

Research Article



## AN OVERVIEW OF MULTIPLE SCLEROSIS WITH GUT EPSILON TOXICITY IN HUMAN: SISTEMATIC LITERATURE REVIEW

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### ABSTRACT

**Background:** Multiple Sclerosis (MS) is a complex autoimmune neurodegenerative disorder that afflicts a significant number of individuals worldwide. This formidable disease, which is often life-threatening, imposes a lifelong impact on those diagnosed, altering their existence in profound ways.

**Methods:** The current review is meticulously crafted, drawing upon a multitude of scholarly articles previously disseminated in both national and international academic journals within the same discipline.

**Results:** This disease inflicts substantial damage to the Central Nervous System (CNS), predominantly affecting the myelin sheath of nerve fibers, spinal cord, and eyes, thereby leading to the development of muscle weakness, movement disorders, and visual impairments. Recent observations have unveiled a potential link between a gut bacterium, *Clostridium perfringens*, and the onset of MS in humans.

**Conclusion:** Given that the precise etiology of Multiple Sclerosis (MS) remains elusive and presents a formidable challenge, this paper endeavors to shed light on the current landscape of the disease. It provides an in-depth exploration of its epidemiology, clinical manifestations, diagnostic procedures, prognosis, and treatment modalities, all underpinned by the most recent advancements in the fields of immunology and medical microbiology about infectious diseases.

**Keywords :** *Multiple Sclerosis, Autoimmune Disorder, Clostridium perfringens, Human Epsilon Toxicity, Neurological Disease.*

## INTRODUCTION

Multiple sclerosis is an autoimmune disorder in which demyelination takes place in nerve fibers. The nerve fibers are damaged in MS leaving the fibers naked as scars or sclerosis. The name multiple sclerosis means the scars are found in many places. The myelin sheath acts like the insulating cover of an electric wire. Sometimes, these scars are also called plaques or lesions. These lesions do not allow the electrical impulses to run smoothly in the targeted nerve. The damage prevents the nerves from relaying signals correctly resulting in gait problems[1-6].

MS affects the human CNS chronically including the brain, spinal cord, and optic nerves. Immunity disorder damages the myelin sheath due to the mistakenly confused attacking their cells opted it as the foreign body. This is an outcome of immunity failure in a system. Scientists do not know the exact cause of MS but are suspected to have a link between *C. perfringens* and the trigger of MS in humans[7-9]. It has been observed that patients suffering from MS are more likely to harbor *C. perfringens* in their gut producing a toxin named epsilon. This is a fascinating pore-forming toxin being produced by *C. perfringens* enhancing the intestinal permeability and breaking the blood-brain-barrier by attacking the spinal cord and brain to produce the neurological symptoms of multiple sclerosis [7,9-14].

*Clostridium perfringens* is a Gram-positive anaerobic bacteria. A new study suggested that gut bacteria especially the *C. perfringens* may trigger the onset and relapse of multiple sclerosis in association with genetic susceptibility. Scientists are still working to establish the link between the two if at all existed [3,15-20].

## METHODS

This review is a comprehensive synthesis of research conducted thus far in the realm of

the autoimmune neurological disorder known as Multiple Sclerosis in humans. The authors have meticulously examined a multitude of research papers, published in journals of both national and international acclaim.

## RESULTS

This paper is a comprehensive review of the current state of knowledge on the autoimmune neurological disorder Multiple Sclerosis (MS) in humans. The paper covers the following aspects of the disease:

**Epidemiology:** The paper provides an overview of the global prevalence, incidence, and distribution of MS, as well as the risk factors and environmental influences associated with it.

**Disease prodrome:** The paper discusses the early signs and symptoms of MS, such as fatigue, cognitive impairment, mood disorders, and sensory disturbances, that may precede the onset of clinical manifestations.

**Clinical symptoms:** The paper describes the various neurological and physical impairments that MS patients experience, such as muscle weakness, movement disorders, vision defects, bladder and bowel dysfunction, pain, and spasticity.

**Stages of MS:** The paper explains the different types and courses of MS, such as relapsing-remitting, primary progressive, secondary progressive, and progressive relapsing, and how they affect the prognosis and treatment of the disease.

**Diagnosis and prognosis:** The paper outlines the diagnostic criteria and tools for MS, such as clinical history, neurological examination, magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analysis, and evoked potentials. The paper also

discusses the factors that influence the prognosis and survival of MS patients, such as age, sex, disability level, disease course, and comorbidities.

**Preventive measures:** The paper reviews the current evidence and recommendations for preventing or delaying the onset or progression of MS, such as vitamin D supplementation, smoking cessation, exercise, diet, and infection control.

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## DISCUSSION

The entire disease is discussed in various steps as under:

### Epidemiology of Multiple Sclerosis

According to an estimate nearly 2.8 million people are affected worldwide with MS. Females 73% are found more affected than males. Similarly, it has also been observed that the most preferred age for MS diagnosis in humans has been 33 years[21]. The Multiple Sclerosis Society of India (MSSI) is established in 1985, in Mumbai[22-24].

### The Disease Prodrome

A disease prodrome is defined as the early-stage onset of symptoms indicating the establishment of a disease in the future. These are subclinical signs that preceded the onset of a disease. A prodromal phase in MS may have major implications for early recognition, improved prognosis, and better prevention of the disease. Some of the prodromal symptoms of multiple sclerosis are headache, body pain, fatigue, and urinary and psychiatric disorders. Another important prodromal symptom may appear as the sudden loss of vision in one of the affected eyes usually lasting for days to weeks[25-27].

### Clinical Symptoms of Multiple Sclerosis

The clinical symptoms of multiple sclerosis are as under:

1. Muscle weakness and fatigue [7,28].
2. Eye defects such as Neuromyelitis Optica, blurred vision and the distortion of red color, pain in eye movement, and finally the loss of vision[29,30].
3. Gait problems, loss of balance, vertigo, walking difficulties and falls, Numbness, tingling in the limbs and paralysis, Dizziness [31,32].
4. Neurologic pain and spasms including brain atrophy, facial pain as trigeminal neuralgia, and Lhermitte's sign[7,28,33].
5. Loss of libido [34].
6. Cognitive and emotional disorders. Nearly 65% of MS patients suffered from cognitive impairment. This is mostly observed as memory loss, learning difficulty, speech problems, difficulty in finding words, and unable to perform executive functions [35,36].
7. MS patients often experience some physical, psychological, behavioral, and psychiatric disorders during disease development such as stress, depression, fatigue, pain, anxiety, bladder and bowel incontinence, irritability, sleep disorder, hallucination, psychosis, and mood disorders [37,41].

### Stages of Multiple Sclerosis

There are four stages of disease development of multiple sclerosis in humans as

1. Clinically Isolated Syndrome (CIS)
2. Relapse – Remitting MS (RRMS)
3. Primary Progressive MS (PPMS)
4. Secondary Progressive MS (SPMS)

### Clinically Isolated Syndrome (CIS)

The symptoms appear for the first time lasting about 24 hours. [42].

### Relapse- Remitting MS (RRMS)

The occurrence of another episode after a later date. Nearly 85% of MS patients experience the same session with progressively worsening symptoms in time intervals[28].

### Primary Progressive MS (PPMS)

The rest of the patients 15% might experience progressively the still worsening symptoms in upcoming episodes occurring frequently in definite time intervals.[43].

### Secondary Progressive MS (SPMS)

This is again a kind of PPMS with extreme symptoms of the disease occurring at any time without any control. It has been observed that nearly 50 and 90% of RRMS patients, if not treated even symptomatically may get the last stage as SPMS within 10 and 25 years respectively [44].

### Diagnosis and Prognosis of the Disease

The disease is usually developed between 20 to 40 years of age. The diagnosis of MS is a tedious job of having CNS a deeper look into the symptoms requiring evidence of the damage in at least two areas in different time intervals [45]. C. perfringens and the toxins produced have been isolated from the feces of MS patients with the help of PCR [46]. The differential diagnosis of MS via the central vein sign detected is sometimes mimicking as leukoaraiosis [28,47].

The prognosis of the disease is very slow. It rarely causes death but is a very challenging disease to live with. Only in certain cases such as extreme bladder and

bowel dysfunctions, severe chest infection and difficulty swallowing could lead to death [23,48]. In addition, there are many environmental factors noted to increase MS in humans. They are age, sex, family history, and infections like human herpes virus- 6, JC virus and Epstein Barr virus damage the myelin sheath of nerves [49,55].

A newly introduced blood test named neurofilament light chain (NfL) can easily predict neurodegenerative diseases like MS, Parkinson's disease, and Alzheimer's [56,58]. However, MRI is often used to locate the lesions in the brain and spinal cord [57,58].

### Preventive Measures

Clostridial zoonotic diseases are usually transmitted in humans via animals [13,59]. Most specifically, the kitchen and kitchen soil are also sometimes easily occupied by the *Clostridium perfringens* [3]. Inactivation strategies of vegetative cells and spores might control the disease physically in the future [60].

### Treatment of Multiple Sclerosis

Multiple sclerosis is an incurable disease. There are no exact medications and vaccines available so far. Managing MS is an ongoing tedious process beginning with the first symptom to the entire disease course throughout. On the off chance, there are certain treatment modalities available to treat MS patients. Recently, disease-modifying therapy (DMT) is applied. A humanized monoclonal antibody, ocrelizumab (Ocrevus) is the only DMT medication for MS. However, it has its side effects with increased risk of infections and breast cancer [35,42,48,61-64]. Interferons like beta- 1a and beta 1b in the form of Avonex and Betaseron have been found effective respectively [43,62]. Similarly, infused

medication such as Tysabri, the natalizumab [65] and oral medications such as Albagio the teriflunomide [66]; Bafiertam, the (monomethylfumarate) [67]; Gilenya (fingolimod) [44]; are the first choice of drugs for physicians [68]. In addition, corticosteroids are also used to treat multiple sclerosis. However, they are inconvenient and expensive having their side effects.[69].

Further, the following symptomatic relieves are also being provided in different dysfunctions of MS [70] as in bladder dysfunction, botox, the onabotulinum toxin A [71]; detrol, the tolterodine [72] and Flomax, the tamsulosin [73]; Bowel dysfunction, Dulcolax, the basicody, enemeez, the laxative, stool softner, milk of magnesia, the magnesium hydroxide and glycerine [74]; Infections, bactrim, the sulfamethoxazole, cipro, the ciprofloxacin, Levaquin, the levofloxacin and macrodantin, the nitrofurantoin [75]; Depression, celexa, the citalopram and Prozac, the fluoxetine; Dizziness and Vertigo; antivert (meclizine) [76,77], Emotional Disorders and Mood swing, nuedextra; Pain; lyrica, the pregabalin, tegetrol, the carbamazepine and Neurontin, the gabapentin [78]; Itching, atarax, vistaril, the hydroxyzine) [79,80] and in Gait problems, ampyra, dalfampridine [81-83].

Moreover, remyelination therapies are also in progress [84] with the use of certain supplements like vitamin D [85] biotin [86] and cannabinoids [87,88]. However, the use of MRI in the detection of MS [89] exercise [90], also physiotherapy [91], and psychological and genetic counseling have their own merits and demerits [37,92].

### CONCLUSIONS

Multiple sclerosis is an autoimmune disease in humans caused by damage to the myelin

sheath of the brain, spinal cord, and optic nerves. The disease is mainly developed as muscular weakness, blurred vision, and gait problems. Approximately 2.8 million people are affected worldwide by multiple sclerosis. There are four stages of disease development in humans clinically isolated syndrome (CIS), relapse-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS). Further, if not treated in time, nearly 85% of the patients certainly go through the RRMS phase. There are no exact medications available so far. However, symptomatic relief is being given to the patient. The prognosis of the disease is also very slow. While the exact cause of MS is still unknown, genetic and some unavoidable environmental factors might be involved in its onset. There are many environmental factors noted to increase MS in humans. They are age, sex, family history, and infections like human herpes virus -6 and JC virus developing progressive multifocal leukoencephalopathy (PML) and Epstein Barr virus damaging the myelin sheath of nerves. Lastly, it has also been observed that the disease also has a link between *Clostridium perfringens* and the trigger of MS in humans. Since the early onset of the disease between 20 to 40 years of age with longer duration often resulted in tremendous losses of individuals including family work productivity and society values more research is still required to know the exact cause and nature of the disease.

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