spasticity in multiple sclerosis. J Mult Scler. 2015;2:148.
- 20. Hauser SL and Goodwin DS. Harrison's Principles of Internal Medicine. 17th ed. McGraw-Hill Medical. New York.
- 21. Weinshenker BC. Epidemiology of multiple sclerosis. Neurol Clin. 1996;142:1-308.
- 22. Londoño AC, et al. Autologous bone marrow transplantation in multiple sclerosis: biomarker relevance for patient recruitment and follow up. J Clin Cell Immunol. 2016;7:455.
- 23. Bsteh G, et al. (2016) A case of eight-and-a-half-syndrome as a presenting manifestation of late onset multiple sclerosis. J Clin Case Rep 2016;6:845.
- 24. Blumberg BM, et al. HHV-6, not JC virus, causes demyelination in PML connections between HHV-6, HIV-1 and JC virus in multiple sclerosis, Neuro-AIDS and PML a commentary and review offering guidelines for treatment. J Neurol Disord. 2016;4:299.
- 25. Hamzeh AS, et al. A case control study: vitamin D status and sun exposure in multiple sclerosis. J Mult Scler. 2015;2:147.
- 26. Kruger PG, et al. Are mast cells the key to multiple sclerosis?. J Mult Scler. 2015;2:146.
- 27. Calabresi PA. Diagnosis and management of multiple sclerosis. Am Fam Physician. 2004;70:1935-1944.
- 28. Solimando AG, et al. B-Cell therapies in relapsing remitting and primary progressive multiple sclerosis: a short clinical review. Biochem Pharmacol. 2016;5:218.
- 29. Backus D, et al. People with multiple sclerosis (MS) improve in measures of health and function after participation in a community-based exercise program. Int J Phys Med Rehabil. 2016;4:349.
- 30. Serag H, et al. Effects of para-spinal repetitive magnetic stimulation on multiple sclerosis related spasticity. Int J Phys Med Rehabil. 2014;2:242.
- 31. Joanna S, et al. What is 'Early Intervention' for work related difficulties for people with multiple sclerosis? a case study report. J Neurol Neurophysiol. 2014;5:252.
- 32. Thiruppathy K, et al. Multiple sclerosis related bowel dysfunction: pathophysiology, clinical manifestation and management. J Neurol Neurophysiol, 2014;5:255.
- 33. Salah S, et al. A novel approach for treatment patients with multiple sclerosis by using DNA polymerase. J Alzheimers Dis Parkinsonism.
- 34. Harirchian MH, et al. Dairy products consumption in multiple sclerosis patients: useful or harmful. Int J Neurorehabilitation Eng. 2016;3:e126.
- 35. Nelson F, et al. Association of multiple sclerosis related cognitive impairment with an MRI derived composite score. J Mult Scler. 2015;2:124.

- 36. Baig AM, et al. Cloned microglias with novel delivery system in multiple sclerosis. J Stem Cell Res Ther. 2014:4:252.
- 37. Oreja-Guevara C, et al. Observational safety study of THC: CBD Oromucosal Spray (Sativex) in multiple sclerosis patients with spasticity. Clin Exp Pharmacol. 2015;5:184.
- 38. Pahan K, et al. Prospects of cinnamon in multiple sclerosis. J Mult Scler. 2015;2:149.
- 39. Johannes D, et al. Immunoadsorption with regenerating columns in treatment of steroid-refractory relapse in multiple sclerosis and optic neuritis. J Mult Scler. 2016;3:178.
- 40. Michael AB, et al. Non-linear techniques reveal adaptive and maladaptive postural control dynamics in persons with multiple sclerosis. J Mult Scler. 2016;3:177.
- 41. Balnyte R, et al. Associations of HLA DRB1 alleles with Igg oligoclonal bands and their influence on multiple sclerosis course and disability status. J Neurol Neurophysiol. 2015;6:273.
- 42. Baig AM, et al. Mitochondrial DNA mutation in microglia can be treated by SCNT cloning and not by reprogramming of olfactory ensheathing cells in the multiple sclerosis treatment. J Mult Scler. 2015;2:1.
- 43. Sinha S, et al. Multiparameter flow cytometric assays to quantify effector and regulatory T-cell function in multiple sclerosis. J Mult Scler. 2014;2:130.
- 44. De Castro L, et al. Could metabolomics clarify the multiple sclerosis vitamin D metabolites relationship?. J Mult Scler. 2016;3:171.
- 45. Chen C, et al. Immunomodulation of glatiramer acetate in multiple sclerosis. Neurochem Neuropharm. 2016;1:110.
- 46. Ongagna JC, et al. Tolerance and efficacy of fampyra in real-life cohort of patients with multiple sclerosis. J Clin Cell Immunol. 2015;6:355.
- 47. Yfantopoulos J, et al. Health and economic impact of relapsing forms of multiple sclerosis in greece: the storms study. Pharmacoeconomics. 2015;1:102.
- 48. Kozela E, et al. Insights into gene expression of activated pathogenic autoimmune T cells- studies in experimental multiple sclerosis-like model. Immunome Res. 2016;12:108.
- 49. Karti O, et al. The evaluation of choroidal vascular changes associated with vascular dysregulation in patients with multiple sclerosis using enhanced depth imaging optical coherence tomography. J Clin Exp Ophthalmol 2016;7:534.
- 50. Caprio MG, et al. Vascular disease in patients with multiple sclerosis: a review. J Vasc Med Surg. 2016;4:259.
- 51. Rasia S, et al. Natalizumab to fingolimod switching in multiple sclerosis: results from a real word retrospective analysis. J Mult Scler. 2015;2:142.
- 52. Khan M, et al. Human Immunodeficiency Virus and Multiple Sclerosis Risk: Probing for a Connection. J Mult Scler. 2015;2:141.
- 53. Habib J, et al. Blood B cell and regulatory subset content in multiple sclerosis patients. J Mult Scler. 2015;2:139.
- 54. Douglas JN, et al. Antibodies to the RNA binding protein heterogeneous nuclear ribonucleoprotein A1 colocalize to stress granules resulting in altered RNA and protein levels in a model of neurodegeneration in multiple sclerosis. J Clin Cell Immunol. 2016;7:402.
- 55. Sjakste T, et al. Disease-specific and common HLA and Non-HLA genetic markers in susceptibility to rheumatoid arthritis, type 1 diabetes mellitus and multiple sclerosis. J Mol Genet Med. 2016;10:206.
- 56. Gambuzza ME, et al. A toll-like receptor 3-agonist as promising candidate in multiple sclerosis treatment. J Clin Cell Immunol. 2015;6:339.
- 57. Charvet LE, et al. The Montreal Cognitive Assessment (MoCA) in multiple sclerosis: relation to clinical features. J Mult Scler. 2015;2:135.
- 58. Sivagowri S. et al. Automatic lesion segmentation of multiple sclerosis in mri images using supervised classifier. IJAREEIE. 2013;2.
- 59. Hegazi AG, et al. Novel therapeutic modality employing apitherapy for controlling of multiple sclerosis. J Clin Cell Immunol. 2015;6:299.
- 60. Canavan PK, et al. Evidence based therapeutic exercise recommendations for patients with multiple sclerosis: a physical therapy approach. J Gerontol Geriatr Res. 2016;5:271.
- 61. Caroline Massot, et al. Back pain and musculoskeletal disorders in multiple sclerosis. J Spine. 2016;5:285.
- 62. Naziha K, et al. Gougerot Sjogren syndrome mimicking multiple sclerosis. J Arthritis. 2015;4:175.
- 63. Aharoni R, et al. Animal models of multiple sclerosis: imperfect but imperative. J Mult Scler. 2015;2:e106.

RRJMHS | Volume 5 | Issue 4 | December, 2016

- 64. Ali NB, et al. Can we speak about a psychiatric attack during a multiple sclerosis?. J Mol Biomark Diagn. 2015;6:237.
- 65. Gambuzza ME, et al. A new era for immunotherapeutic approaches in multiple sclerosis treatment. J Clin Trials. 2016;6:253.
- 66. Opara JA, et al. Palliative care in polish patients with multiple sclerosis. J Palliat Care Med. 2016;6:245.
- 67. Geldenhuys S, et al. UV irradiation of skin regulates a murine model of multiple sclerosis. J Mult Scler. 2015;2:144.
- 68. Kurna VK, et al. Multiple sclerosis diagnosis by Flow Cytometry. RRJMHS. 2015;4.
- 69. Vijay Kumar Kurna, et al. Multiple Sclerosis (MS) its Disorders and Diagnostic Research. RRJMHS. 2015;4.
- 70. Elpers C, et al. Prediction of multiple sclerosis after childhood isolated optic neuritis. Int J Pediatr Neurosci. 2015;1:103.
- 71. Contini C, et al. Role of chlamydophila pneumoniae in the pathogenesis of chronic cerebrospinal venous insuffiency in patients with multiple sclerosis. J Mult Scler. 2015;2:150.
- 72. Motamedi MHK and Danial Z. Multiple Sclerosis: the status quo. J Mult Scler. 2015;2:e104.
- 73. Ben-Zacharia AB, et al. Screening for depression in adult patients with multiple sclerosis. J Mult Scler. 2015;2:140.
- 74. Granella F, et al. Eligibility criteria to natalizumab therapy in patients with relapsing remitting multiple sclerosis: a real-life study in an Italian population-based cohort. J Clin Case Rep. 2015;5:649.
- 75. Francesco M, et al. Sustained disease-activity-free status in a woman with relapsing- remitting multiple sclerosis treated with antiretroviral therapy for human immunodeficiency virus type 1 infection. J Mult Scler. 2015;2:152.
- 76. Chahine NHA, et al. Treatment of long standing multiple sclerosis with regentime stem cell technique. J Stem Cell Res Ther. 2015;5:299.
- 77. Rima R, et al. A cohort study of cognitive impairment in patients of multiple sclerosis. J Mult Scler. 2015;3:161.
- 78. Haq E, et al. Multiple Sclerosis and Gene Polymorphisms: are we Groping in the Dark?. J Mult Scler. 2015;3:162.
- 79. Totaro R, et al. Cognitive rehabilitation in multiple sclerosis. Int J Neurorehabilitation Eng. 2015;2:e116.
- 80. Perusquía-Ortega E, et al. A therapeutic trial of bioequivalence between two interferons beta 1a for treating relapsing remitting multiple sclerosis. J Mult Scler. 2015;2:145.
- 81. Ali NB, et al. Neurobehavioral aspects of different forms of multiple sclerosis. J Neurol Neurophysiol. 2015;6:293.
- 82. Pedriali M, et al. The pathology of the internal jugular vein wall in multiple sclerosis. J Mult Scler. 2015;2:160.
- 83. Lucassen EB, et al. Treatment of multiple sclerosis in Switzerland and the United States: what can be learned from our differences?. J Mult Scler. 2015;2:e107.
- 84. Bak TH, et al. Impairment of visual cognition in progressive multiple sclerosis. J Mult Scler. 2014;1:129.
- 85. Bifulco M and Malfitano AM. Advances in flow cytometry investigation of cannbinoid CB2 receptor agonists in multiple sclerosis: commentary. J Mult Scler. 2015;2:128.
- 86. Laing CM, et al. Anger, quality of life and mood in multiple sclerosis. J Mult Scler. 2015;2:127.
- 87. Gudesblatt M, et al. Outcomes of a switch to fingolimod to treat relapsing multiple sclerosis: a patient subgroup post hoc analysis. J Mult Scler. 2015;2:123.
- 88. Rudick RA, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N Engl J Med. 2006;354:911-923.
- 89. Singh VK, et al. The paradigm of Th1 and Th2 cytokines: Its relevance to autoimmunity and allergy. Immunol Res. 1999;20:147-161.
- 90. Beck RW, et al. The effect of corticosteroids for acute optic neuritis on the subsequent development of multiple sclerosis. N Engl J Med. 1993;329:1764-1769.
- 91. Alotaibi S, et al. Epstein-Barr virus in pediatric multiple sclerosis. JAMA. 2004;291:1875-1879.
- 92. Compston A and Coles A. Multiple sclerosis. Lancet. 2002:359;1221-1231.
- 93. Rosati G. The prevalence of multiple sclerosis in the world; an update. Neurol Sci. 2001;22:117-139.
- 94. Koch M, et al. The natural history of secondary progressive multiple sclerosis. J Neurol Neurosurg Psychiatry. 2010;81:1039-1043.
- 95. Thompson AJ, et al. Pharmacological management of symptoms in multiple sclerosis: current approaches and future directions. Lancet Neurology. 2010;9:1182-1199.

- 96. Alspaugh MA, et al. A search for rheumatoid arthritis-associated nuclear antigen and Epstein-Barr virus specific antigens or genomes in tissues and cells from patients with rheumatoid arthritis. Arthritis Rheum. 1983;26:712-720.
- 97. Flensner G, et al. Sensitivity to heat in MS patients: a factor strongly influencing symptomatology-an explorative survey. BMC Neurol. 2011;11:27.
- 98. Matti Al, et al. Patients' knowledge and perception on optic neuritis management before and after an information session. BMC Ophthalmol. 2010;10:7.
- 99. Mills RJ, et al. Development of a patient reported outcome scale for fatigue in multiple sclerosis: The Neurological Fatigue Index (NFI-MS). Health Qual Life Outcomes. 2010;8:22.
- 100. Jacobs LD, et al. A profile of multiple sclerosis: the New York State multiple sclerosis consortium. Mult Scler. 1999;5:369-376.
- 101. Compston A and Coles A. Multiple sclerosis. Lancet. 2008;372:1502-1517.
- 102. Kearney H, et al. Cervical cord lesion load is associated with disability independently from atrophy in MS. Neurology. 2015;84:367-373.
- 103. Frischer JM, et al. The relation between inflammation and neurodegeneration in multiple sclerosis brains. Brain. 2009;132:1175-1189.
- 104. Marriott JJ, et al. Evidence report: the efficacy and safety of mitoxantrone (Novantrone) in the treatment of multiple sclerosis: report of the therapeutics and technology assessment Subcommittee of the American Academy of Neurology. Neurology. 2010;74:1463-1470.
- 105. Comi G, et al. Oral laquinimod in patients with relapsing-remitting multiple sclerosis: 36-week double-blind active extension of the multi-centre, randomized, double-blind, parallel-group placebo-controlled study. Mult Scler. 2010;16:1360-1366.
- Bruck W, et al. Effect of laquinimod on cuprizone-induced demyelination in mice. Neurology. 2011;76:P05-30.
- 107. Linker RA, et al. Fumaric acid esters exert neuroprotective effects in neuroinflammation via activation of the Nrf2 antioxidant pathway. Brain. 2011;134:678-692.
- 108. Schimrigk S, et al. Oral fumaric acid esters for the treatment of active multiple sclerosis: an open-label, baseline-controlled pilot study. Eur J Neurol. 2006;13:604-610.
- 109. Coles AJ, et al. Alemtuzumab versus interferon beta-1a in early relapsing-remitting multiple sclerosis: posthoc and subset analyses of clinical efficacy outcomes. Lancet Neurol. 2011;10:338-348.
- 110. Havrdova E, et al. Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: a retrospective analysis of the Natalizumab safety and efficacy in relapsing-remitting multiple sclerosis (AFFIRM) study. Lancet Neurol. 2009;8:254-260.
- 111. Haghikia A, et al. Therapies for multiple sclerosis: translational achievements and outstanding needs. Trends Mol. Med. 2013;19:309-319.
- 112. Feinstein A, et al. Treatment of progressive multiple sclerosis: what works, what does not, and what is needed. Lancet Neurol. 2015;14;194-207.
- 113. Friese MA, et al. Mechanisms of neurodegeneration and axonal dysfunction in multiple sclerosis. Nat Rev Neurol. 2014;10:225-238.
- 114. Barr TA, et al. B cell depletion therapy ameliorates autoimmune disease through ablation of IL-6-producing B cells. J Exp Med. 2012;209:1001-1010.
- 115. Venken K, et al. Natural naive CD4+CD25+CD127 low regulatory T-cell (T-reg) development and function are disturbed in multiple sclerosis patients: recovery of memory T-reg homeostasis during disease progression. J Immunol. 2008;180:6411-6420.
- 116. Martinez-Forero I, et al. IL-10 suppressor activity and ex vivo Tr1 cell function are impaired in multiple sclerosis. Eur J Immunol. 2008;38:576-586.
- 117. Fritzsching B, et al. Intracerebral human regulatory T-cells: Analysis of CD4+ CD25+ FOXP3+ T-cells in brain lesions and cerebrospinal fluid of multiple sclerosis patients. 2011;6:e17988.
- 118. Yogev N, et al. Dendritic cells ameliorate autoimmunity in the CNS by controlling the homeostasis of PD-1 receptor+ regulatory T cells. Immunity. 2012;37:264-275.
- 119. Roychoudhuri R, et al. BACH2 represses effector programs to stabilize T-reg mediated immune homeostasis. Nature. 2013;498:506-510.

- 120. Vahedi G, et al. Super-enhancers delineate disease-associated regulatory nodes in T-cells. Nature. 2015;520:558-562.
- 121. Schattling B, et al. TRPM4 cation channel mediates axonal and neuronal degeneration in experimental autoimmune encephalomyelitis and multiple sclerosis. Nat Med. 2012;18:1805-1811.
- 122. Mayo L, et al. Regulation of astrocyte activation by glycolipids drives chronic CNS inflammation. Nat Med. 2014;20:1147-1156.
- 123. Popescu BF and Lucchinetti CF. Pathology of demyelinating diseases. Annu Rev Pathol. 2012;7:185-217.
- 124. Beecham AH, et al. Analysis of immune-related loci identifies 48 new susceptibility variants for multiple sclerosis. Nat Genet. 2013;45:1353-1360.
- 125. Charcot JM. Histologie de la sclérose en plaques [French]. Gazette des Hopitaux. 1868;41:554-555.
- 126. Dawson JD. The histology of disseminated sclerosis. Trans Royal Soc Edin. 1916;50:517-740.
- 127. Ascherio A and Munger KL. Environmental risk factors for multiple sclerosis. Part I: the role of infection. Ann Neurol. 2007;61:288-299.
- 128. Rivers TM, et al. Observations on attempts to produce acute disseminated encephalomyelitis in monkeys. J Exp Med. 1933;58:39-56.
- 129. Compston A and Sadovnick AD. Epidemiology and genetics of multiple sclerosis. Curr Opin Neurol Neurosurg. 1992;5:175-181.
- 130. Rudick RA, et al. Pharmacotherapy of multiple sclerosis: current status. Cleve Clin J Med. 1992;59:267-277.
- 131. Weinshenker BG. The natural history of multiple sclerosis. Neurol Clin. 1995;13:119-146.
- 132. Okuda DT, et al. Asymptomatic spinal cord lesions predict disease progression in radiologically isolated syndrome. Neurology2011;76:686-692.
- 133. Amato MP, et al. Association of MRI metrics and cognitive impairment in radiologically isolated syndromes. Neurology 2012;78:309-314.
- 134. Okuda DT, et al. Radiologically isolated syndrome: 5-year risk for an initial clinical event. 2014;9:e90509.
- 135. Trapp BD, et al. Axonal transection in the lesions of multiple sclerosis. N Engl J Med. 1998;338:278-285.
- 136. Coles AJ, et al. The window of therapeutic opportunity in multiple sclerosis: evidence from monoclonal antibody therapy. J Neurol. 2006;253:98-108.
- 137. Hauser SL, et al. Multiple sclerosis: prospects and promise. Ann Neurol. 2013;74:317-327.
- 138. Havrdova E, et al. Freedom from disease activity in multiple sclerosis. Neurology. 2010;74:S3-S7.
- 139. Dhib-Jalbut S and Marks S. Interferon-β mechanisms of action in multiple sclerosis. Neurology. 2010;74:S17-24.
- 140. The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology. 1993;43:655-661.
- 141. Jacobs LD, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. Ann Neurol. 1996;39:285-294.
- 142. Ebers GC. PRISMS (Prevention of Relapses Disability by Interferon  $\beta$ -1a Subcutaneously in Multiple Sclerosis) Study Group. Randomised double-blind placebo controlled study of interferon  $\beta$ -1a in relapsing/remitting multiple sclerosis. Lancet. 1998;352:1498-1504.
- 143. PRISMS Study Group and the University of British Columbia MS/MRI Analysis Group. PRISMS 4: Long-term efficacy of interferon-β-1a in relapsing MS. Neurology. 2001;56:1628-1636.
- 144. Calabresi PA, et al. Pegylated interferon  $\beta$ -1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. Lancet Neurol. 2014;13:657-665.
- 145. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. Neurology. 1995;45:1277-1285.
- 146. Randomised double-blind placebo-controlled study of interferon β-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Lancet. 1998;352:1498-1504.
- 147. Van der Mei IA, et al. Past exposure to sun, skin phenotype, and risk of multiple sclerosis: case-control study. BMJ. 2003;327-316.

- 148. Johnson KP, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology. 1995;45:1268-1276.
- 149. Hartung HP, et al. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. Lancet. 2002;360:2018-2025.
- 150. Polman CH, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006;354:899-910.