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Brief Overview about Correlation between CD8 and Multiple Sclerosis: Review Article

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ABSTRACT

Background: There is now conclusive evidence that multiple sclerosis (MS) belongs to the group of primary neurodegenerative illnesses. Myelin is the protective layer around nerve fibres in the brain and spinal cord, and it is the target of an autoimmune attack in multiple sclerosis, a debilitating neurological illness. Immune protection against intracellular pathogens like viruses and bacteria, as well as tumour surveillance, rely heavily on CD8+ T cells. There are three main mechanisms that CD8+ T lymphocytes use to eliminate contaminated or cancerous cells after they have become activated by recognizing their antigen.

Objective: To have overview about Correlation between CD8 and multiple sclerosis**.**

Methods: We looked for data on CD8, T cell and multiple sclerosis in medical journals and databases like PubMed, Google Scholar, and Science Direct. However, only the most recent or extensive study was taken into account between January 2000 and May 2021. References from related works were also evaluated by the writers. There are not enough resources to translate documents into languages other than English, hence those documents have been ignored. It was generally agreed that documents such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations did not qualify as legitimate scientific study**.**

Conclusion: Autoreactive CD8+ cytotoxic T cells significance in the pathogenesis of multiple sclerosis is becoming increasingly apparent. It is of great interest to learn whether or not these CD8+ Tregs play a function in regulating the progression of multiple sclerosis.

Keywords: CD8, T cell, Multiple sclerosis.

INTRODUCTION

In recent years, multiple sclerosis (MS) has been recognized as a primary neurodegenerative condition. Myelin is the protective covering enclosing nerve fibres in the brain and spinal cord, and MS is defined pathologically by an autoimmune attack on this substance. Inflammation, neuronal degeneration, and demyelinating lesions in both white and grey matter are hallmarks of this disorder **(1).**

Regardless of how the disease progresses in a given patient, untreated multiple sclerosis always leads to a significant impairment and a decline in quality of life. New treatments have improved the outlook for those with MS, but the disease remains incurable **(2)**.

By 2020, experts predict that the global MS population will grow to 2.8 million. By the same measures used eight years ago, the new rate is 30% higher. In 2020, we predict a global incidence rate of 35.9 cases per 100,000 people. When comparing the two time periods, only 14% of countries saw a steady or declining prevalence. The annual rate of new cases of multiple sclerosis was determined to be 2.1 per 100,000 people across 75 nations.

By Walton *et al.* (3), it is estimated that one person will be diagnosed with multiple sclerosis every five minutes.

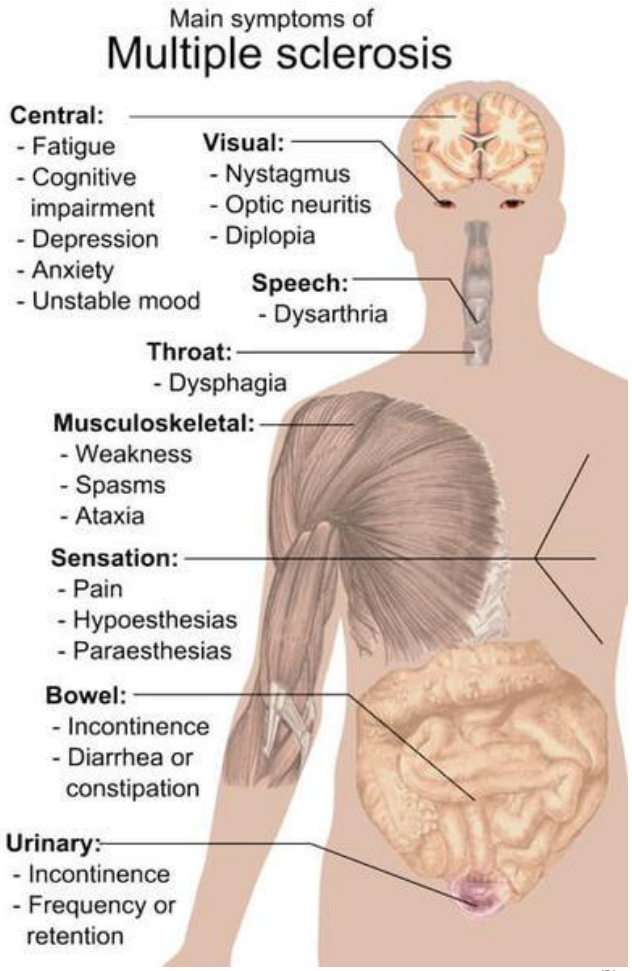

Figure (1): Main Symptoms of Multiple sclerosis **(3).**

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B cells and T cells in the adaptive immune system are responsible for both humoral immune and cell-mediated immune systems. Antibodies, which are secreted by B cells, attach to epitopes on invading pathogens and stimulate the activation of other immune system cells like macrophages, which then destroy the threat. When it comes to cell-mediated immunity, T cells are crucial.

The two most prevalent forms of T cells are the helper T cell (CD4) as well as cytotoxic T cell (CTL) (CD8). Helper T cells contribute in the formation and function of other immune system cells, while cytotoxic T cells specifically target and destroy infected cells and tumor's. Immune protection against intracellular pathogens including viruses and bacteria, as well as tumour surveillance, rely heavily on CD8+ T cells. Once triggered by identifying an antigen, CD8+ T lymphocytes can destroy contaminated or malignant cells through one of three basic ways [(4)].

CD8 and multiple sclerosis:

Autoreactive CD8+ cytotoxic T cells role in multiple sclerosis pathogenesis has been shown by extensive study. Clonally increased CD8 T cells can be seen in the blood and CSF of multiple sclerosis patients. These cells contribute significantly to the escalation of inflammation in MS by secreting granzyme and perforin, as well as producing molecules with the capacity to produce tissue damage, such as Fas and Fas lig [(5)].

CD8 cytotoxic T cells inducing Axonal damage and demyelination:

Babbe *et al.* [(6)] found a significant correlation between CD8+ T lymphocytes and MS lesions by utilizing polymerase chain reaction on individual cells (PCR). Demyelination and axonal degeneration are hallmarks of multiple sclerosis (MS), and they discovered that CD8 lymphocytes significantly impact MS by directly targeting axons with their components (granzyme cyto-toxic granules). Increased numbers of CD8 lymphocytes and macrophages have been linked to acute axonal damage.

Time-dependent elevation of MHC class I antigen over, oligodendrocytes, astrocytes, axons, and neurons indicate that these cell types may be attacked by pathogenic bacteria. Injury severity is linked with CD8+ T cell activation. Peripheral chronic and active lesions include antigen-presenting cells that engage with CD8+ T lymphocytes [(7)].

When comparing multiple sclerosis (MS) patients to healthy control participants, **Redwine *et al.*** [(8)] found that Multiple sclerosis patients, compared to healthy controls, were shown to have significantly higher numbers of CD8 T lymphocytes multiplying in their CSF as well as blood.

Increasing data suggests that CD8 lymphocytes in MS patients display clonal proliferation throughout a wide variety of tissue compartments, including the central nervous system, peripheral blood, and cerebrospinal fluid [(9)].

T-cell receptor -chain diversity was studied by isolating CD8+ T cells from MS patients' peripheral blood and CSF. Extensive postmortem examination of the brains of multiple sclerosis patients, researchers found that the same T-cell clone was present in at least two different brain areas for each patient, and that certain clones were present in all regions tested. Human Leucocyte Antigen (HLA) class I molecules were similar between these patients, which is an interesting coincidence [(10)].

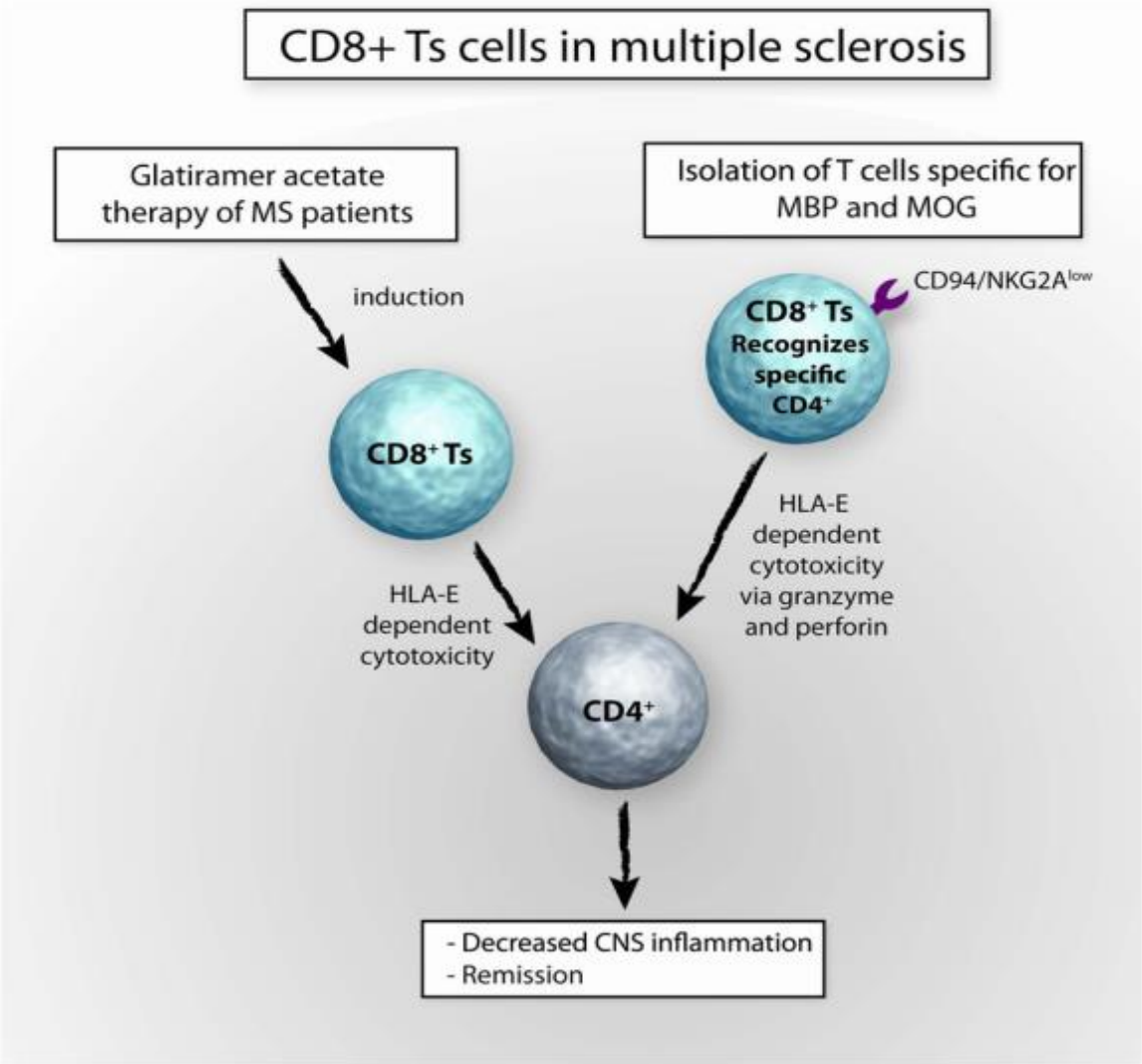

Figure (2): CD8 + Ts cells roles in multiple sclerosis [10].

More recent research utilizing cutting-edge methods like single-cell analysis has confirmed these findings, showing that CD8 cells are present in early cortical lesions in addition to white matter [9].

CD8 and Cognition in MS:

It has been hypothesized that persistent immune activation contributes to additional brain damage and slows the healing process. CNS inflammation causes a cascade of neurological dysfunctions, including impaired cognition and possibly contributing to accelerated brain ageing, as shown by both short- and long-term studies of inflammation's effect on neurons. The reason for this is that adaptive immune cells might congregate in the lesion and stay there for a very long time, even months [11].

Cognitive loss in multiple sclerosis has been linked to CD8 cell infiltration into the hippocampus. The use of flow cytometry revealed that CD8+ T lymphocytes predated the hippocampal invasion by residing in the brain's lymph nodes. Hippocampal memory impairment was detected during the acute as well as early stages of the inflammatory reaction. MRI imaging showed a disruption of the blood-brain barrier and edoema in the hippocampus. CD8 cells specifically targeted neurons, which resulted in a segmented pattern of neuronal death, astrogliosis, and microglial activation. Persistent memory loss was present in chronic stage individuals, who also had CD8+ T lymphocytes in their sclerotic hippocampus [12].

CD8 and Disability in MS:

It has been hypothesized in numerous investigations that immune effectors, such as CD8+ T lymphocytes, can access the axo-lemma after axon and myelin loss. Relapse and disease progression in MS patients show a strong correlation with cytokine-mediated toxicity, FasL induction, and target cell death are all examples of how CD8+ T lymphocytes exert their cytotoxic effects. This suggests that CD8+ T cells mediate de- myelination and axonal injury in the brain and spinal cord in MS patients via a perforin and MHC class I-dependent pathway, ultimately resulting in a profound motor dysfunction [13].

CD8 and MS progression:

Accumulated neuro-axonal loss in a chronically inflamed central nervous system environment and the imbalance between damage and repair are key factors in multiple sclerosis clinical development. Parenchymal and leptomeningeal inflammation driven by CD8 cytotoxic T cells appears to be a key driver. The glial response to this inflammatory insult has been identified in a recent perspective study as a key factor in pathological and clinical consequences [14].

Pathogenic Character of CD8$^+$ T-Cells among MS:

Due to the extreme difficulties of examining CD8 cell activity in the brain, only indirect evidence shows that CD8 cells have a pathogenic function in MS. In multiple sclerosis patients, CD8 cells fill neurological lesions in CNS at a far higher rate than any other cell type. Patients with active disease saw an increase in CD8 cell numbers from the lesion's core to its periphery. Lymphocytic perivascular cuffs around dynamic plaques might have a CD8/CD4 ratio as high as 50:1 [15].

The cytotoxicity of CD8+ T lymphocytes toward central nervous system (CNS) cells such glia and axons in MS lesions remains unknown. Human myelin peptide-specific T cells (CD8+ T cells) have been found to destroy ODCs in vitro by escaping MHC class I restriction. MS patients' peripheral blood was used to separate MBP-specific memory CD8+ T lymphocytes, which were then demonstrated to generate cytokines (TNF and IFN) and lyse cells expressing endogenous MBP (COS-MBP/HLA-A2-transfected cells) [16].

In MS patients, CD8 cells have been discovered close to ODCs and demyelinated axons. MHC class I molecules are present in many cell types, including astrocytes, oligodendrocytes, neurons, and endothelial cells. IFN has been shown to enhance MHC class I molecules, and this increase has been linked to a more severe disease. In addition, MHC class I molecules capable of cross-presenting foreign peptides are expressed by the endothelium lining blood vessels in the central nervous system. At the periphery of CNS plaques, it makes sense for CD8 cells to interact with APCs [17].

Effector cytokines secreted by CD8+ T cells can amplify the inflammatory cascades already present in the brain by upregulating cytotoxic activity and activating other immune cells. For instance, CD8+ T cells that identify neuroantigens in the peripheral blood are capable of producing interferon alpha and tumour necrosis factor alpha when activated with their respective antigen in vitro [18].

CD8 cells must secrete interferon-gamma and interleukin-17 in response to apoptotic T-cell-associated self-epitopes in order to infiltrate the central nervous system. CD8 cells were more likely to be recruited in inflammatory CNS venules in individuals with acute RRMS compared to CD4+ T cells. And the frequency of CD8+ IL-17 secreting T cells is substantially higher in MS patients with recent CNS lesions. Multiple sclerosis patients have been found to have an increased blood level of CD8+CD161+ T-cells, which are responsible for the production of interferon-gamma and interleukin-17. CD8+ T cells, which produce cytotoxic chemicals like perforin, are commonly higher in relapsing multiple sclerosis cases [19].

CD8+ T-Regulator Cell Induction for Therapy:

Medications that suppress the immune system are commonly used indefinitely to treat multiple sclerosis. In order to better understand how these drugs work, researchers are always delving further into the field. Evidence suggests that GA treatment can generate functional CD8+ Tregs for therapeutic purposes [20].

MS patients and healthy donors alike have GA-reactive CD4+ and CD8 lymphocytes floating about in their blood's periphery. CD4+ T-cell responses are similar across the two groups, whereas GA-induced CD8+ T-cell responses are lower in untreated MS patients and rise after therapy. Despite being functionally restricted to the HLA-E allele, the GA-reactive CD8 cells' suppressive activity on CD4+ T-cells is extremely allele-specific. Untreated MS patients can have the suppressor function of GA-reactive CD8+ T cells restored with treatment with GA [21,22].

These revolutionary findings connected the medication's curative benefits to the regulatory function of CD8 cells. The findings of our EAE trials demonstrated proof of concept by demonstrating that GA is ineffective in treating EAE in mice when CD8 cells are reduced, as we have already mentioned. These results provide compelling evidence that CD8 cells are critical for GA activity and imply that the drug's other reported immunomodulatory effects may be a consequence of its generation of CD8+ Tregs [23].

We may use this perspective to take a quick look back at the potential functions of CD8 cells in MS. Figure 3 displays the several lines of evidence suggesting that CD8 cells may play both pathogenic and regulatory functions in MS/EAE disease. Although their complete spectrum of antigenic specificity yet to be explained, CD8+ T cells have been linked to a number of disease-driving processes, including cytotoxicity, demyelination, and the generation of pro-inflammatory cytokines. This is additional proof of activation, alongside the well-known indications of oligoclonal band expansion and interferon- production at disease locations. Notably, the model's prologue reveals that this does not rule out the recruitment of a regulatory population [24].

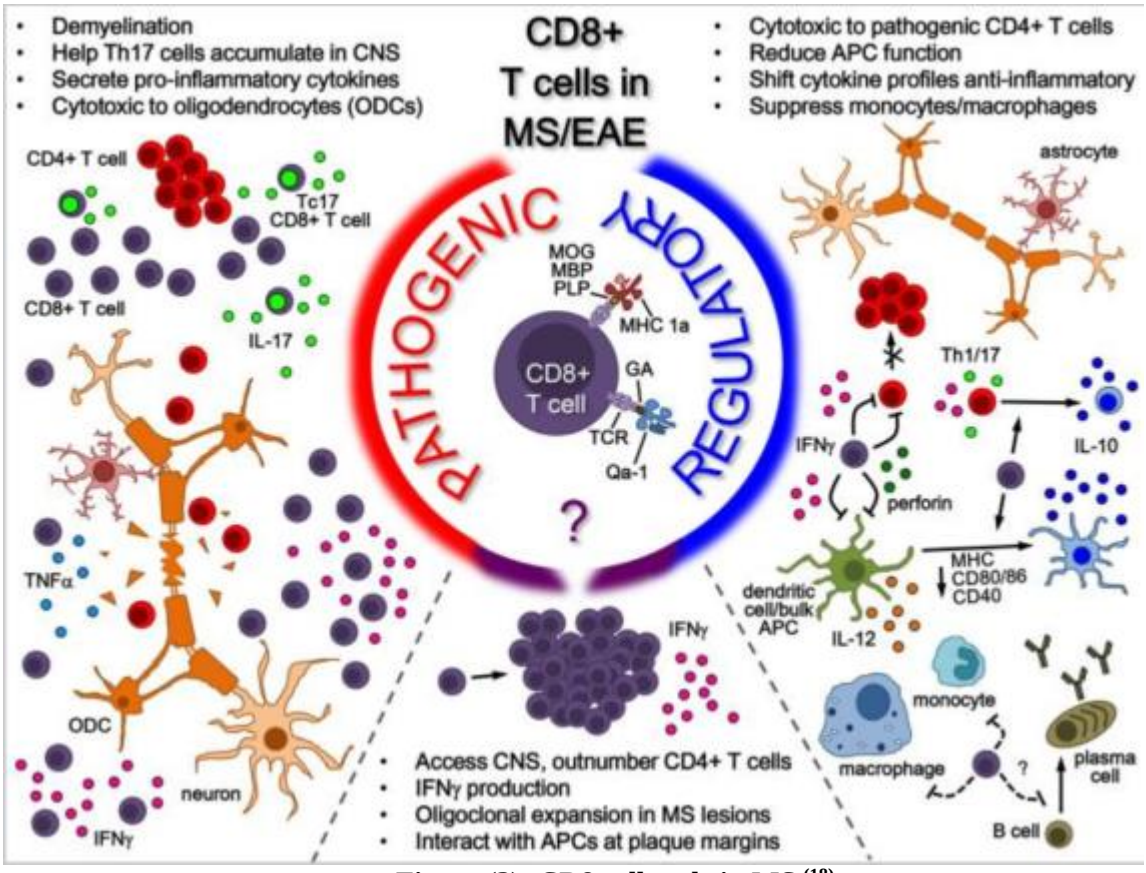

Figure (3): CD8 cells role in MS [18].

As a result, unregulated effector T-cell activity may develop in MS patients because their effector T cells are resistant to dominant tolerance mechanisms such as those triggered by interaction with regulatory T cells (Tregs) [25].

CONCLUSION

Autoreactive CD8+ cytotoxic T cells significance in multiple sclerosis pathogenesis is becoming increasingly apparent. It is of great interest to learn whether or not these CD8+ Tregs play a function in regulating the progression of multiple sclerosis.

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