INTRODUCTION

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system and the leading cause of disability in young adults. Afferent pregeniculate visual pathways (retina, optic nerves, chiasm, and tracts) are preferential targets of inflammation, demyelination, and axonal degeneration. [1] Acute idiopathic demyelinating optic neuritis (ON) is frequently the initial clinical manifestation of multiple sclerosis and nearly half of the MS patients develop this entity. [2,3] Apart from ON, current investigations have reported subtle visual impairments (e.g., worse scores on low-contrast acuity and colour-sensitivity testing) in MS patients. [4,5] With the advent of newer technology, structural information about optic nerve disease is attainable, it has been shown that MS patients demonstrate loss of axons in the retinal nerve fiber layer (RNFL). [6,7]

Aim of the Work

The aim of work in our study was to find and correlate visual field findings in multiple sclerosis patients with clinical data.

Review of Literature

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system and the leading cause of disability in young adults. Afferent pregeniculate visual pathways (retina, optic nerves, chiasm, and tracts) are preferential targets of inflammation, demyelination, and axonal degeneration. [1] (figure 1) Acute idiopathic demyelinating optic neuritis (ON) is frequently the initial clinical manifestation of multiple sclerosis and nearly half of the MS patients develop this entity. [2,3] Apart from ON, current investigations have reported subtle visual impairments (e.g., worse scores on low-contrast acuity and colour-sensitivity testing) in MS patients. [4,5] With the advent of newer technology, structural information about optic nerve disease is attainable, it has been shown that MS patients demonstrate loss of axons in the retinal nerve fiber layer (RNFL). [6,7]

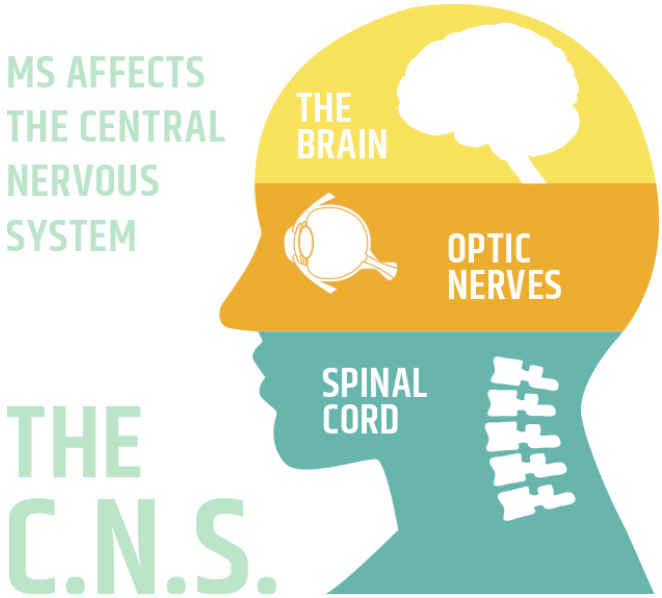

Figure (1): MS main target [8].

MS is one of the world's most common neurologic disorders, and the estimated number of patients with MS increased from 2.1 million in 2008 to 2.3 million in 2013. [9]Recent data from natural history studies and clinical trials have shown that the interplay between 'immunological' and 'neurodegenerative' processes of MS plays an important role for entire disease courses. [10,11]

Multiple sclerosis typically presents in young and middle-aged individuals, although attention to the disorder in the pediatric population has increased in recent years. The ratio of women to men with the disease is 2:1. The prevalence varies depending on location but ranges from 5-30 per 100,000 people and may be increasing. [12] Approximately 300,000 to 350,000 people in the USA are estimated to have MS. [12] (figure2)

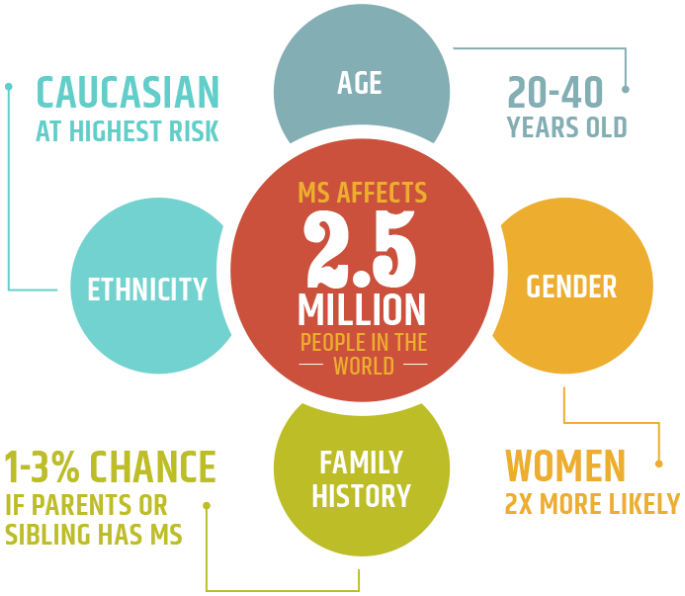

Figure (2): Demography of MS [13].

Multiple sclerosis was first described by Charcot in 1868, but etiology and pathogenesis of the disease are still incompletely understood. [14] Pathogenesis of the lesions of MS is heterogeneous, it is not surprising that no single predominant mechanism for this disease has emerged. Indeed, with a condition that includes fulminant as well as chronic forms with such a wide-ranging phenotype, multiple pathogenetic mechanisms have been proposed. It is generally held that MS is considered to be an autoimmune disorder with inflammation, demyelination, and neurodegeneration of the CNS in which there is a breach in the integrity of the blood-brain barrier in a person who is genetically predisposed to the disease. [15] (figure 3)

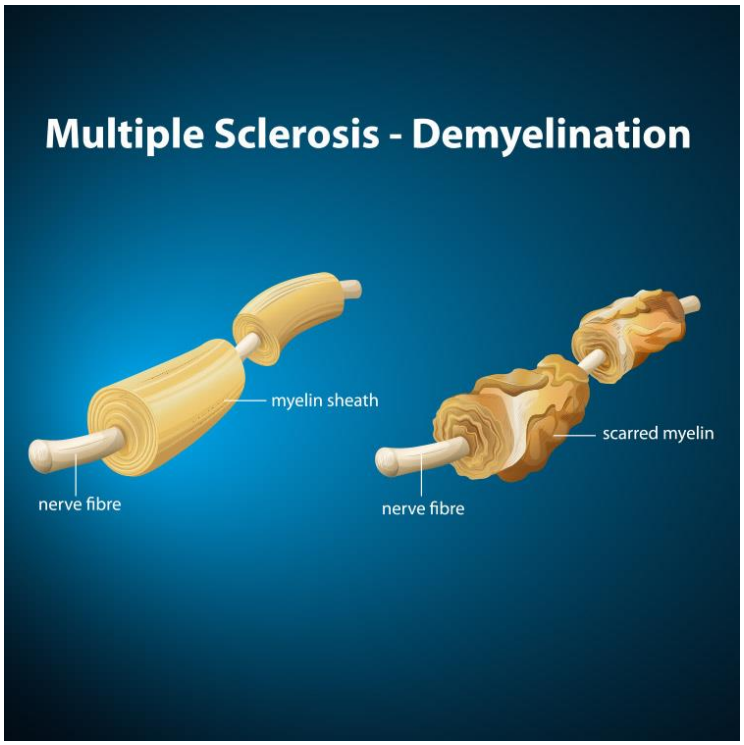

Figure (3): Demyelination process in MS [(16)].

Pathogenesis:

A genetic predisposition to MS exists, as the concordance rate for disease in monozygotic twins approaches 30% but is only 3-5% in dizygotic twins. Investigators have proposed that infections or other environmental agents may trigger MS. This hypothesis is supported by the observations that the risk of acquiring the disease varies by geographical area and that epidemics of MS have occurred. Despite vigorous scientific efforts, no particular etiologic agent has been isolated.

Regardless of the etiology of MS, the subsequent disease pathogenesis is considered to be autoimmune in nature. Evidence suggests that autoreactive T_H1 cells are activated systemically and then migrate into the CNS. There, the T_H1 cells are exposed to and reactivated by various autoantigens, leading to a cascade of inflammation. This process ultimately causes demyelination and loss of oligodendrocytes and axons. [17,18,19] While lesions can develop anywhere within the CNS, including the optic nerve, spinal cord, brain parenchyma, and nerve root entry zones, focal areas of MS activity are characteristically located in the periventricular white matter. These foci, or plaques, can be appreciated on MRI and on pathologic examination. The pathology of MS has been described in white matter, cortex, meninges and cerebrospinal fluid. [20] (figure 4)

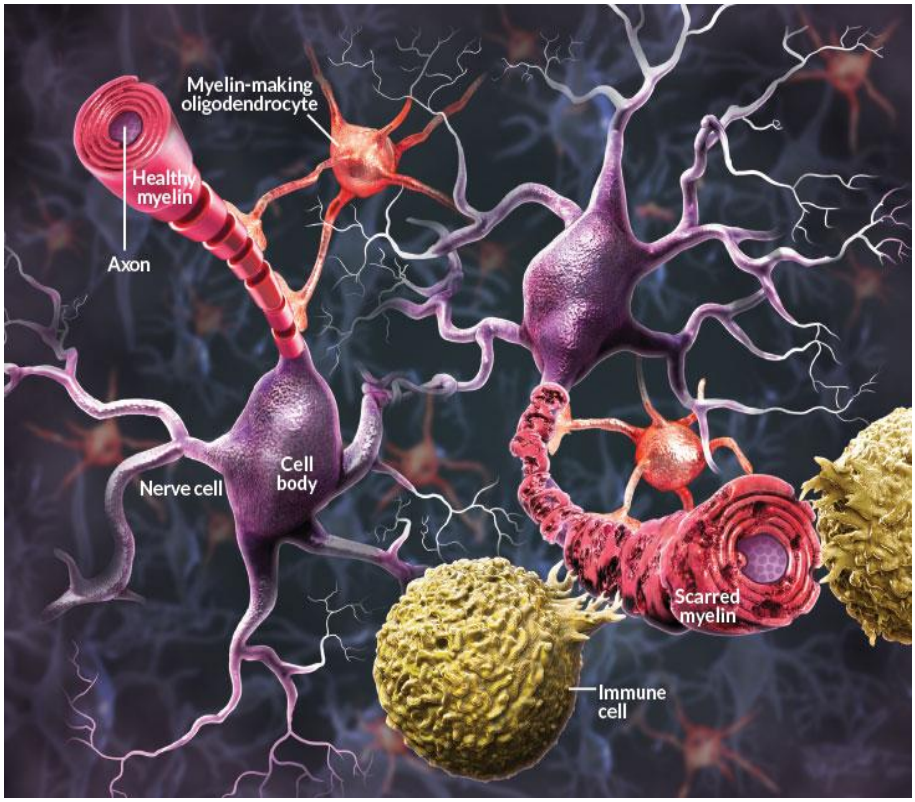

Figure (4): Autoimmunity attacks myelin (MS pathogenesis) [21].

White matter pathology

In adult MS, the hisopathological hallmark of MS pathology is the plaque which is a perivascular inflammatory lesion associated with demyelination and axonal injury in the white matter. [20] (figure 5)

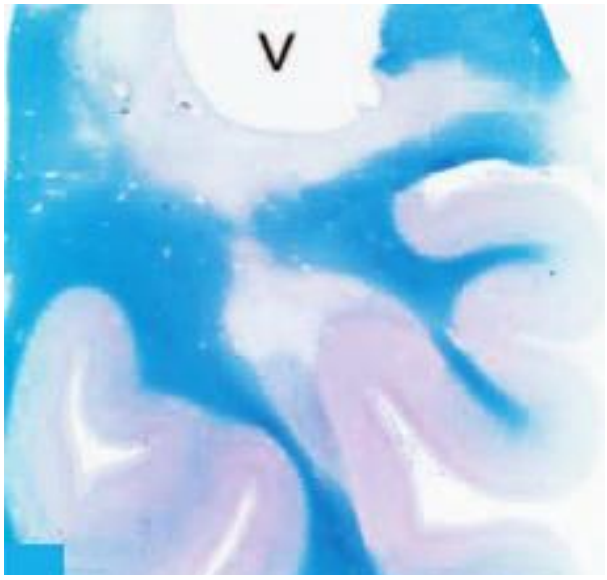

Figure (5): White matter pathology.

MS plaque in human tissue. A section of temporal lobe stained with Luxol fast blue for myelin reveals a periventricular plaque extending to a cup-shaped zone of demyelination beneath the sulcus to the lower right. Some areas around the margins of the lesion stain pale blue (e.g., adjacent to the affected sulcus), probably indicative of remyelination. V denotes ventricle. [20]

Cortical pathology

A pathological study using biopsy specimens from adult patients with early-stage MS demonstrated cortical lesions in 40% in subpial, intracortical, and leukocortical locations. Perivascular T-cell infiltrates were present in the majority of patients, and macrophage-associated demyelination was present inapproximately half, diffuse meningeal inflammation was present in a minority of samples. [20] (figure 6)

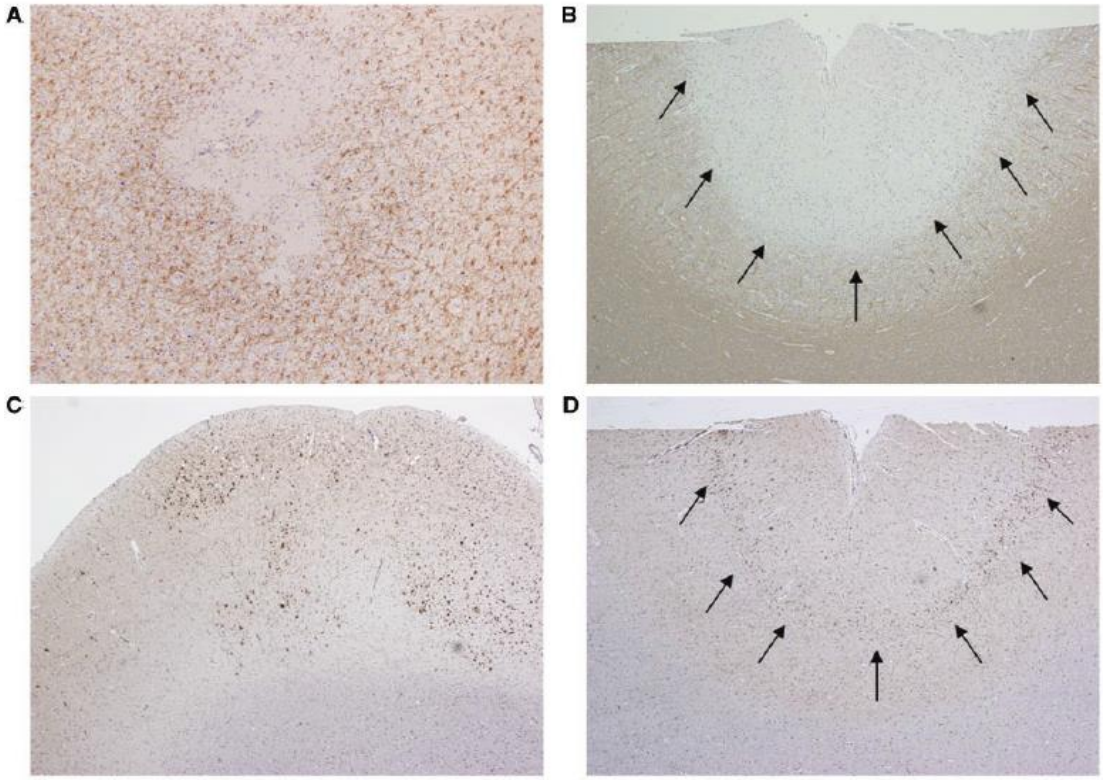

Figure (6): Patterns of cortical pathology in MS. (A) Perivenous intracortical demyelinated lesion (20x); (B) subpial demyelination (arrows) (4x); (C) multifocal aggregates of cortical migroglial activation (4x); (D) macrophage/microglial activation concentrated in cortical layer 3 (arrows) (4x). Immunocytochemistry for proteo lipid protein. [22]

Meningeal pathology

Related to the concept of meningeal inflammation is the finding in adult-onset MS specimens of immune cells identified within the pia-arachnoid, some of which appear to recapitulate features of lymph node tissue, including characteristics of germinal centers and are commonly termed "B-cell follicles". These B-cell follicles were more common in secondary progressive disease as well as in those with earlier onset of

disease, and may represent a more general phenomenon of chronic inflammation within the target organ of autoimmune diseases, as has been described for rheumatoid arthritis, type 1 diabetes, and Sjogren syndrome. [20]

Cerebrospinal fluid (CSF) pathology

CSF provides insights into the inflammatory processes of the CNS. CSF profiles, including cellular profiles, oligoclonal bands, and immunoglobulin G (IgG) Index has been used to characterize MS and differentiate it from other diseases. There are limited longitudinal data regarding the CSF profile in children and adolescents with MS. [20]

Etiology and risk factors:

The etiology of MS is complex, it is assumed that both a complex genetic background and environmental factors and their interactions contribute to disease manifestation. [23]

Genetic etiology

Monozygotic twins carry a concordance rate of approximately 30%, whereas dizygotic twins of the same gender display a 2.3% concordance rate. The incidence for first-degree relatives of MS patients is 2% to 5%, whereas the incidence for the general population is under 0.1%. [20]

Environmental etiology

Infectious agents

The inflammatory component of MS has been thought, at least in part, to be relate to immune responses to environmental agents such as viruses, mostly encountered during the pediatric-age. [23]

Epstein-Barr virus

Despite the fact that previous Epstein-Barr virus infection is very common in the general adult population (90 – 95 %), this virus is strongly associated with the development of multiple sclerosis. [24] Virtually all adults with the disease have been infected, and a prospective study showed that infection occurs before the onset of multiple sclerosis symptoms. [25]

Previous infection also increases the risk of multiple sclerosis in children, but not all children with the disease are seropositive for Epstein-Barr virus. [23] Possible mechanisms by which EpsteinBarr virus infection may predispose to multiple sclerosis include immunological crossreaction, that the virus protects autoreactive B cells from apoptosis, and activation of autoreactive T cells by an excessive immune response against the Epstein-Barr virus. [24] (figure 7)

In accordance with an immunological mechanism, it seems that T cells directed against the virus accumulate in the cerebrospinal fluid of persons with multiple sclerosis. [26]

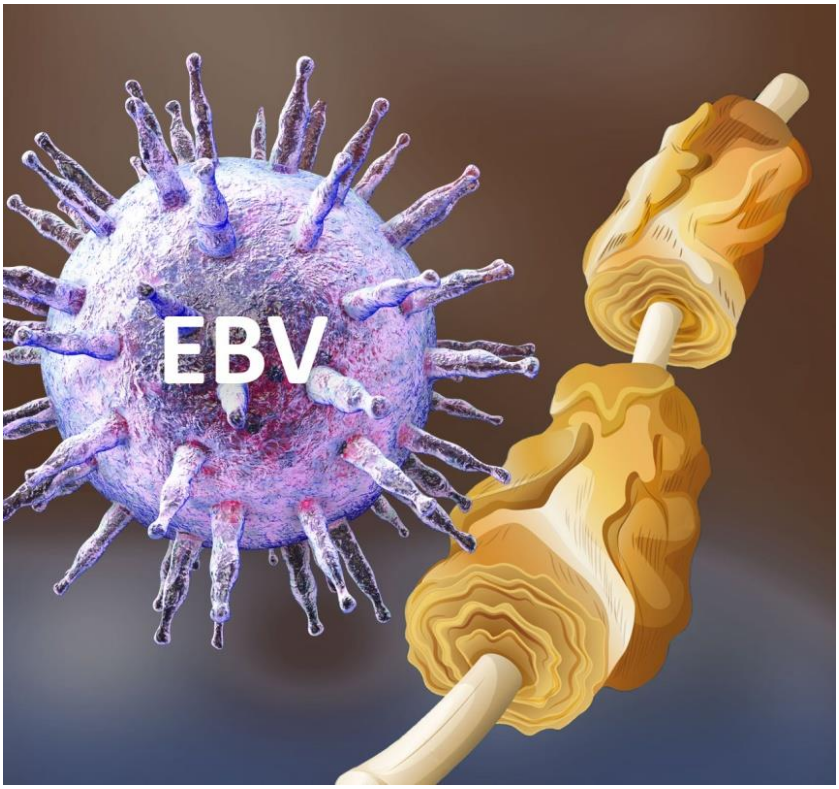

Figure (7): EBV and MS [27].

Vitamin D

Early studies have suggested that increasing latitude in both the northern and southern hemispheres were associated with increased MS risk. This led to the hypothesis and demonstration of an inverse association between sunlight exposure and MS. [23]

Smoking

Smoking increases the risk of adult MS. Similarly, the risk of childhood-onset MS is increased with passive smoking by 2-fold. [24]

Obesity

Obesity at the age of 18 in women was related to a 2-fold increased risk for MS. [21]

Types:

Clinically, MS is classified into four phenotypes

- Relapsing-remitting MS

Is the most common, with 85% of people initially diagnosed with this type. It is characterized by exacerbations of worsening neurologic function that lasts at least 24 hours. [25]

Relapses usually begin with symptoms of neurologic deficits such as optic neuritis, asymmetric numbness, weakness, or ataxia that develops over several days. These symptoms are followed by remission in which no disease progression occurs. In 40% of attacks, mild residual symptoms remain during the remission. [25]

- Secondary-progressive MS occurs in about 40% to 45% of people diagnosed with relapsing-remitting MS after about 10 years. It is defined as a progressive accumulation of disability with no relapses. Temporary, minor improvements may occur but disease progression continues. [26]

- In Primary-progressive MS, neurologic function slowly worsens over time without relapses or remissions. These patients may have an occasional plateau and temporary

minor improvements in symptoms with return to a variable rate of progression. Ten percent of MS patients are diagnosed with this type. [28]

- Progressive-relapsing MS is a rare form that occurs in only 5% of patients diagnosed. This subtype of MS is characterized by steadily worsening disease from onset with acute exacerbations and no remission periods usually presents with slow onset of spastic paraparesis followed by cerebellar or hemiplegic symptoms. Progressive-relapsing MS does not respond to disease modifying medications. The diagnosis includes evidence of lesions in at least 2 places in the central nervous system at least 1 month apart and differential diagnoses are ruled out. [29]

Clinical picture:

Demyelinating optic neuritis (DON) occurs at some point in approximately 27–37% of patients with MS [28] while eye movement abnormalities have been noted to occur in 40–76% of patients. [30-32]

Optic Neuritis:

Optic neuritis refers to inflammation of the optic nerve. The term may be used broadly in reference to many causes of optic nerve inflammation including systemic inflammatory disorders (e.g., lupus, sarcoidosis, Crohn's disease among others), infectious disorders (e.g., Lyme disease, syphilis,

varicella zoster virus among others), and demyelinating disorders (e.g., MS and acute demyelinating encephalomyelitits). More commonly, however, the term optic neuritis is used as a synonym for idiopathic, DON (demyleinating optic neuritis) associated with MS. DON is a hallmark feature of MS and often presents as the initial clinical event. The large, multicenter ONTT trial has provided invaluable data about DON and helped to define the clinical features, visual prognosis, acute treatment, and long-term MS risk for patients with DON.

DON shares a similar demographic with MS affecting younger patients (mean age: 31.8 years) and displaying a female sex predilection (female:male ratio of 3:1).[33] While DON can occur in all races, it is more common in white Caucasians, constituting 85% of subjects in the ONTT. [33] DON remains a primarily clinical diagnosis.[34,35] Characteristic symptoms include acute vision loss, pain and diminished color perception. The ocular pain associated with DON typically lasts 3–5 days, is worse with eye movement and may arise from extraocular muscle traction on the inflamed optic nerve sheath near the orbital apex.[36]Phosphenes, or flashing lights, occur in about 30% of DON cases but are diagnostically nonspecific and occur in other maculopathies and optic neuropathies. [33, 37] (figure 8)