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Therapeutic management of multiple sclerosis in patients consulting the neurology department of the Frantz Fanon University Hospital.

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To my beloved mother, **SOURAYA** no words will ever be enough to express what you mean to me. You are the heart of everything I am. You worked hard outside the home, giving your best in your job, and then came home and gave us even more. You gave us your time, your care, your strength without ever showing the weight you carried. Even when you were tired, even when life was heavy, you smiled for us. You were our provider, our comfort, our guide. You held this family together with silent strength and unconditional love. Your sacrifices, your presence, and your unwavering faith in me are the foundation of this achievement. This work, this success, this dream come true it all begins with you. You are, and always will be, my first hero and my forever home.

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And to **all the people I love**, whether near or far, present or remembered your love is part of who I am.

HIDAYA

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List of abbreviations

APCs: Antigen-Presenting Cells

Aqp4: Aquaporin 4

ARR: Annualized Relapse Rate

BBB: Blood-Brain Barrier

CBC:Complete blood count

CD: Cluster of Differentiation

CD19 :Cluster of Differentiation 19

CD20: Cluster of Differentiation 20

CD4: Cluster of Differentiation 4

CD40, CD80, CD86 :Costimulatory molecules involved in immune signaling

CD8 :Cluster of Differentiation 8

CNS: Central Nervous System

CSF: Cerebrospinal Fluid

DMTs :Disease-Modifying Therapies

DNA: Deoxyribonucleic Acid

DRB1*15 :A shorter version of the HLA allele

EAE: Experimental Autoimmune Encephalomyelitis

EBNA1: EBV Nuclear Antigen 1

EBV: Epstein-Barr Virus

EDSS: Expanded Disability Status Scale

FLAIR :Fluid-Attenuated Inversion Recovery (MRI sequence)

GCs: Glial Cells

GWAS: Genome-Wide Association Study

HHV-6: Human Herpesvirus 6

HHV-8: Human Herpesvirus 8

HLA-DRB1*15:01: Human Leukocyte Antigen DR Beta 1 *15:01 Allele

HSV-1: Herpes Simplex Virus 1

HSV-2: Herpes Simplex Virus 2

IFN-γ: Interferon Gamma

IL-10: Interleukin 10

IL-12: Interleukin 12

IL-17: Interleukin 17

IL-23: Interleukin 23

IV :Intravenous

Krox20: Early Growth Response Protein 2 (EGR2)

LB: B Lymphocytes

LT: T Lymphocytes

MAG: Myelin-Associated Glycoprotein

MBP: Myelin Basic Protein

MHC :Major Histocompatibility Complex (general form)

MHC-II: Major Histocompatibility Complex Class II

MOG: Myelin Oligodendrocyte Glycoprotein

MRI: Magnetic Resonance Imaging

MS: Multiple Sclerosis

NORB: Retrobulbar Optic Neuritis

NRG-1: Neuregulin-1

NRNs: Neurons

NTZ: Natalizumab

OCREVUS: Ocrelizumab (brand name)

OLs: Oligodendrocytes

PBMC: Peripheral Blood Mononuclear Cells

PCR : Polymerase Chain Reaction

PLP: Proteolipid Protein

PML :Progressive Multifocal Leukoencephalopathy

PNS: Peripheral Nervous System

PPMS :Primary Progressive Multiple Sclerosis

PRMS :Progressive-Relapsing Multiple Sclerosis

ROS: Reactive Oxygen Species

RRMS: Relapsing-Remitting Multiple Sclerosis

SCs: Schwann Cells

Sox10: SRY-Box Transcription Factor 10

SPMS Secondary Progressive Multiple Sclerosis

SPSS :Statistical Package for the Social Sciences (if mentioned for data analysis)

T25FW : Timed 25-Foot Walk Test

TMEV-IDD: Theiler's Murine Encephalomyelitis Virus-Induced Demyelinating Disease

TNF-α: Tumor Necrosis Factor Alpha

Treg: Regulatory T Cell

TRUXIMA: Rituximab biosimilar (brand name, used once)

TYSABRI: Commercial name for Natalizumab (if you're using brand names)

VCAM-1 :Vascular Cell Adhesion Molecule-1

VDR: Vitamin D Receptor

VLA-4 :Very Late Antigen-4

Abstract

This study aims to evaluate the therapeutic management of patients with multiple sclerosis, focusing on the clinical use, efficacy, and safety of monoclonal antibodies (Natalizumab, Rituximab, and Ocrelizumab) in a real-world hospital setting.

A retrospective descriptive study was conducted on a group of patients diagnosed with multiple sclerosis and followed at the Neurology Department of CHU Frantz Fanon in Blida. Data collection included patient demographics, clinical forms of MS, annual relapse rate ,Expanded Disability Status Scale (EDSS) scores, and MRI findings. Therapeutic data related to the initiation, duration, and type of monoclonal antibody used were also recorded. In addition, patient tolerance, side effects, and adherence to treatment protocols were evaluated through clinical monitoring and medical records, following national and international therapeutic recommendations.

A total of 55 patients were included. The majority were women (81.8%) and aged between 31 and 40 years. Treatment with monoclonal antibodies showed significant reductions in ARR and stabilization or improvement in EDSS scores and MRI lesion load. Natalizumab was effective but required careful JC virus monitoring. Rituximab offered a cost-effective and well-tolerated alternative, while Ocrelizumab showed high efficacy and tolerability. Most patients reported good adherence, and adverse effects were generally mild and manageable. The study also revealed the socio-economic impact of MS, particularly unemployment among patients.

Key words: Multiple sclerosis, monoclonal antibodies, Natalizumab, Rituximab, Ocrelizumab, EDSS, ARR.

<u>Résumé</u>

Cette étude vise à évaluer la prise en charge thérapeutique des patients atteints de sclérose en plaques, en mettant l'accent sur l'utilisation clinique, l'efficacité et la tolérance des anticorps monoclonaux (Natalizumab, Rituximab et Ocrelizumab) en milieu hospitalier.

Une étude descriptive rétrospective a été menée auprès d'un groupe de patients diagnostiqués avec une sclérose en plaques et suivis au service de neurologie du CHU Frantz Fanon de Blida. La collecte des données a porté sur les caractéristiques démographiques, les formes cliniques de la maladie, le taux annuel de rechutes ,le score EDSS, ainsi que les résultats d'IRM. Les données thérapeutiques concernaient le type, la durée et le moment d'initiation du traitement par anticorps monoclonaux. La tolérance, les effets indésirables et l'adhésion thérapeutique ont également été évalués à partir du suivi clinique et des dossiers médicaux, selon les recommandations thérapeutiques nationales et internationales.

Au total, 55 patients ont été inclus. La majorité étaient des femmes (81,8 %), âgées de 31 à 40 ans. Le traitement par anticorps monoclonaux a permis une réduction significative du taux de rechutes et une stabilisation, voire une amélioration, des scores EDSS et de la charge lésionnelle à l'IRM. Le Natalizumab a montré une efficacité notable mais nécessitait une surveillance stricte du virus JC. Le Rituximab a été bien toléré et constitue une alternative économique, tandis que l'Ocrelizumab a montré une efficacité et une tolérance élevées. L'adhésion au traitement a été bonne dans l'ensemble, avec peu d'effets secondaires graves signalés. L'étude a également mis en évidence l'impact socioéconomique de la maladie, notamment sur l'emploi.

Mots-clés : Sclérose en plaques, anticorps monoclonaux, Natalizumab, Rituximab, Ocrelizumab, EDSS, ARR.

ملخص

تهدف هذه الدراسة إلى تقييم الرعاية العلاجية المقدمة للمرضى المصابين بالتصلب المتعدد، مع التركيز على الاستخدام السريري، في الوسط الاستشفائي (Ocrelizumabو Rituximab، Natalizumab) الفعالية، وتحمل الأجسام المضادة أحادية النسيلة .

تم إجراء دراسة وصفية استعادية على مجموعة من المرضى المشخّصين بالتصلب المتعدد والمتابعين على مستوى مصلحة طب الأعصاب في مستشفى CHU فرانتز فانون بالبليدة. شملت عملية جمع البيانات الخصائص الديموغرافية، الأشكال السريرية للمرض، معدل الانتكاسات السنوي (ARR)، مؤشر الإعاقة العصبية(EDSS) ، بالإضافة إلى نتائج التصوير بالرنين المغناطيسي(IRM) . أما البيانات العلاجية فقد تناولت نوع العلاج، مدته، وتاريخ بدء استخدام الأجسام المضادة أحادية النسيلة. كما تم تقييم مدى التحمل، الآثار الجانبية، والالتزام بالعلاج من خلال المتابعة السريرية والملفات الطبية، وفقًا للتوصيات العلاجية الوطنية والدولية

النتائج والمناقشة :

شملت الدراسة 55 مريضًا مصابًا بمرض التصلب المتعدد. كانت الغالبية من الإناث بنسبة 81.8%، وتتراوح أعمار معظمهم بين 31 و40 سنة. أظهرت نتائج العلاج باستخدام الأجسام المضادة أحادية النسيلة (Ocrelizumab، Rituximab، Natalizumab) فعالية ملحوظة في تقليل معدل الانتكاسات السنوي (ARR)، وتحسين أو استقرار درجات الإعاقة العصبية(EDSS) ، إلى جانب انخفاض في عدد وتطور الآفات الظاهرة في التصوير بالرنين المغناطيسي (IRM).

أثبت دواء Natalizumab فعالية كبيرة، لكنه تطلب مراقبة منتظمة لمستوى الأجسام المضادة لفيروس JC لتفادي خطر الإصابة باعتلال بيضاء الدماغ متعدد البؤر التقدمي (PML). أما Rituximab، فقد وفر خيارًا علاجيًا فعّالًا وأقل تكلفة، مع مستوى جيد من التحمل لدى المرضى، رغم استخدامه خارج التوصيات الرسمية في بعض الحالات. وأظهر Ocrelizumab بدوره نتائج قوية من حيث تقليل نشاط المرض وتحسن الاستجابة السريرية، مع تحمّل ممتاز وآثار جانبية قليلة

كما بينت الدراسة أن التزام المرضى بالبروتوكولات العلاجية كان مرضيًا إلى حد كبير، وأن الآثار الجانبية المبلغ عنها كانت طفيفة إلى معتدلة في أغلب الحالات، مما يعكس إمكانية دمج هذه العلاجات بشكل فعال في الممارسة السريرية اليومية في الجزائر. بالإضافة إلى ذلك، كشفت النتائج عن التأثير الاجتماعي والاقتصادي للمرض، وخاصة ارتفاع معدلات البطالة وفقدان العمل بين المرضى في سن النشاط

الكلمات المفتاحية

التصلب المتعدد، الأجسام المضادة أحادية النسيلة، ناتاليزوماب، ريتوكسيماب، أوكرليزوماب، EDSS، ARR.

<u>Contents</u>

INTRODUCTION

Introduction

Multiple sclerosis is a chronic inflammatory disease of the central nervous system , characterized by demyelinating lesions, progressive neurodegeneration, and abnormal activation of the immune system. It is currently the leading cause of non-traumatic neurological disability among young adults (**Absinta *et al*., 2021; Babbe *et al*., 2000**). Although its exact mechanisms remain partially understood, it is widely accepted that a complex interaction between genetic susceptibility—particularly involving the HLA-DRB1*15:01 allele—and environmental factors such as Epstein-Barr virus (EBV) infection, vitamin D deficiency, and tobacco use plays a major role in triggering the autoimmune response (**Zrzavy *et al*., 2021; Jacob *et al*., 2021; Ascherio & Munger, 2015; Mahad *et al*., 2015; Maric *et al*., 2021**).

To understand the impact of multiple sclerosis, it is essential to briefly consider the structure and function of the nervous system. The nervous system is one of the most complex and vital systems in the human body, responsible for coordinating and regulating bodily functions such as movement, sensation, cognition, and emotional responses. It is composed of two main parts: the central nervous system (brain and spinal cord) and the peripheral nervous system, which connects the CNS to limbs and organs (**Betts *et al*., 2022; Thau *et al*., 2022).** Neurons are the functional units of the nervous system, transmitting electrical and chemical signals throughout the body, and are supported by glial cells , which maintain the structural and metabolic integrity of neural tissue (**StatPearls, 2022; Jessen & Mirsky, 2024**).

In MS, the immune system mistakenly attacks the protective myelin sheath that surrounds axons in the CNS. This disruption impairs nerve impulse transmission, leading to a wide array of neurological symptoms such as muscle weakness, sensory disturbances, coordination problems, visual impairment, and cognitive dysfunction (**Dendrou *et al*., 2015; Lassmann, 2018; Serafini, 2016**). Over time, this damage can become irreversible, resulting in progressive disability and a marked decline in the patient's quality of life (**Babbe *et al*., 2000; Cavallo, 2020**).

Although MS currently has no definitive cure, therapeutic strategies have significantly evolved. The treatment approach includes high-dose corticosteroids for acute relapses, disease-modifying therapies to reduce disease activity, and the use of monoclonal antibodies such as

Natalizumab, Rituximab, and Ocrelizumab. These biological agents have demonstrated significant efficacy in reducing relapse rates, slowing disability progression, and improving MRI outcomes in relapsing forms of MS (**Michel, 2016; Edan & Le Page, 2013; Kesselring & Kesselring, 2020; Gray *et al*., 2020; Bouzid *et al*., 201**2). However, their long-term use raises questions regarding safety, cost, accessibility, and the need for individualized treatment strategies.

This research aims to evaluate the therapeutic management of MS in patients followed at the Neurology Department of Frantz Fanon University Hospital in Blida, with a particular focus on the use of monoclonal antibodies, which currently represent a key therapeutic option in active forms of the disease. These therapies have shown promising results in reducing relapse frequency, delaying progression, and improving clinical and radiological outcomes.

In addition, the study aims to describe the sociodemographic and clinical characteristics of the affected patients, identify the types of treatments used (including DMTs, symptomatic treatments, and relapse management strategies). It also seeks to evaluate drug tolerance, document reported side effects, and measure adherence to treatment protocols.

This work is presented in three chapters:

In the first chapter, generalities and literature review on nervous system and multiple sclerosis are developed.

The second describes the material used and the methods followed in patients enrollement and studied parameters .

The third chapter presents the different results obtained and their discussion. Finally, a general conclusion closes the present study.

Chapter 1

Literature review

1.1. General Organization of the Nervous System

1.1.1. Anatomy and Functions

The nervous system is one of the most intricate and vital systems in the human body. It governs perception, movement, cognition, and homeostatic regulation. Anatomically and functionally, it is divided into the central nervous system (CNS) which includes the brain and spinal cord and the peripheral nervous system (PNS), which consists of all neural structures outside the CNS, including peripheral nerves and ganglia (**Betts *et al*., 2022 ; Thau *et al*., 2022**).

The CNS is responsible for integrating and processing all incoming and outgoing information. It is enclosed and safeguarded by the skull and vertebral column. The PNS consists of sensory and motor pathways that link the CNS with peripheral organs, muscles, and glands (**Betts et al., 2022 ; Thau et al., 2022**). Nervous tissue in both systems includes neurons (NRNs), which transmit signals, and glial cells (GCs), which preserve the integrity and functionality of neural networks (**StatPearls, 2022 ; Jessen & Mirsky, 2024**).

1.1.2. Protective Barriers of the CNS

The brain and spinal cord are encased within three meningeal layers: the dura mater**,** arachnoid mater**,** and pia mater. These are suspended in cerebrospinal fluid (CSF), and the entire structure is further protected by the blood-brain barrier (BBB), which prevents harmful substances from reaching the CNS (**StatPearls, 2022; Drk, 2025**).

1.1.3. Neurons: Structure and Function

1.1.3.1. General Structure

The neuron (NRN) is the basic structural and functional unit of the nervous system. It consists of a cell body (cytone) and two types of extensions: dendrites and a single axon (**Betts *et al*., 2022 ; Drk, 2025**). The cytoplasm, or neuroplasm (Cyt**)**, contains a nucleus**,** Nissl bodies (NBs) involved in neurotransmitter synthesis, neurofibrils (NFs) responsible for intracellular transport, mitochondria, Golgi apparatus, and glycogen granules (**Betts *et al*., 2022 ; Drk, 2025**). All these elements are enclosed within the plasma membrane (PM) (**Figure 1**).

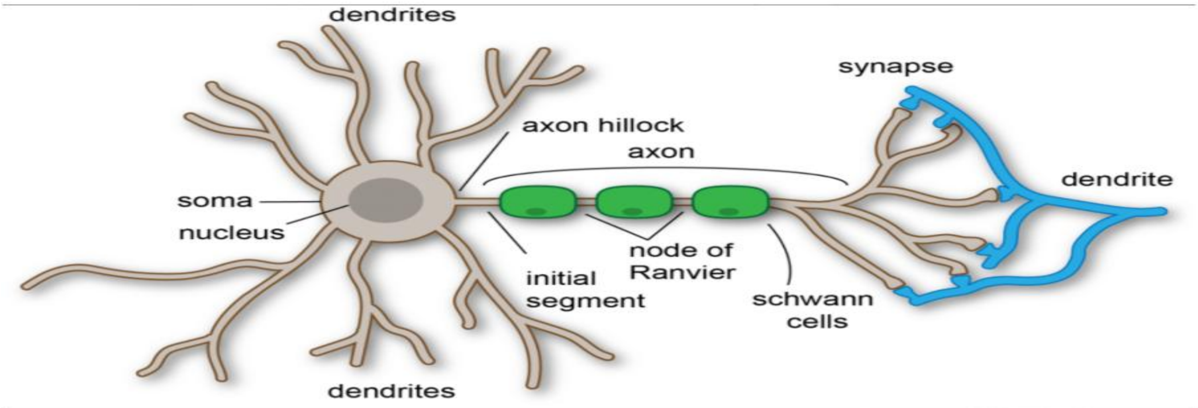


Figure 1: Diagram showing the basic structure of a neuron (Baecher-Allan *et al*., 2018).

1.1.3.2. Axons and Dendrites functions

- **Axons** conduct impulses away from the cell body toward the synapse.
- **Dendrites** receive stimuli and transmit them toward the cell body. Axons are often covered in a myelin sheath, which enhances signal transmission (**Drk, 2025 ; Varatharaj & Galea, 2020**).

1.1.3.3. Classification of Nerve Fibers

- **Myelinated Nerve Fibers with Schwann Sheath**

These fibers are located in peripheral nerves. The axon is wrapped in a myelin sheath formed by Schwann cells (SCs)**.** The myelin segments are separated by nodes of Ranvier (NR)**,** allowing saltatory conduction, which accelerates impulse transmission (**Jessen & Mirsky, 2024 ; Varatharaj & Galea, 2020**).

- **Myelinated Nerve Fibers without Schwann Sheath**

In the CNS**,** oligodendrocytes (OLs) produce myelin for multiple axons fsimultaneously. Unlike SCs, each OLs extends several processes to wrap different axons, and no Schwann sheath is present (**AP News, 2023 ; Jessen & Mirsky, 2024**).

- **Unmyelinated Fibers with Schwann cells**

These fibers are typically found in the autonomic nervous system**.** Although not myelinated, axons are surrounded by SCs, which provide structural and metabolic support (**Jessen & Mirsky, 2024**).

- **Unmyelinated Fibers without Schwann cells**

Located in the gray matter of the CNS, these axons lack both SCs and myelin, relying on the surrounding GCs for support (**StatPearls, 2022 ; Perea *et al*., 2022**).

1.1.3.4. Schwann Cells and the Schwann Sheath

The SCs are glial cells in the PNS that play key roles in both myelinated and unmyelinated nerve fibers. In myelinated fibers, SCs wrap their PM around the axon multiple times, forming compact layers known as the myelin sheath (**Figure 2**). The outermost layer forms the Schwann sheath (neurilemma), essential for axonal regeneration (**Jessen & Mirsky, 2024** ; **Varatharaj & Galea, 2020 ; AP News, 2023**)

Following nerve injury, SCs undergo differentiation, proliferate, and produce neurotrophic factors that promote axonal regrowth and remyelination (**Jessen & Mirsky, 2024** ; **AP News, 2023**).

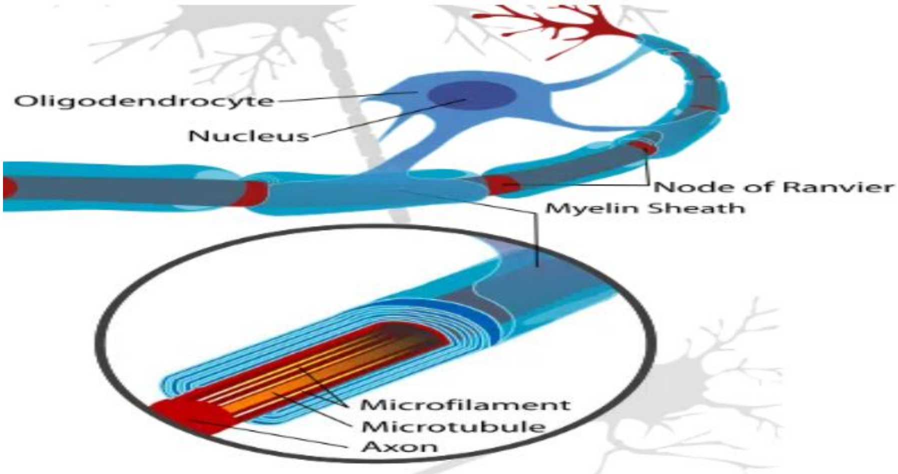


Figure 2: Axon Structure with Oligodendrocyte and Myelin Sheath (**Varatharaj & Galea, 2020)**.

1.1.4. Glial Cells (Neuroglia)

The GCs are non-neuronal cells that perform various support functions in the nervous system (**Figure 3**):

- **Astrocytes**: Maintain the BBB and regulate the extracellular ionic balance (**StatPearls, 2022; Perea *et al*., 2022**).
- **Oligodendrocytes** : Myelinate CNS axons (**Jessen & Mirsky, 2024** ; **AP News, 2023**).

- **Microglia**: Act as immune effector cells (**Perea & Araque, 2022 ; Varatharaj & Galea, 2020**).

- **Ependymal cells**: Line the ventricles and produce CSF (**Betts *et al*., 2022 ; Monk *et al*., 2021**).

- **Schwann Cells**: Myelinate or support PNS axons (**Jessen & Mirsky, 2024 ; Varatharaj & Galea, 2020**).

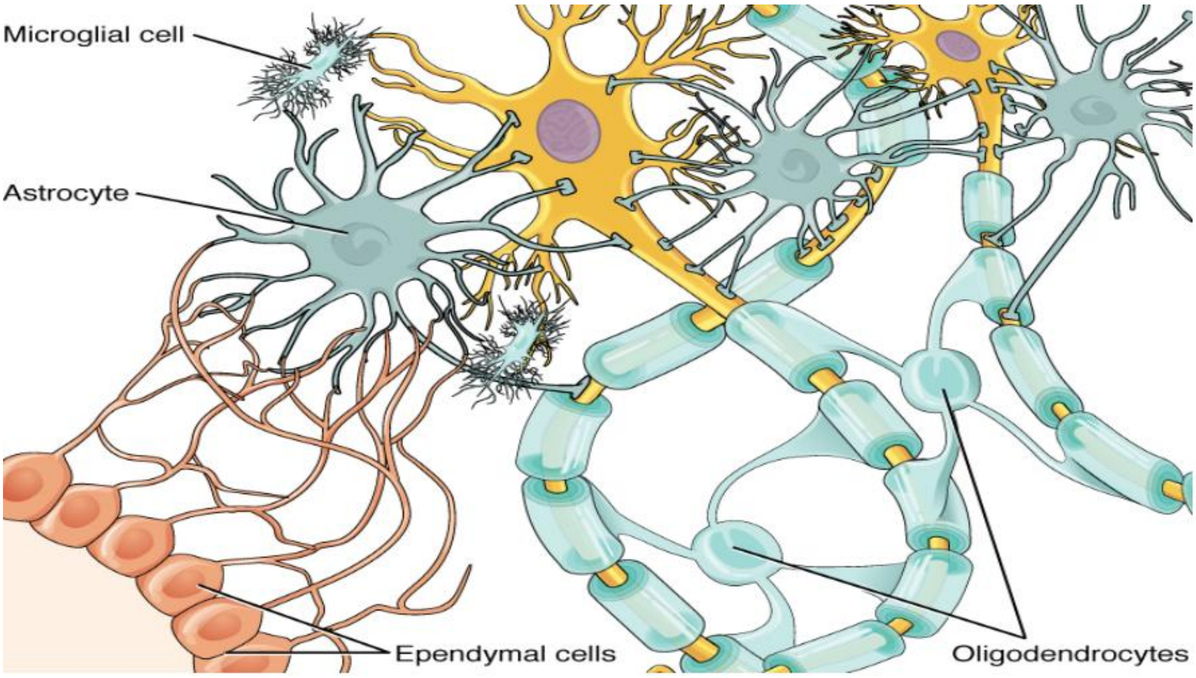


Figure 3: Glial Cells of the CNS The CNS has astrocytes, oligodendrocytes, microglia, and ependymal cells that support the neurons of the CNS in several ways (**Jessen & Mirsky, 2024**).

1.2. Multiple sclerosis

1.2.1. Definition

Multiple sclerosis (MS) is a chronic neurological disease associated with CNS inflammation and neurodegeneration mediated by the adaptive and innate arms of an unregulated immune response **(Serafini, 2016; scherio & Munger, 2015).** MS pathology is characterized by well-demarked inflammatory infiltrates, breakdown of myelin sheaths, microglia activation, proliferation of astrocytes and gliosis, and variable grades of axonal degeneration linked to oxidative stress and mitochondrial injury **(Babbe *et al.*, 2000; Absinta *et al*., 2021)**. Demyelinated lesions are disseminated through the CNS, involving both the white and gray matter. MS is a common cause of progressive neurological deficits in young adults, but disease expression is heterogeneous, varying from a mild illness to a rapidly evolving, incapacitating disease requiring profound lifestyle adjustments.

1.2.2. Genetic factors and hereditary susceptibility

MS is not considered a hereditary disease in the traditional Mendelian sense. Unlike single-gene disorders such as cystic fibrosis, MS does not follow a dominant or recessive inheritance pattern. There is no single defective gene that causes the disease to be passed directly from one generation to the next. Rather, MS is a polygenic condition in which multiple genes contribute to disease susceptibility without necessarily involving pathogenic mutations.

These genetic variants often exist as common polymorphisms in the general population. However, when combined with certain environmental factors, they can significantly increase the risk of developing MS. This interaction is why MS is described as a result of genetic susceptibility interacting with environmental triggers, which are often more difficult to quantify **(Zrzavy *et al*., 2021).**

The HLA-DRB1*15:01 allele, located in the human leukocyte antigen (HLA) region, is the strongest known genetic risk factor for MS. Individuals who carry this allele have a 3-fold higher risk of developing the disease(**Zrzavy *et al.*, 2021; Maric *et al*., 2021**). In addition, genome-wide association studies (GWAS) have identified over 200 non-HLA loci associated with MS, each contributing modestly to the overall risk **(Mahad *et al*., 2015).**

Statistical data also reveal the influence of genetics in familial clustering. For example, the risk of developing MS is approximately 20–30% in monozygotic (identical) twins if one sibling is affected. This figure drops to around 3–5% for siblings or children of someone with MS **(Mahad *et al.*, 2015**).If MS were a purely genetic disease, the concordance rate among identical twins would approach 100%, but the lower percentage underscores the importance of non-genetic factors in disease development (**Figure 4**).

Finally, MS is known to affect women two to three times more often than men. This disparity may be partially explained by X-linked genetic variants and hormonal influences, which modulate immune responses and disease susceptibility **(Kuhlmann, 2017).**

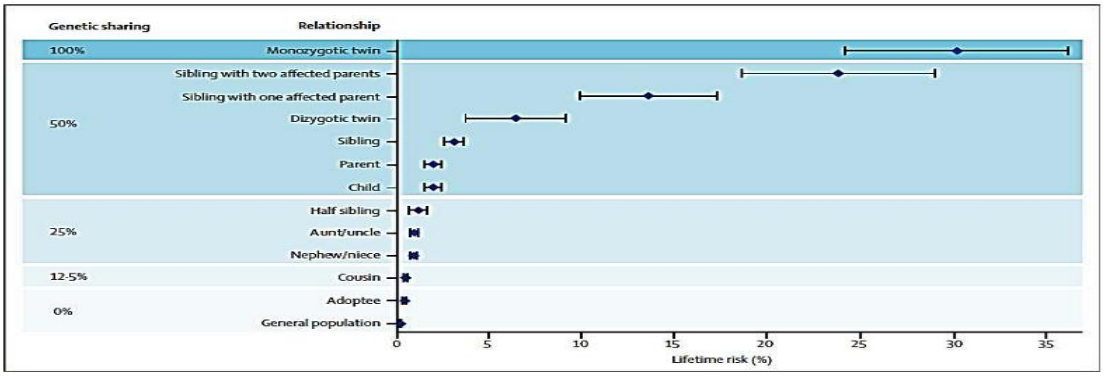


Figure 4: Risk of developing multiple sclerosis according to degree of genetic relatedness with an affected individual **(Pellegrini *et al*., 2020).**

1.2.3. Environmental factors

1.2.3.1. Viral infections

Viral infections have long been suspected of playing a triggering role in the development of MS, particularly in genetically predisposed individuals. Among these, the Epstein-Barr virus (EBV) shows the strongest association. Virtually all patients with MS are seropositive for EBV, and recent longitudinal studies have shown that EBV infection often precedes the onset of the disease by several years, suggesting a possible causal link **(Babbe *et al*., 2000)**. Other viruses, such as human herpesviruses 6 (HHV-6), 8 (HHV-8), herpes simplex viruses (HSV-1 and HSV-2) **(scherio & Munger, 2015)**, and the measles virus, have also been studied, but their associations with MS remain less well established and sometimes controversial **(Lassmann, 2018).**

Two main mechanisms have been proposed to explain the involvement of viruses in MS: The non-specific activation of autoreactive T lymphocytes by pro-inflammatory cytokines produced during infection.
Molecular mimicry, in which viral peptides share similarities with central nervous system antigens, Therapy inducing a cross-reactive autoimmune response **(Absinta *et al*., 2021)**.

1.2.3.2. The Role of Vitamin D in multiple sclerosis

A growing body of research has demonstrated a strong association between vitamin D levels and the risk of developing MS (**Figure 5**). Ultraviolet (UV) radiation from sunlight stimulates cutaneous synthesis of vitamin D, which has been shown to exert immunomodulatory effects that may protect against autoimmune diseases, including MS **(Jacob *et al.*, 2021).**

Vitamin D interacts with the immune system through its nuclear receptor (VDR), which is expressed on dendritic cells, T lymphocytes, B lymphocytes, and within the CNS. Through these interactions, vitamin D downregulates the expression of major histocompatibility complex class II (MHC-II) molecules and co-stimulatory molecules such as CD40, CD80, and CD86 on antigen-presenting cells. Additionally, vitamin D suppresses the differentiation of naive T cells into pro-inflammatory Th1 and Th17 subtypes, reduces the production of cytokines like IFN-γ, IL-17, IL-12, and IL-23, and promotes the expansion of regulatory T cells and the anti-inflammatory cytokine IL-10 **(Dendrou *et al.*, 2015;Lassmann, 2018)**.

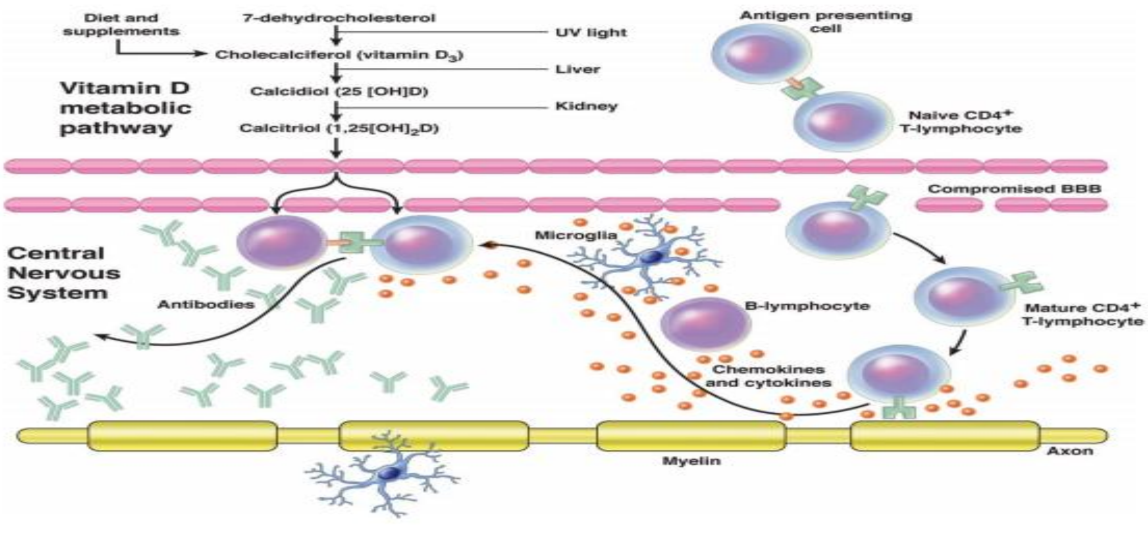


Figure 5: Vitamin D Metabolism and Its Immunomodulatory Effects in MS (**Jacob *et al.*, 2021**)

1.2.3.3. Smoking Role of in multiple sclerosis

Tobacco smoking has been strongly implicated in increasing both the risk of developing MS and accelerating its progression. The underlying mechanisms remain multifactorial and complex due to the presence of over a thousand chemical compounds in tobacco smoke.

Nicotine, one of its primary components, is thought to increase the permeability of the BBB, thereby facilitating the infiltration of autoreactive lymphocytes and myelin-toxic agents into the CNS **(Anonymous, 2023).**

Furthermore, nicotine can stimulate the endogenous production of nitric oxide (NO), a reactive molecule associated with axonal degeneration. In parallel, cyanide derivatives produced during tobacco combustion may contribute to the demyelination process by directly damaging oligodendrocytes and the myelin sheath **(Anonymous, 2023)**.

1.2.4. Pathophysiological Mechanisms in multiple sclerosis

The MS is driven by a complex interplay of genetic and environmental factors that lead to an aberrant immune response targeting components of the CNS, especially myelin. Autoreactive CD4^{+} T-cells primarily of the Th1 and Th17 lineages are activated in the periphery by APCs presenting myelin peptides via MHC class II molecules (**Figure 6**). These activated T-cells migrate across a permeabilized BBB and become reactivated by CNS-resident APCs such as microglia and astrocytes, initiating a robust neuroinflammatory cascade **(*Dendrou et al.*, 2015; Lassmann, 2018)**.

Within the CNS, these T-cells secrete pro-inflammatory cytokines including IFN-γ, IL-17, and TNF-α, which amplify local inflammation and recruit additional immune cells such as macrophages and microglia. These cells contribute to demyelination and axonal injury through the release of ROS, nitric oxide, and proteolytic enzymes (**Dendrouet *et al.*, 2015**). Simultaneously, the failure of Tregs and reduced IL-10 signaling impair immune regulation, favoring disease progression (**Lassmann, 2018**).

B-cells are also central to MS pathophysiology. They act as APCs, secrete inflammatory cytokines, and produce autoantibodies against myelin components like MOG, MBP, PLP, and MAG. The presence of oligoclonal IgG bands in CSF a hallmark of MS is evidence of intrathecal B-cell activation (**Serafini, 2016**). Moreover, B-cells can form ectopic germinal centers within the meninges, maintaining chronic inflammation and correlating with cortical demyelination and worse clinical outcomes (**Babbe *et al.*, 2000**).

In addition, CD8^{+} cytotoxic T-cells contribute to axonal damage via direct cytotoxicity, particularly in progressive disease forms (**Babbe *et al.*, 2000**). Emerging evidence also implicates EBV in MS pathogenesis. Infected B-cells may express cross-reactive antigens such as EBNA1, triggering activation of autoreactive T-cells through molecular mimicry (**scherio & Munger, 2015**).

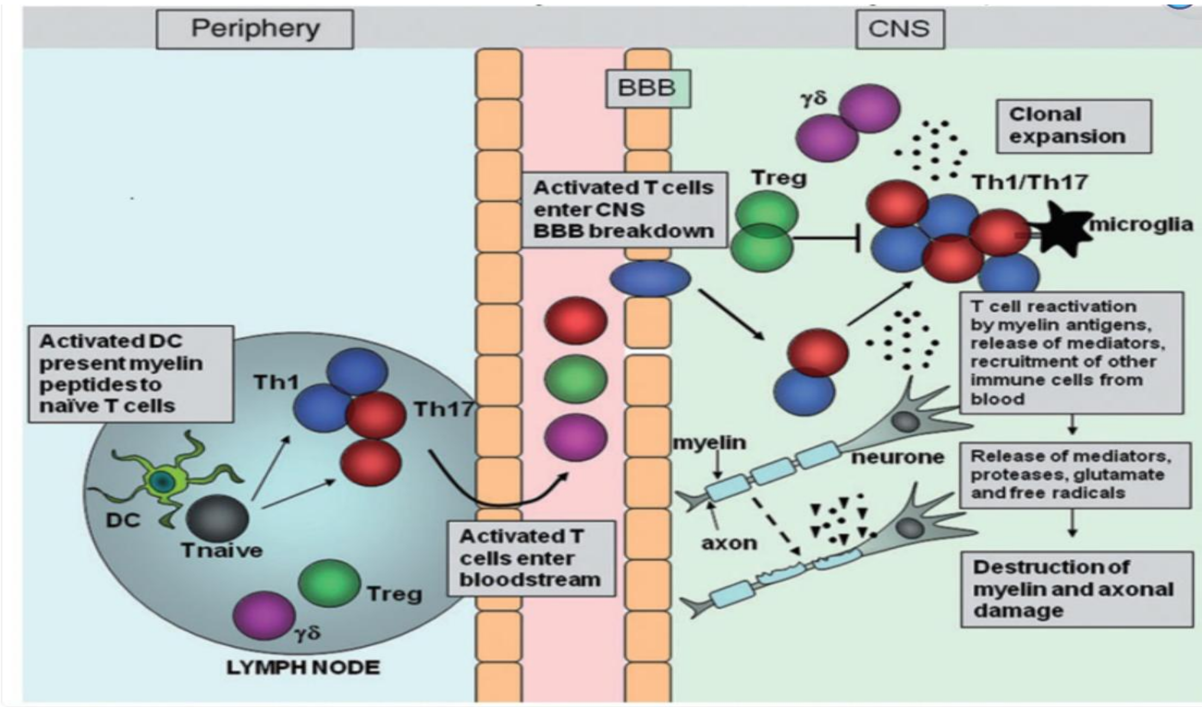


Figure 6: Migration and Effector Function of T Cells in the CNS (**Cavallo, 2020**).

The pathophysiology of the disease occurs in four main stages, as detailed below:

- **Initial Demyelination**

o Mild myelin sheath damage (axons initially spared) slows and disrupts nerve conduction.

o **Immune mechanism:** Autoreactive **CD4**$^{+}$ **T-cells (Th1/Th17),** activated peripherally by myelin peptides presented via MHC-II, cross a compromised BBB. Reactivated by CNS APCs (microglia/astrocytes), they secrete **pro-inflammatory cytokines (IFN-γ, IL-17, TNF-α),** recruiting macrophages/microglia that exacerbate demyelination via **ROS, nitric oxide, and proteases** (**Dendrou** ***et al.*****, 2015;Lassmann, 2018**).

- **Remyelination (Reversible Phase**)

o Oligodendrocytes attempt repair, but remyelination is often incomplete, leaving scars.

o **Immune dysregulation:** Impaired **Treg function** and reduced **IL-10** weaken suppression of inflammation, though partial recovery may occur post-relapse (**Lassmann, 2018**).

- **Chronic Demyelination (Worsening)**

- Persistent inflammation further degrades myelin, severely disrupting nerve conduction.

- **B-cell involvement:** B-cells amplify damage by acting as APCs, secreting cytokines, and producing **autoantibodies** (e.g., anti-MOG/MBP). **Oligoclonal IgG bands** in CSF reflect intrathecal antibody production (**Serafini, 2016**). Ectopic meningeal germinal centers sustain inflammation, linked to cortical demyelination (**Babbe *et al*., 2000**).

- **Axonal Degeneration (Irreversible Disability)**

- Chronic inflammation leads to **axonal transection** and neuronal loss, driven by:

- **CD8^{+} T-cell cytotoxicity** (progressive forms) (**Babbe *et al*., 2000**).

- **EBV molecular mimicry**: Cross-reactive EBNA1 antigens may perpetuate autoimmunity (**scherio & Munger, 2015**).

- Failed remyelination and cumulative axonal damage result in permanent deficits.

1.2.5. Clinical Manifestations of multiple sclerosis

The MS is a chronic inflammatory disease of the CNS marked by demyelination and axonal degeneration. Its clinical presentation is highly variable and depends on the location and extent of lesions.

- **Motor symptoms**: Patients commonly experience muscle weakness, spasticity, and impaired coordination, which can result in gait disturbances and postural instability.
- **Sensory disturbances**: Paresthesia (tingling), numbness, and neuropathic pain are frequently reported, reflecting involvement of sensory pathways.
- **Visual disturbances**: Optic neuritis (NORB) is one of the earliest and most frequent symptoms, characterized by painful, unilateral vision loss. Other oculomotor symptoms may include diplopia, nystagmus, and internuclear ophthalmoplegia due to brainstem or cerebellar lesions.

- **Cognitive and affective changes**: Many patients exhibit memory impairment, reduced attention span, executive dysfunction, and emotional disturbances such as depression and anxiety.
- **Fatigue**: Fatigue is reported in up to 80% of MS patients and is often one of the most debilitating symptoms. It may occur independently of physical activity and can worsen with heat or stress.
- **Bladder, bowel, and sexual dysfunction**: Urinary urgency, incontinence, constipation, and sexual dysfunction (e.g., erectile dysfunction in men, reduced libido in women) are common due to spinal cord involvement.
- **Vertigo and balance issues**: Lesions in the cerebellum and vestibular pathways can cause vertigo, ataxia, and coordination problems.
- **Cranial nerve involvement**: MS can affect multiple cranial nerves, leading to dysarthria, dysphagia, trigeminal neuralgia, and even auditory symptoms.
- **Cerebellar involvement**: Damage to the cerebellum manifests as ataxia, intention tremor, dysmetria, and scanning speech (dysarthria) (**Larousse, 2020**).

1.2.6. Clinical Forms and Prognosis of multiple sclerosis

The MS presents in different clinical subtypes. The most common is **Relapsing-Remitting MS (RRMS)**, accounting for approximately 85% of initial diagnoses, and is characterized by episodes of neurological dysfunction (relapses) followed by periods of remission. Over time, many RRMS patients evolve into **Secondary Progressive MS (SPMS)**, defined by gradual neurological deterioration independent of relapses. In contrast, **Primary Progressive MS (PPMS)** affects about 10–15% of patients and involves continuous worsening from onset without distinct relapses. A less common subtype, **Progressive-Relapsing MS (PRMS)**, features steady progression combined with occasional acute exacerbations (**Lublin *et al*., 2014**).

The prognosis in MS is influenced by several factors, including age at onset, initial symptomatology, relapse rate, and early treatment response. Earlier onset (typically before age 40), female sex, and initial sensory rather than motor or cerebellar symptoms are generally linked to a more favorable prognosis (**Confavreux & Vukusic, 2006**). On the other hand, high relapse frequency, early cerebellar involvement, or poor response to disease-modifying therapies are associated with faster disability accumulation (**Rotstein *et al*.,2018**).

1.2.7. Diagnostic of multiple sclerosis

1.2.7.1. Magnetic Resonance Imaging (MRI)

MRI is the most valuable paraclinical tool for diagnosing multiple sclerosis, offering high sensitivity in detecting demyelinating lesions. It plays a crucial role in establishing both the spatial and temporal dissemination of CNS lesions required by the McDonald criteria. Brain and spinal cord MRI should be performed as early as the first clinical event, even before a second relapse, to enable timely diagnosis and early initiation of treatment (**Thompson, 2017**).

Modern MRI protocols include various sequences that visualize lesions in the white matter. T2-weighted and FLAIR (Fluid-Attenuated Inversion Recovery) sequences reveal hyperintense signals indicating demyelination. T1-weighted sequences, particularly after gadolinium injection, help identify active lesions by showing contrast enhancement, which indicates blood–brain barrier breakdown-a hallmark of recent inflammation (typically within three weeks) (**Wattjes *et al*., 2015**).

MRI also allows classification of lesions based on their location: **periventricular**, **juxtacortical**, **infratentorial**, and **spinal** which supports the diagnosis of MS and helps exclude differential diagnoses. Serial imaging further aids in assessing disease activity and therapeutic response over time (**Filippi *et al*., 2019).**

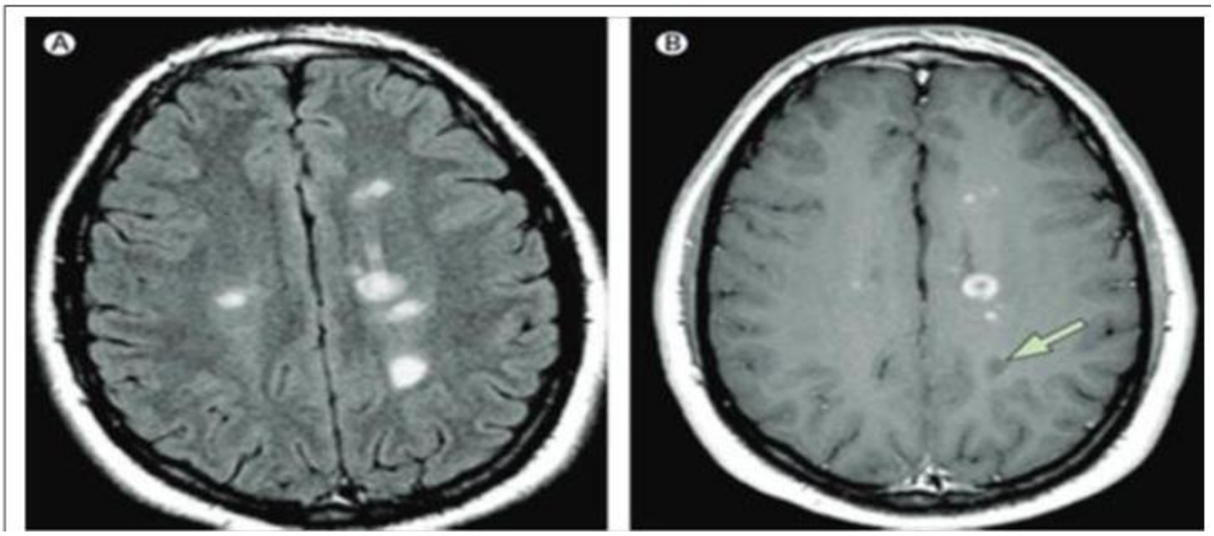


Figure 7: **Brain MRI of a Patient with MS** (**Filippi *et al*., 2019**).

(A) Axial FLAIR image: Multiple round and ovoid hyperintense lesions are visible (*white arrows*).
(B) T1-weighted sequence post-gadolinium injection (**Filippi *et al*., 2019**)

1.2.7.2. The CSF Analysis

The CSF analysis plays a critical role in diagnosing MS, especially in early disease stages or when MRI findings are inconclusive. CSF is obtained through lumbar puncture and analyzed for signs of CNS-specific inflammation.

The hallmark of MS-related CSF abnormalities is the presence of oligoclonal IgG bands (OCBs), which reflect intrathecal synthesis of immunoglobulins and are found in over 90% of patients. An elevated IgG index may also be detected, supporting the diagnosis of MS in the context of compatible clinical and radiological findings **(Edan, Le Page, 2013)**.

In the updated 2021 revision of the McDonald diagnostic criteria, the presence of OCBs in CSF can substitute for demonstration of dissemination in time, thus allowing earlier diagnosis and prompt initiation of disease-modifying therapy (**Fournier, 2017**).

1.2.7.3. Measuring MS Progression Using the EDSS Score

Introduced by J.F. Kurtzke in 1983, the EDSS is an ordinal scale ranging from 0 to 10 that assesses disability across eight functional systems: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral and mental functions, and other residual functions (**Thompson, 2017**). A score of 0 on the EDSS reflects a normal neurological exam (**Figure 8**). A score of 3.5 indicates moderate disability in more than one functional system (for instance, visual, cerebellar, sensory, bowel, bladder, etc.), while the patient can still walk any distance without assistance. Scores between 4.0 and 6.0 reflect increasing limitations in walking distance. A score of 6.0 means the patient requires one-sided assistance to walk (like a cane or crutch), while 6.5 means bilateral assistance is needed. Beyond a score of 7, the patient is no longer ambulatory. A score of 10 indicates death due to MS (**Casez, 2012**).

Figure 8: Echelle EDSS pour l'évaluation de la sclérose en plaques (**Thompson, 2017**).

1.2.8. Treatment of multiple sclerosis

There is no medication that can stop this chronic disease. Disability occurs early, and half of the disease course involves a dependent state. Treating a patient with MS also means providing care to improve their condition and manage complications throughout the disease progression. Symptomatic treatments constitute the majority of these therapies. Therapeutic efficacy is judged based on the frequency of relapses and the progression of neurological disability, clinically assessed using validated scales such as the **EDSS (Anonymous, 2023).**

Therapeutic drug management is limited to three objectives:

- **Treatment of relapses**, primarily with corticosteroids.
- **Disease-modifying therapies (DMTs),** aimed at reducing and slowing relapse frequency without altering disease progression. Immunomodulators and immunosuppressants are the mainstays.
- **Symptomatic treatment**, which is the final component.

These treatments are particularly recommended for **RR forms** of the disease **(Anonymous, 2023;Larousse, 2020).**

1.2.8.1. Treatment of Relapses

The standard treatment for an MS relapse involves **high-dose intravenous corticosteroids** administered over a short period. The most common regimen is **methylprednisolone 1 g per day for 3 to 5 days**. The decision to use high-dose corticosteroids must be made by a neurologist after confirming the relapse and assessing treatment necessity (**Morand , 2020**)

Corticosteroids act solely on the acute relapse by reducing inflammation and symptom severity but do **not prevent future relapses** (**Fournier, 2017**).

Since 2016, relapses can also be treated **outpatient** with **oral methylprednisolone (100 mg, 10 tablets per day for 3 days).** The tolerability and efficacy of oral methylprednisolone are nearly identical to the IV route (**Morand, 2020**).

However, potential side effects must be considered, especially with prolonged use. Common issues include insomnia, hyperglycemia, and gastrointestinal disturbances, though corticosteroids are generally well-tolerated in short courses.

1.2.8.2. Disease-Modifying Therapies (DMTs)

These include **three classes**: **immunomodulators**, **immunosuppressants**, and **monoclonal antibodies**. Their primary goal is to **reduce relapse frequency and slow short-term disability progression (Table 1).** Since they target inflammation, DMTs are mostly effective in the **relapsing phase** of MS (**Casez, 2012 ; Depaz, 2013**).

Table 1 : Summary of DMTs in Multiple Sclerosis .

Class	**Drug**	**Mechanism of Action**	**Administration**	**Efficacy**	**Side Effects**	**Special Notes**
Immunomodulators	Interferon Beta	Reduces T-cell activation, BBB crossing; promotes Th2 shift	IFN-β1a: Rebif® (22/44 µg SC 3x/wk); Avonex® (30 µg IM 1x/wk) IFN-β1b: Betaferon® / Extavia® (250 µg SC qod)	↓ Relapse rate 30%, ↓ Lesion progression 50%	Flu-like symptoms, headache, fatigue, liver enzyme elevation, cytopenias, neutralizing Abs	Safe in pregnancy (possible lower birth weight); used in CIS, RRMS, SPMS w/ relapses (**Kesselring&Kesselring, 2020 ; Larousse, 2020**)

Immunomodulators	Glatiramer Acetate	Mimics MBP, induces Th2 response	Copaxone® 20 mg SC daily	↓ Relapse rate 29%, delays CIS→MS progression	Injection site reactions, rare systemic (palpitations, dyspnea)	No increased miscarriage/malformation risk (**Kesselring&Kesselring, 2020 ;Les échelles d'évaluation de la SEP, 2020**)
Immunomodulators	Dimethyl Fumarate	Activates Nrf2 pathway, anti-inflammatory	Oral: 2tablets/day	Effective in RRMS	Flushing, GI upset, lymphopenia	Monitor lymphocytes (**Tourbah, 2008**)
Immunomodulators	Teriflunomide	Inhibits pyrimidine synthesis, reduces activated T/B cells	Oral: 1tablet/day	Moderate efficacy in RRMS	Hepatotoxicity, teratogenicity, alopecia, neuropathy	Contraindicated in pregnancy (**Tourbah, 2008**)
Immunosuppressants	Azathioprine	Purine synthesis inhibitor, decreases lymphocyte proliferation	Oral	Limited efficacy	Leukopenia, hepatotoxicity, infection risk	Rarely used today (**Kurtzke, 2017**)
Immunosuppressants	Methotrexate	Folate antagonist, anti-inflammatory	Oral 7.5 mg/week (or intrathecal)	Stabilization in progressive MS	CNS toxicity (encephalopathy), hepatotoxicity	Monitor liver/CNS; off-label (**Cohen, 2011**)
Immunosuppressants	Cyclophosphamide	DNA alkylating agent, cytotoxic to	IV pulse: 600–700 mg/m^2 monthly	May delay disability	Nausea, alopecia, bladder toxicity	Limited evidence, used in aggressive MS (**Collège des**

		lymphocytes				**Enseignants de Neurologie, 2016**)
Immunosuppressants	Mitoxantrone	Anthracycline; suppresses T and B cells	IV infusion	Reduces relapse and disability progression	Cardiotoxicity (max 120 mg lifetime dose), infertility	Cardiac monitoring required; contraindicated in pregnancy (**Kesselring; Kesselring, 2020)**
Oral herapy	Fingolimod	S1P receptor modulator; prevents lymphocyte egress from lymph nodes	Oral	Effective in RRMS	Bradycardia, macular edema, elevated liver enzymes, infections	First-dose monitoring recommended (**Clanet, 2010**)

- **Monoclonal Antibodies**

➢ **Natalizumab**

Natalizumab (NTZ) is an immunosuppressive monoclonal antibody produced through mammalian cell DNA recombination technology. As the flagship drug in the class of selective adhesion molecule inhibitors, NTZ has demonstrated remarkable efficacy in treating RRMS since its approval in the United States (2004) and France (2007) (**Michel, 2016**). In Europe, TYSABRI® received restricted market authorization in 2006 for highly active RRMS, specifically as monotherapy for: (1) patients with inadequate response to ≥ 1 year of immunomodulator therapy, or (2) those experiencing ≥ 2 disabling relapses in the previous year accompanied by gadolinium-enhancing MRI lesions or significant T2 lesion load progression compared to baseline imaging (**Michel, 2016; Edan & Le Page, 2013**).

- **Mechanism of Action of NTZ**

NTZ is a recombinant monoclonal antibody targeting the α4 chain of adhesion molecules (CD49d), which forms part of two key integrins: VLA-4 (α4β1) and LPAM-1 (α4β7).

These integrins play distinct roles in lymphocyte trafficking-LPAM-1 mediates homing to gastrointestinal lymphoid tissue, while VLA-4 is critical for lymphocyte migration into the CNS. By binding to VLA-4 on activated lymphocytes, NTZ blocks their interaction with VCAM-1 (vascular cell adhesion molecule-1) on inflamed endothelial cells, preventing transmigration into the CNS. This mechanism underpins its efficacy in MS and Crohn's disease. **(Figure 9)**

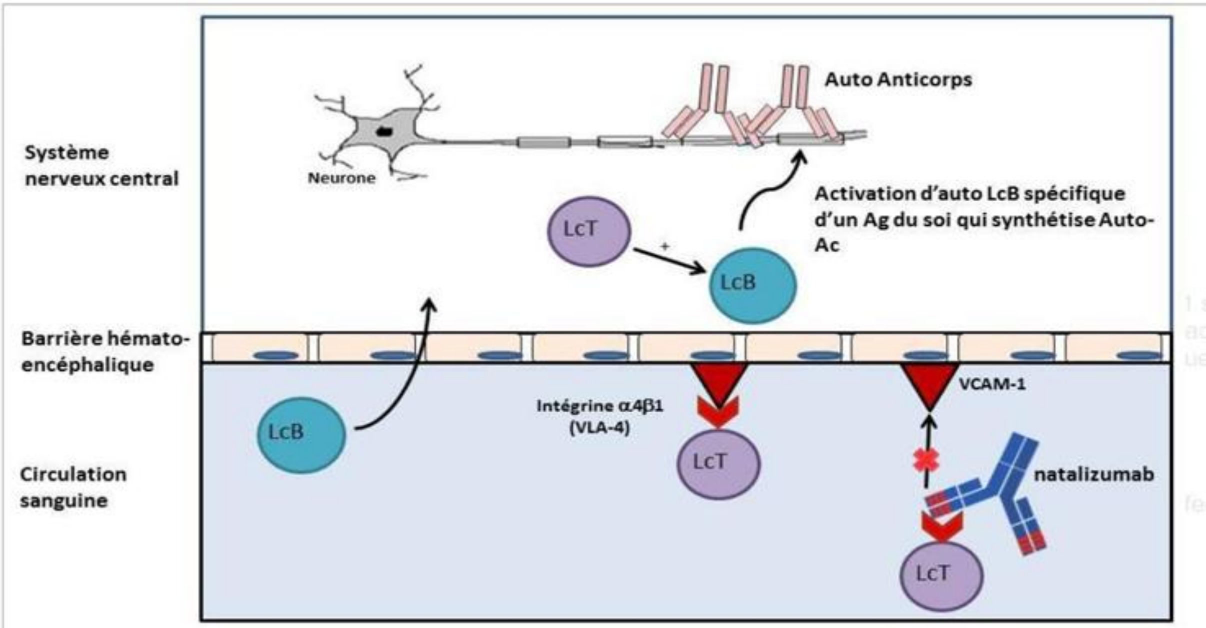


Figure 9: Mechanism of Action of NTZ (Edan &Le Page, 2013).

- **NTZ** adverse effects

The key safety concerns and reported adverse effects associated with Natalizumab are summarized in (**Table 2)**.

Table 2: NTZ adverse effects.

Category	Summary
Leukoencephalomyelopathy (LEMP) Risk Factors	Positive JC virus serology, treatment duration > 2 years, prior immunosuppressant use. (**Ouallet &Brochet , 2004**)
LEMP Mechanism	Uncontrolled JC virus proliferation in brain; also linked to JC virus-induced

	granulocyte cell neuropathy (NCG). (**Ouallet & Brochet, 2004)**
Immune Reconstitution Inflammatory Syndrome (IRIS).	Possible deterioration of brain function after LEMP treatment due to immune reconstitution. (**Ouallet &Brochet, 2004)**
Hepatic Issues	Severe liver disorders, elevated liver enzymes, hyperbilirubinemia reported (**Edan & Le Page, 2013**).
Cancer Risk	No significant difference between Tysabri and placebo over 2 years; long-term monitoring needed. (**Debouverie *et al.*, 2007**).
Hematological Effects	Increased lymphocytes, monocytes, eosinophils, basophils, erythroblasts; slight decreases in hemoglobin, hematocrit, and erythrocytes; normalized within 16 weeks post-treatment. (**Vidal, 2020**).

➢ **Rituximab and Ocrelizumab**

Rituximab is a chimeric anti-CD20 monoclonal antibody originally developed for hematologic malignancies, repurposed off-label for multiple sclerosis as a B-cell-depleting therapy. It binds to the CD20 antigen, inducing antibody-dependent cellular cytotoxicity (ADCC) and complement-mediated lysis of B-cells.

Ocrelizumab, a humanized anti-CD20 antibody engineered for reduced immunogenicity, is specifically approved for multiple sclerosis. It targets the same CD20 epitope but with optimized Fc receptor interactions to enhance B-cell depletion.

Both agents demonstrate potent suppression of inflammatory activity in MS through peripheral B-cell depletion, with effects persisting for several months post-infusion. Their mechanisms involve indirect modulation of T-cell responses via antigen-presenting cell depletion and cytokine network alterations (**Vidal, 2020**).

Both rituximab and ocrelizumab target B-cells via CD20 binding but differ in key aspects (**Table 3**).

Table 3: Comparison of Rituximab and Ocrelizumab (**Bouzid *et al.*, 2012;Gra y et al., 2020**).

Feature	**Rituximab**	**Ocrelizumab (Ocrevus®)**
Structure	Chimeric (mouse/human)	Humanized
AMM Status in MS	Off-label (3rd-line) (Bouzid K et al 2012)	Approved(1st-line RMS/PPMS) (**Gray *et al.*, 2020**)
Dosing	1,000 mg IV ×2, then q6–12mo	600 mg IV q6mo
Efficacy	~50–70% relapse reduction (Bouzid K et al 2012)	~50–70% relapse reduction (**Gray *et a.*, *l* 2020**)
Cost	Lower (~$1,500/dose)	Higher (~$6,500/dose) (**Gray *et al.*, 2020**)

1.2.8.3. Symptomatic Treatment

This treatment aims to improve quality of life and includes:

- **Pain**: Antiepileptics (gabapentin), acetaminophen (paracetamol).
- **Spasticity**: Baclofen, tizanidine, botulinum toxin.
- **Bladder dysfunction**: Anticholinergics (oxybutynin).
- **Fatigue**: multivitamin and vitamin D
- **Tremors**: Propranolol, clonazepam (**Kesselring & Kesselring, 2020**).
- **Sexual dysfunction** :be referred to specialists.

CHAPTER

2

Material and methods

2.1. Study objectives

The main objective of this study is to evaluate the therapeutic management of multiple sclerosis in patients consulting at the neurology department of Frantz Fanon University Hospital. Specially, the use of biological therapies (monoclonal antibodies) in the treatment protocol of MS.

Secondary Objectives

- ✓ To describe the sociodemographic and clinical characteristics of patients with multiple sclerosis. To identify the types and frequency of treatments used (disease-modifying therapies, symptomatic treatments, and relapse management).
- ✓ To evaluate drug tolerance, reported adverse effects, and treatment adherence among patients.
- ✓ To examine the impact of therapeutic management on clinical progression and patients' quality of life.

2.2. Study setting and design

This clinical study was conducted over three months (March to June 2024) in the neurology department of Frantz Fanon Hospital in Blida, Algeria, focusing on Multiple Sclerosis (MS) treatment outcomes through a comprehensive dual-phase approach that combined retrospective analysis of patient records (2019-2023) with prospective monitoring of over 50 active MS cases.

2.2.1. Hospital and department background

The Neurology Department at Frantz Fanon Hospital in Blida has long been a regional referral center for neurodegenerative and inflammatory disorders, including Multiple Sclerosis. Established in the late 20th century as part of Algeria’s expanding tertiary healthcare network, the hospital bears the name of the renowned psychiatrist and revolutionary Frantz Fanon, reflecting its commitment to both clinical excellence and patient-centered care. The neurology unit, equipped with specialized neuroimaging facilities (MRI, CT) and a dedicated neuroimmunology clinic, has played a pivotal role in advancing MS management in North

Africa, participating in multicenter trials and adapting international guidelines to local epidemiological profiles. Over the past decade, the department has pioneered early-diagnosis protocols and biologic therapies, serving a diverse patient population from Blida and neighboring provinces, while addressing challenges such as treatment accessibility and multidisciplinary follow-up.

2.3. Study population

The study included patients diagnosed with multiple sclerosis who were followed at the Neurology Department of Frantz Fanon University Hospital in Blida, Algeria. Patients were identified through hospital medical records and selected based on predefined eligibility criteria.

❖ **Inclusion criteria**

- Adults aged 18 years and older of both sexes.
- A confirmed diagnosis of multiple sclerosis (RRMS).
- Follow-up in the neurology department during the study period.
- treatment with Natalizumab, Rituximab, or Ocrelizumab for a minimum of 12 months

Availability of complete and accessible medical records, including clinical, biological, and MRI data.

❖ **Exclusion criteria**

- Missing diagnostic criteria for multiple sclerosis (RRMS).
- Diagnosis of other neurological or autoimmune disorders that could interfere with MS assessment.
- Patients lost to follow-up or referred to another healthcare facility before treatment evaluation.
- Patients Showed high and positive JC virus serology, which led to discontinuation or change of therapy.
- Patients scheduled to stop monoclonal antibody treatments due to safety concerns or intolerance.

A total of 55 patients met the inclusion criteria and were enrolled in the prospective study. However, 50 medical records was analyzed for the retrospective study.

2.4. Material

2.4.1. Biological material

- ❖ Peripheral blood samples for CBC, IgG levels, JC virus PCR, liver enzyme analysis.
- ❖ The CSF for oligoclonal band analysis via isoelectric focusing.
- ❖ Brain MRI with gadolinium contrast for demyelinating lesion assessment.

2.4.2. Non biological material

The complete list of materials used in this study is provided below. Additional technical details can be found in **Appendix 1**.

- ❖ Monoclonal antibodies: TYSABRI® (natalizumab), TRUXIMA® (rituximab) et OCREVUS® (ocrelizumab).
- ❖ Infusion pumps (PHIZHIX D-CP / FOURSS).
- ❖ Intravenous drug administration sets and infusion kits.
- ❖ Patient examination equipment: reflex hammer, visual acuity charts (Sloan 100%), chronometer.
- ❖ Timed 25-Foot Walk Test (T25FW): used to assess lower limb mobility and walking speed. Patients were instructed to walk a distance of 25 feet (7.6 meters) as quickly and safely as possible while the time was recorded using a manual chronometer.

2.5. Methods

2.5.1. Data collection

A data collection sheet (**Appendix 2**) was developed and completed prospectively during the day-care treatment of each patient hospitalized in the neurology department of the BLIDA University Hospital (CHU), and retrospectively from their medical records.

The questionnaire consists of two forms: an information sheet and a patient follow-up sheet (on Natalizumab / on Rituximab).

The information sheet is composed of four sections described below:

- The first section focuses on the patient's medical history, dedicated to recording medical, surgical, and familial antecedents not related to MS.
- The second section investigates the date and nature of the initial symptoms of the disease, the initial clinical assessment, the clinical and revealing symptoms, the disease course, and includes both clinical and neurological evaluations.
- The third section is intended to outline the treatment history, including disease-modifying therapies, symptomatic treatments, and any other therapies, with start and end dates, reasons for initiation and discontinuation, and the results of the initial MRI.
- The fourth section records initial biological results, particularly the complete blood count (CBC), inflammatory markers, CSF analysis, and isoelectric focusing results.

The two patient follow-up forms (for those on Natalizumab or Rituximab) each consist of three sections:

- The first section, "before today's infusion," is dedicated to reporting any adverse effects related to the treatment that occurred prior to the current infusion and were noted in the patients' medical records.
- The second section, "during today's infusion," focuses on the day's infusion session and the drug preparation procedures. Any adverse effects occurring during the infusion and their progression are described here.

- The final section is dedicated to evaluating the effectiveness of Natalizumab or Rituximab. Three parameters are considered: relapse rate, EDSS score progression, and MRI results. These parameters, assessed during the treatment phase (at 12 and 24 months), are compared to baseline measurements.

2.5.2. Multiple sclerosis treatment Protocol

The treatment protocol of multiple sclerosis with monoclonal antibodies is presented in **Table 4**:

2.5.2.1.Natalizumab

Patients received Natalizumab at a dose of 300 mg administered via intravenous infusion every 28 days (±3 days) The drug was diluted in 100 mL of 0.9% sodium chloride and infused over approximately one hour using an automated infusion pump. followed by mandatory post-infusion observation for one hour. Routine monitoring included CBC and liver enzyme panels. For patients seropositive for the JC virus, quarterly PCR monitoring was implemented. Brain MRI with gadolinium contrast was performed biannually. In cases of a JC virus index above 1.5 or persistent lymphopenia below 800/mm^3, the dosing interval was extended to every 6 weeks. Treatment was discontinued in cases of high PML risk or after two treatment failures based on clinical or radiological criteria.

2.5.2.2. Rituximab

Rituximab was administered in an induction-maintenance regimen. The induction phase consisted of two 1000 mg infusions on day 0 and day 15, each preceded by premedication with 100 mg methylprednisolone and 10 mg chlorphenamine. Maintenance dosing was adjusted based on CD19+ cell levels: patients received 500 mg every 6 months or 1000 mg every 12 months if CD19+ was below 5 cells/uL. Monitoring included CBC, immunoglobulin G (IgG), and CD19+ levels prior to each infusion. Serum sickness symptoms were assessed 48 hours after infusion, and an annual chest X-ray was performed for tuberculosis risk assessment.

2.5.2.3. Ocrelizumab

Patients received Ocrelizumab as two initial 300 mg intravenous infusions given two weeks apart, followed by a 600 mg infusion every six months. Each dose was preceded by premedication with corticosteroids and antihistamines to prevent infusion reactions. Infusions lasted between 2.5 and 3.5 hours, followed by at least one hour of post-infusion monitoring. Routine blood tests and CD19+ B-cell counts were performed before each cycle.

2.5.2.4. Corticosteroid Protocol (for Relapses)

Acute relapses were treated with intravenous methylprednisolone at a dosage of 1 g per day for 3 to 5 days. An oral prednisone taper (1 mg/kg/day for 5 days) was added in cases of incomplete recovery. Blood analysis, including CBC, was conducted before initiating corticosteroids and again 7 days after treatment.

2.5.2.5. Patients Treated Only with Corticosteroids

In clinical practice, a subset of patients diagnosed with multiple sclerosis receive no DMT and are managed exclusively with corticosteroids during acute relapses. This approach is often observed in individuals with a mild or inactive form of the disease, sometimes referred to as "benign MS," where relapses are infrequent and the level of long-term disability remains minimal. In such cases, the potential risks and side effects associated with long-term immunosuppressive therapy may outweigh the expected benefits. Additionally, some patients present with contraindications to DMTs, such as chronic infections, autoimmune comorbidities, hepatic dysfunction, or high anti-JC virus antibody levels, making immunomodulatory treatment either risky or unsuitable. In certain settings, especially in low-resource environments, limited access to DMTs due to cost, unavailability, or administrative delays can also lead to reliance on corticosteroids as the primary treatment option. Other patients may decline long-term treatment due to fear of side effects, lack of awareness, or personal choice. Moreover, some individuals discontinue DMTs after experiencing adverse reactions or finding the treatment burdensome. In all these situations, high-dose corticosteroid therapy typically intravenous methylprednisolone is administered during relapses to reduce inflammation and accelerate recovery, although it does not impact the underlying disease progression. This management strategy reflects the need for individualized care plans in MS, tailored to clinical presentation, patient preferences, risk factors, and resource availability.

Table 4: Clinical Use of Monoclonal Antibodies by Patient status **(ECTRIMS/EAN, 2022)**.

Patient status	Natalizumab (TYSABRI®)	Ocrelizumab (OCREVUS®)	Rituximab (TRUXIMA®)
Pregnant women	May be continued with extended dosing until 30-34 weeks; final dose before delivery	Use with caution; limited data; consider only if strictly necessary	Limited data; use only in highly active disease; weigh risk/benefit
Breastfeeding women	Excreted in small amounts; not contraindicated in Europe; infant monitoring recommended	Excreted in low levels; can be used with caution; avoid live vaccines in infants	Limited data; generally not contraindicated, but close pediatric monitoring advised
Children (<18 years)	Not approved; off-label in exceptional pediatric cases only	Not approved; studies ongoing; off-label use discouraged	Not approved; occasionally used off-label in severe pediatric MS
Adult men	Standard use	Standard use	Standard use
Women of childbearing age	Effective; contraception recommended during use; monitor if planning pregnancy	Effective; avoid pregnancy for at least 6 months after last dose	Same as Ocrelizumab; longer washout may be advised depending on dose
Patients with autoimmune comorbidity	Use with caution; may exacerbate underlying autoimmune diseases	Generally tolerated; monitor for worsening autoimmunity	Higher risk of immune suppression; monitor carefully
Patients without autoimmune disease	Standard indication	Standard indication	Standard indication
Elderly patients (>65)	Limited data; generally avoided due to PML risk	Limited safety data; not first choice unless highly active disease	Use with caution; increased infection risk in immunosenescence

2.5.2.6. Evaluation Criteria

To assess the effectiveness of each treatment, several clinical markers were evaluated both before treatment and after 12 to 24 months of follow-up:

- Annual Relapse Rate (ARR): the number of relapses per year, used to measure inflammatory activity

❖ **Calculation of the ARR**

ARR = (1 - Post-tx relapses/year / Pre-tx relapses/year) x 100%

A positive ARR indicates a therapeutic benefit in slowing disease progression. An **ARR ≤ 0 %** suggests a lack of efficacy or possible incresed disease progression under treatment.

❖ **Comparison of ARR Before and After Treatment**

We compare the number of relapses a patient had before starting treatment to the number they experienced after beginning therapy, over 12 and 24 months. This helps us understand how well the treatment is working. If the relapse rate drops after treatment, it means the therapy is likely helping to control the disease. But if the relapse rate stays the same or goes up, it may mean the treatment isn't effective enough, and another option should be considered.

- EDSS score (Expanded Disability Status Scale): used to track progression of neurological disability
- MRI results: especially changes in lesion load and enhancement, to visualize disease activity in the CNS

These parameters provided a solid basis for comparing outcomes and evaluating therapeutic impact.

2.6. Ethical Considerations

The study followed ethical standards in line with institutional regulations. All patients or their legal guardians gave informed consent for the use of their medical data. Personal information was anonymized and handled confidentially. No procedures outside standard clinical care were performed.

2.7. Data Analysis

Data were entered and analyzed using Microsoft Excel and SPSS version (**Debouverie *et al* .,2007**). Descriptive statistics were used to summarize the data: Quantitative variables were presented as means ± standard deviation (SD). Categorical variables were expressed as frequencies and percentages. Statistical analysis was performed using Chi-square test for categorical variables. A *p*-value of less than 0.05 was considered statistically significant.

CHAPTER 3

Results and discussion

3.1. Results and discussion

3.1.1. General characteristics of the studied population

The following section presents a detailed analysis of the demographic, medical, and psychosocial characteristics of the 55 patients diagnosed with multiple sclerosis (MS) who were included in this study.

3.1.1.1. Sociodemographic Characteristics

❖ **Population distribution by age and age groups**

The patients' ages ranged from 19 to 57 years, with a mean age of 35.34 ± 10.03 years. The highest representation was among individuals aged 31-40 years (30.9%), followed closely by those aged 41-50 years (29.1%) and 21–30 years (27.3%) (**Figure 10**). These results align with the known epidemiology of MS, which typically manifests in young adults, often in the third or fourth decade of life.

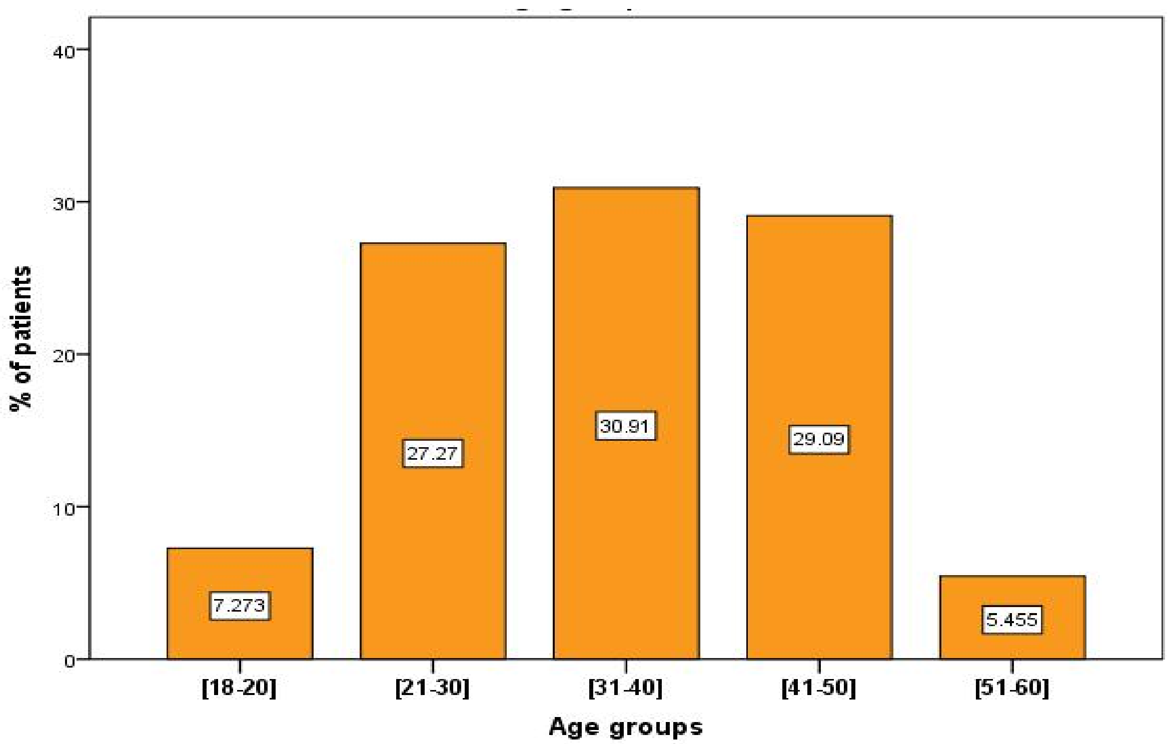


Figure 10 : Age Distribution of the Study Population.

❖ **Population distribution by Sex**

The study population was predominantly female (81.8%), with only 18.2% male patients (**Figure11**). This is consistent with the well-established female predominance in MS, where women are affected approximately 2 to 3 times more frequently than men, possibly due to hormonal and genetic factors.

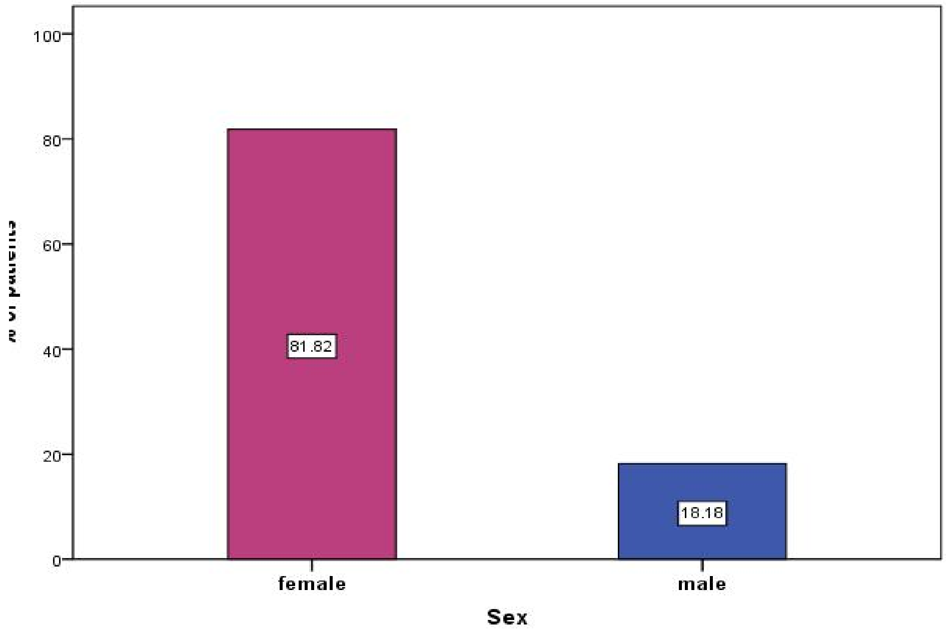


Figure 11 : Sex Distribution among MS Patients.

- **Population distribution by Occupation**

A significant proportion of the patients (61.8%) were unemployed, and an additional 9.1% reported having lost their job due to MS. Only 29.1% of the participants were actively working or studying (**Figure 12**). This underscores the socioeconomic burden and functional limitations imposed by the disease, particularly among individuals of working age.

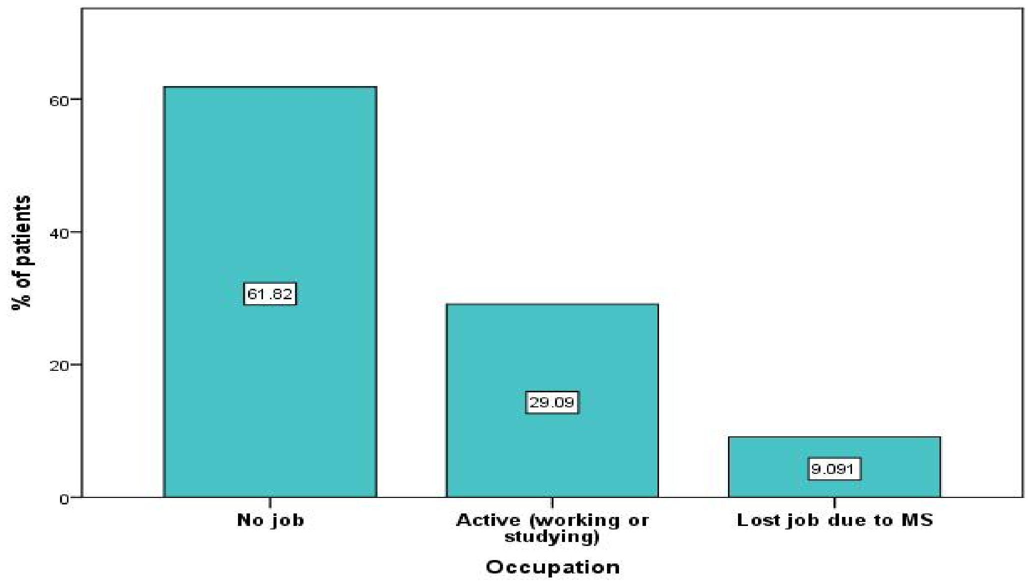


Figure 12: Occupational Status of Participants.

3.1.1.2. Clinical and Comorbidity Profile

❖ **Population distribution by Autoimmune Diseases**

The vast majority of patients (92.7%) did not report any coexisting autoimmune disease, whereas only 7.3% did (**Figure 13**). Although MS is itself an autoimmune condition, the association with other autoimmune diseases such as thyroiditis, type 1 diabetes, or lupus can occur and may influence prognosis and management.

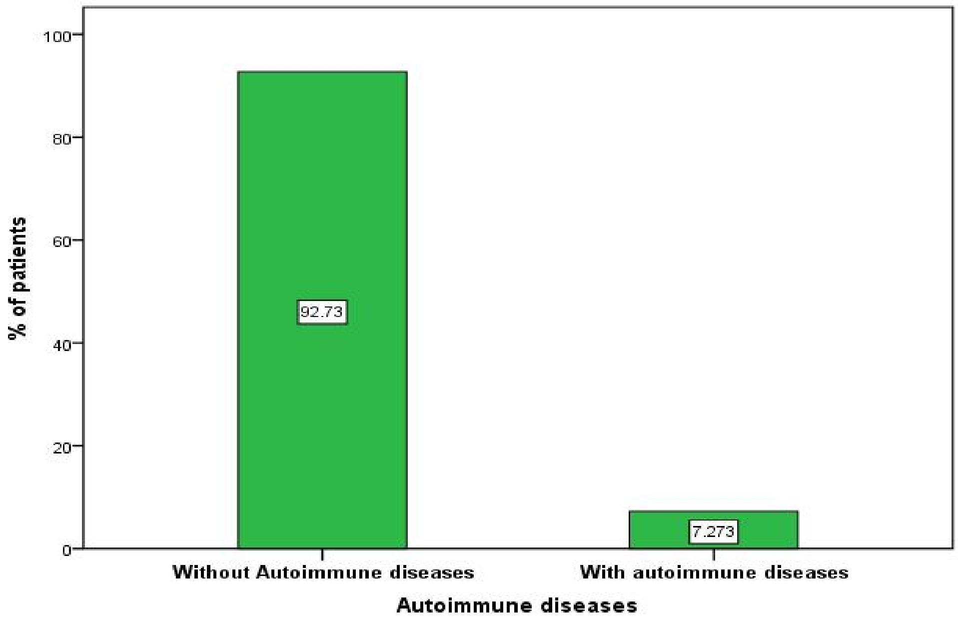


Figure 13: Prevalence of Autoimmune Diseases in the study population.

❖ **Population distribution by Diabetes**

Only 4 out of 55 patients (7.3%) reported having diabetes, indicating a relatively low co-occurrence in this cohort (**Figure14**). While type 1 diabetes shares autoimmune pathophysiology with MS, no strong correlation was observed here.

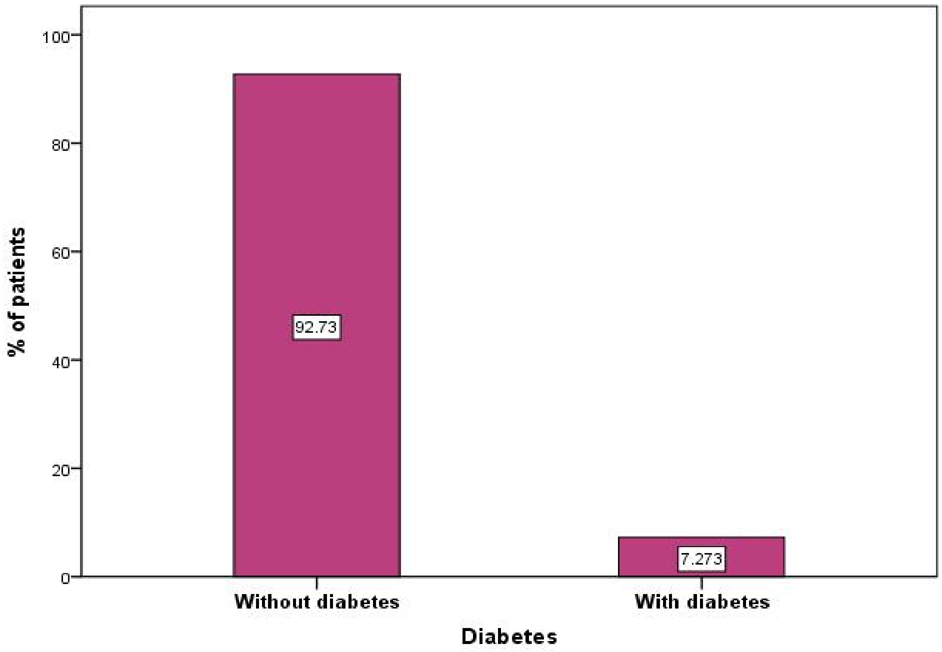


Figure 14 : Diabetes Occurrence among MS Patients.

❖ **Population distribution by Cardiovascular Diseases**

Just 5.5% of the participants had cardiovascular comorbidities (**Figure 15**), suggesting a generally low cardiovascular risk profile in this sample. However, cardiovascular health remains an important consideration in MS due to its potential interaction with mobility and fatigue.

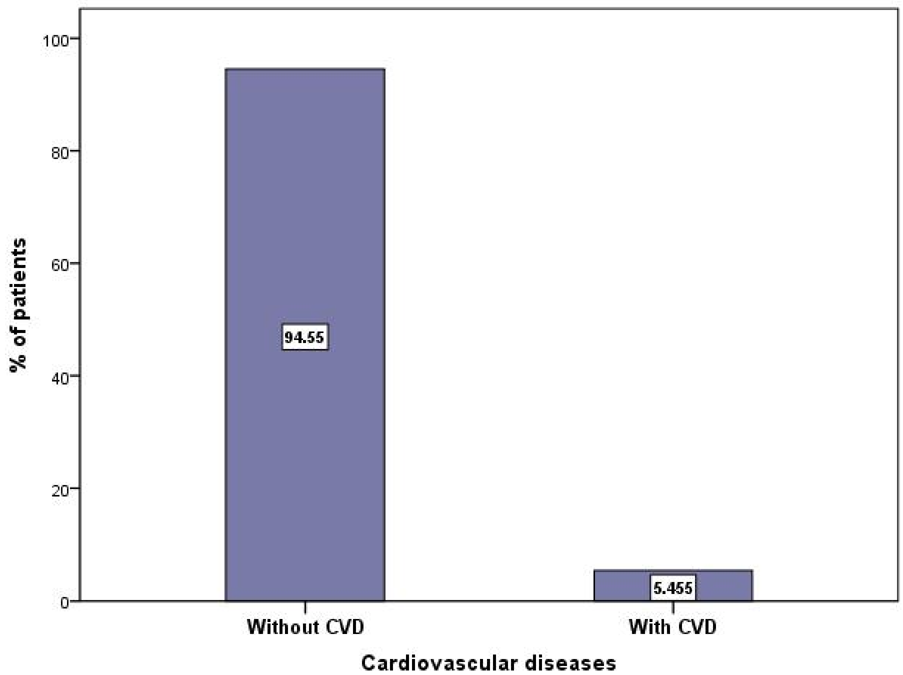


Figure 15: Cardiovascular Comorbidities in the Study Population.

❖ **Population distribution by Respiratory Diseases**

Respiratory conditions were reported by 7.3% of the patients (**Figure 16**). These conditions may exacerbate MS symptoms and increase the risk of complications such as infections or fatigue, although they were relatively rare in this cohort.

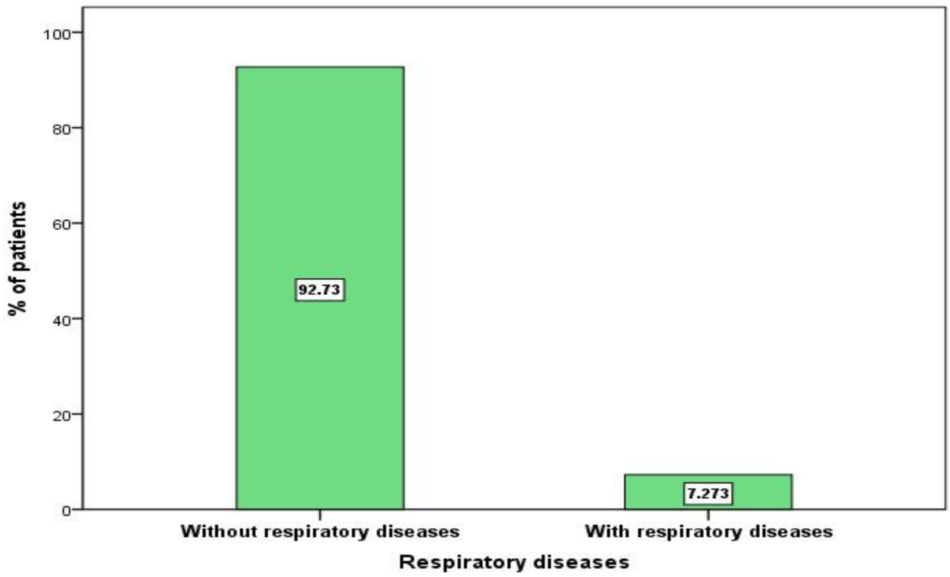


Figure 16: Presence of Respiratory Conditions among Participants.

❖ **Population distribution by Other Neurological Diseases**

Only 3 out of 55 patients (5.5%) had a history of additional neurological disorders (**Figure 17**). This low rate supports the relative diagnostic clarity of MS in this group, with minimal overlapping neurological pathologies.

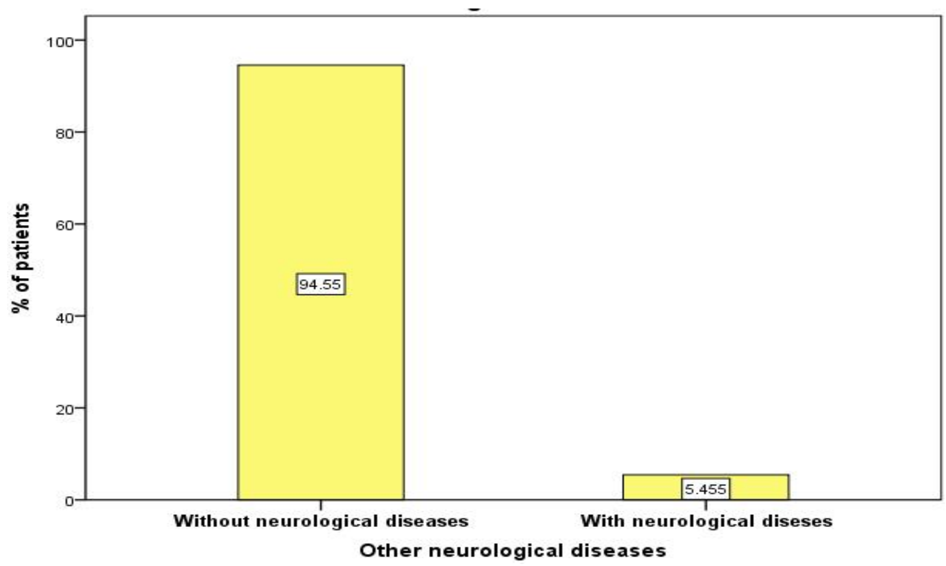


Figure 17: Co-occurrence of Other Neurological Diseases.

3.1.1.3. Reproductive and Hormonal Factors

❖ **Population distribution by Pregnancy Status (in Female Patients)**

Among the 45 female participants, 13 (28.9%) were pregnant at the time of data collection (**Figure 18**). MS is known not to impair fertility, and pregnancy can have a transiently protective effect on disease activity. However, the postpartum period is associated with an increased relapse risk, requiring close follow-up.

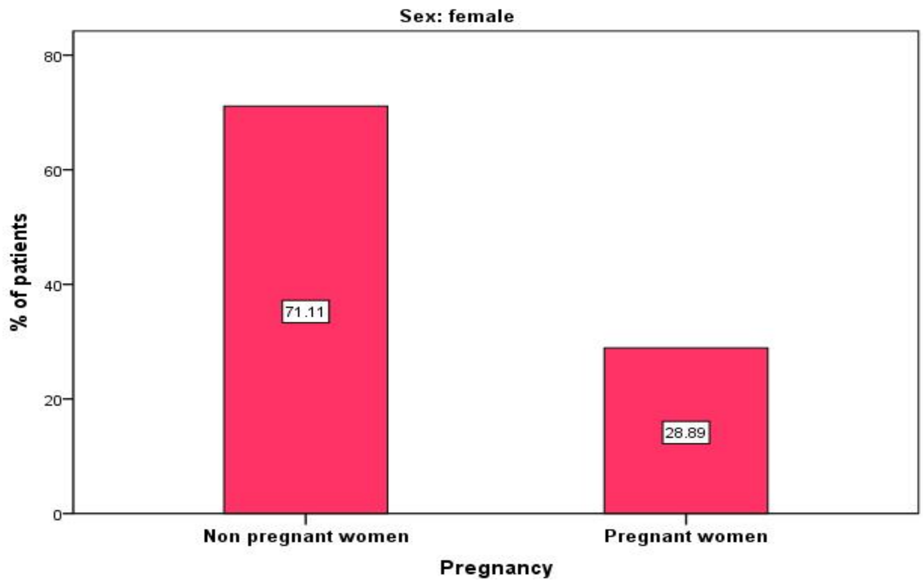


Figure 18 : Pregnancy Status among Female MS Patients.

3.1.1.4. Lifestyle and environmental factors

- **Population distribution by Smoking**

A large majority of the cohort (85.5%) were non-smokers, while 14.5% reported being current smokers (**Figure19**). Smoking is a known modifiable risk factor for MS progression and poorer outcomes, making this finding relevant for patient education and clinical management.

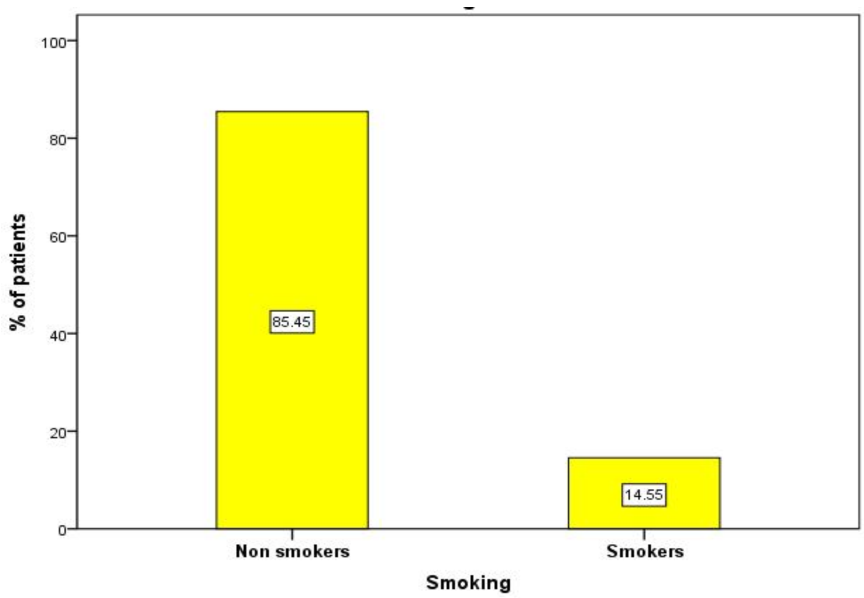


Figure 19 : Smoking Habits of the Study Population.

- **Population distribution by Consanguineous Marriage**

30.9% of participants were born from consanguineous unions, which may be relevant in genetic susceptibility studies, particularly in populations with high consanguinity rates (**Figure 20**). This parameter could be investigated further for potential links to autoimmune and demyelinating conditions.

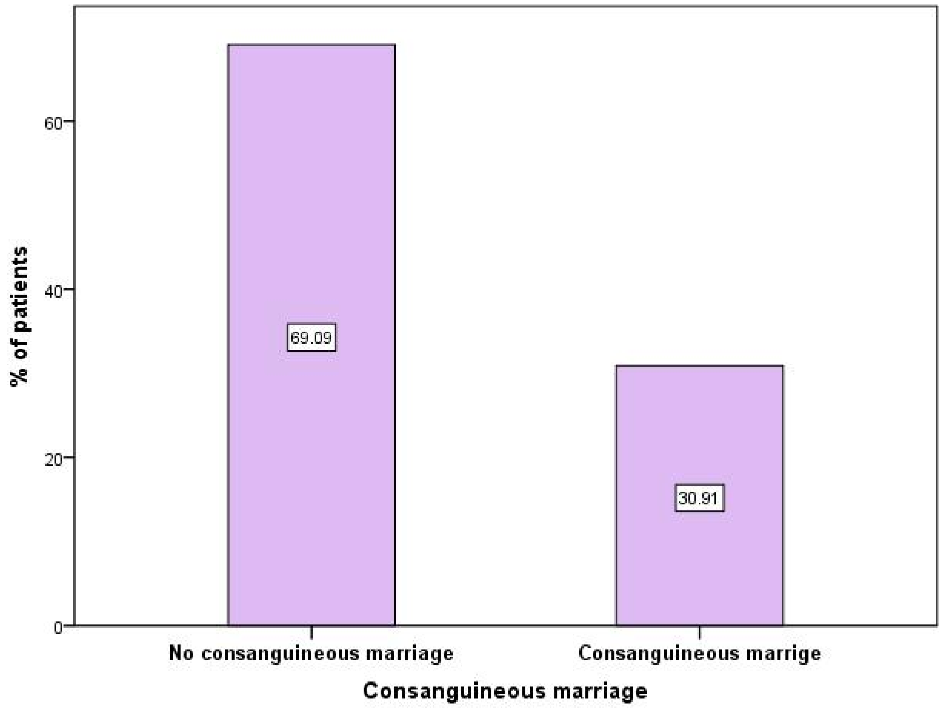


Figure 20: Prevalence of Consanguineous Marriages

3.1.1.5. Genetic and Familial Predisposition

- **Population distribution by Family History of Neurological Diseases**

29.1% of the patients reported a positive family history of neurological disease, suggesting a possible genetic predisposition to MS or related disorders (**Figure 21**). While MS is not inherited in a Mendelian fashion, familial clustering has been documented in numerous studies.

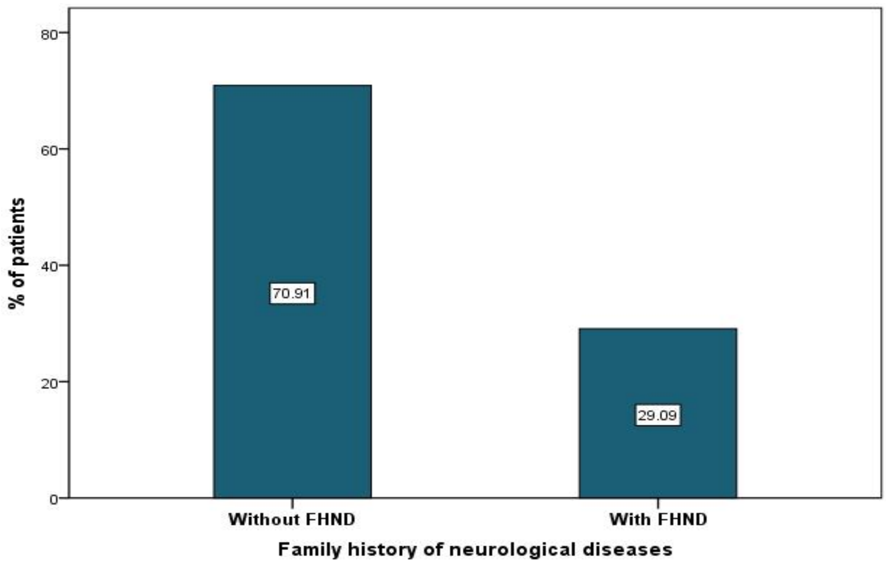


Figure 21 : Family History of Neurological Diseases.

❖ **Population distribution by Blood Group**

The most frequent blood group among patients was Group A (60%), followed by Group O (29.1%), and Groups B and AB (5.5% each) (**Figure22**). Although the relationship between blood group and MS is not fully established, some recent studies have explored potential immunological links worth further investigation.

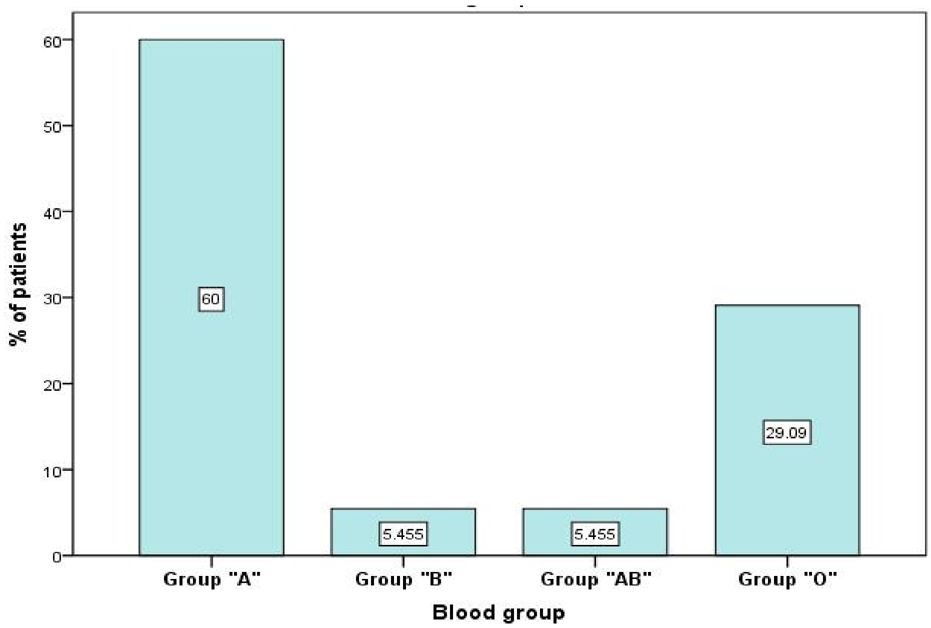


Figure 22 : Distribution of Blood Groups among Patients

3.1.1.6. Psychological and mental health status

❖ **Population distribution by Psychological Status**

In terms of psychological health, 61.8% of patients were classified as psychologically normal, while 32.7% reported anxiety, and 5.5% reported depression (**Figure 23**). These results highlight the psychosocial impact of MS, and underline the need for integrated mental health support in clinical management.

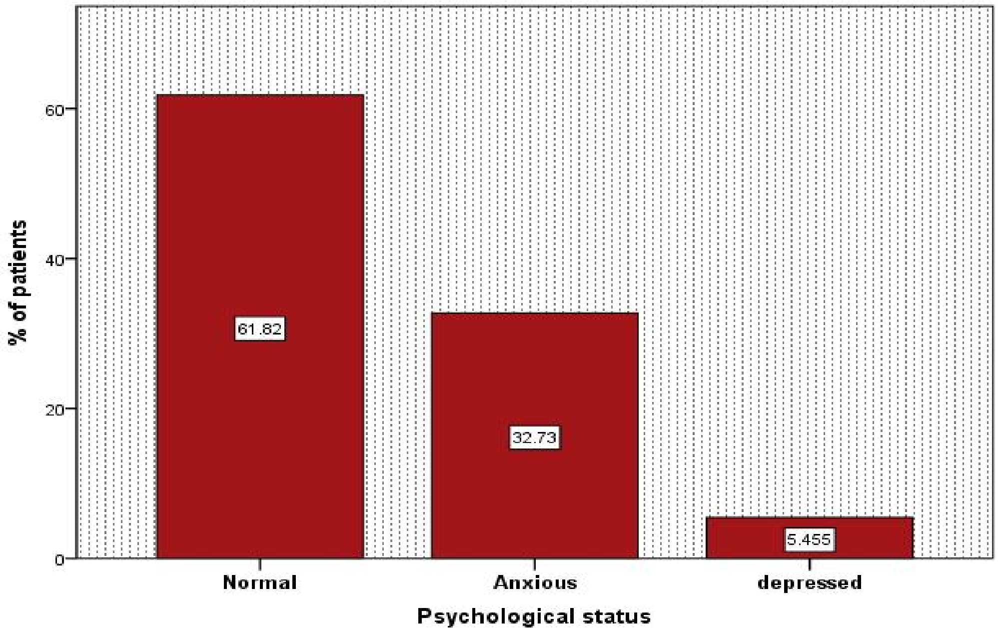


Figure 23 : Psychological Status of MS Patients.

3.1.2. Clinical History and Disease Course

3.1.2.1. Age of Symptoms Onset

The onset of symptoms occurred at a mean age of 27.29 ± 9.24 years, with a minimum of 12 and a maximum of 44 years. These results confirm that MS typically begins in early adulthood, aligning with its classification as a disease of young adults.

3.1.2.2. Age of Diagnosis

The mean age at diagnosis was 30.60 ± 9.28 years, with values ranging from 14 to 47 years. This approximately three year delay between symptom onset and diagnosis is consistent with the literature and reflects common challenges in the timely identification of MS, particularly when initial symptoms are non-specific or intermittent.

3.1.2.3. Number of Relapses Before Diagnosis

Patients reported a mean of 2.8 ± 1.42 relapses prior to diagnosis (range: 0 to 6). This suggests that, in most cases, diagnosis was made after several distinct clinical episodes, reinforcing the chronic and relapsing nature of the disease.

3.1.2.4. Interval Between the First and the Second Relapse

The analysis of the interval between the first and second relapse revealed considerable variability among patients. The most frequent interval was within the first six months, reported by 32.7% of the participants. An additional 18.2% experienced their second relapse between 6 months and 1 year after the first. Notably, 30.9% of patients reported an interval of 1 to 3 years, suggesting a relatively slower disease reactivation in a significant portion of the cohort. A smaller subset experienced longer remission periods: 10.9% relapsed between 3 and 5 years, and 7.3% after 5 to 7 years (**Figure 24**). These findings highlight the heterogeneity of relapse dynamics in MS. While one-third of patients had early relapses, indicating a more active disease course, others experienced longer quiescent phases, which may reflect differences in disease phenotype, early treatment response, or immune modulation.

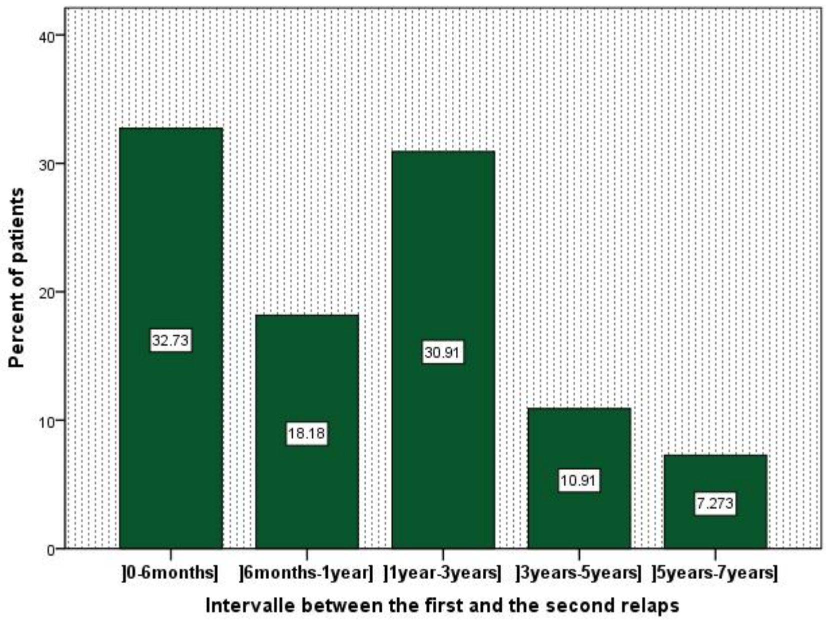


Figure 24 : Interval Between the First and Second Relapse in MS patients.

3.1.2.5. Clinical Form of MS

In terms of clinical classification, relapsing-remitting MS (RRMS) was the predominant form, affecting 80% of patients. Secondary progressive MS (SPMS) accounted for 18.2%, while primary progressive MS (PRMS) was rare (1.8%) (**Figure 25**). This distribution mirrors global patterns, where RRMS typically represents the initial form, with some patients later transitioning to SPMS.

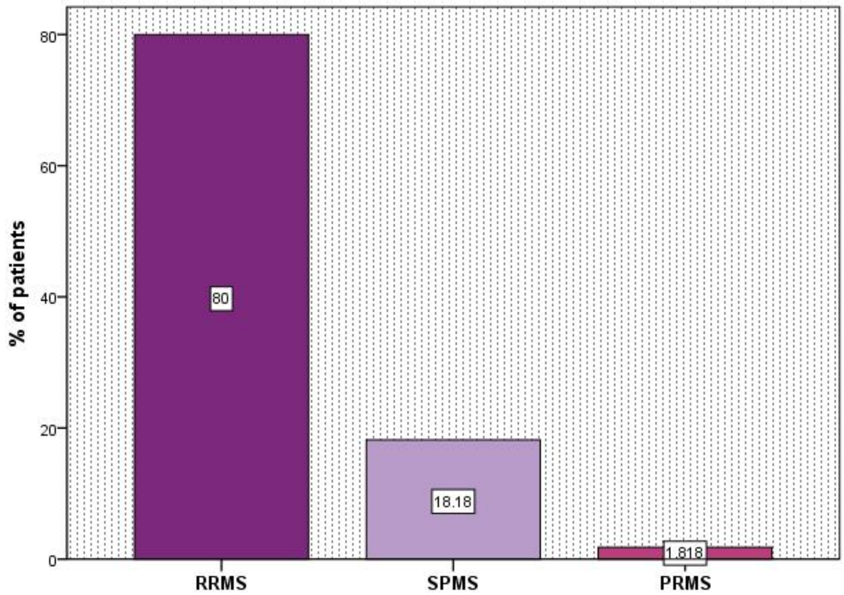


Figure 25: Distribution of Clinical Forms of Multiple Sclerosis.

3.1.3. Neurological and Functional symptomes of MS

3.1.3.1. Motor Disorders

Motor disorders were highly prevalent, observed in 92.7% of patients (**Figure26**). This finding underscores the importance of motor pathway involvement in MS and its role in functional impairment.

3.1.3.2. Sensory Disturbances

Similarly, sensory symptoms were reported in 92.7% of patients (**Figure 26**). These often include paresthesia, numbness, and altered sensory thresholds, which are hallmark features of MS and often among the first symptoms reported.

In our cohort, **92.7%** of patients reported sensory disturbances, such as paresthesias, numbness, and altered sensory thresholds. This high prevalence aligns closely with existing literature indicating that sensory symptoms are typically among the earliest and most common clinical manifestations of MS. In a major literature review, sensory disturbances were identified as hallmark early features, frequently appearing before motor or cognitive deficits (**Taheri *et al.*, 2012**). Similarly, a comprehensive review by (**Thompson *et al.*, 2018**) noted that **40–43%** of MS patients present initially with sensory symptoms resulting from demyelinating lesions in regions like the brainstem and spinal cord. The frequency in our study is even higher, possibly reflecting heightened patient awareness or early-stage detection in a clinical setting. These findings underscore the importance of recognizing sensory signs as critical indicators for early MS diagnosis and management.

3.1.3.3. Cerebellar Disorders

Cerebellar dysfunction was present in only 3.6% of the cohort (**Figure 26**), suggesting either a relatively low frequency of cerebellar lesions in this population or subclinical presentation not captured by initial assessments.

3.1.3.4. Cranial Nerve Disorders

Cranial nerve involvement was identified in 9.1% of patients, reflecting potential demyelinating lesions in the brainstem (**Figure 26**). This can manifest clinically as diplopia, facial numbness, or dysphagia, and supports the dissemination of lesions in space.

3.1.3.5. Retrobulbar Optic Neuritis (RBON)

Retrobulbar optic neuritis, a common early manifestation of MS, was observed in 45.5% of cases (**Figure 26**). This high prevalence confirms the importance of visual symptoms as a clue to early diagnosis.

3.1.3.6. Sphincter Disturbances

Sphincter dysfunction was reported in 7.3% of the sample (**Figure 26**). While relatively infrequent here, such symptoms often indicate spinal cord involvement and become more prominent in progressive stages of the disease.

3.1.3.7. Sexual Disorders

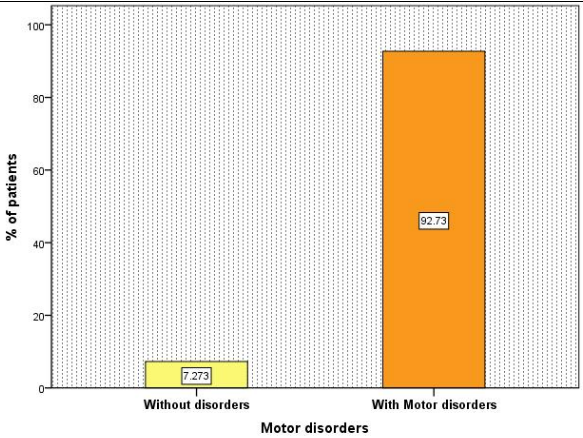
Sexual dysfunction was reported by 7.3% of patients. Though underreported, it can significantly affect quality of life and is often associated with both neurological and psychological factors in MS(**Figure 26**).

3.1.3.8. Vertigo

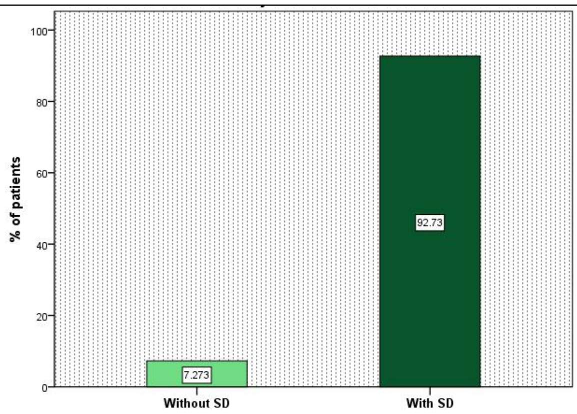
Vertigo was present in 81.8% of patients (**Figure 26**), illustrating a frequent involvement of vestibular pathways, which may result from lesions in the brainstem or cerebellum.

3.1.3.9. Fatigue

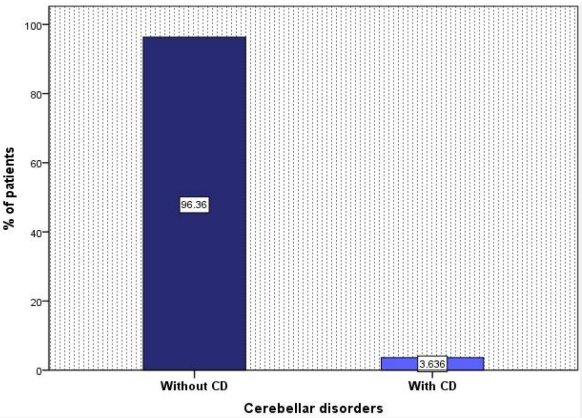
Fatigue was the most commonly reported symptom, affecting 96.4% of patients (**Figure 26**). This aligns with existing data identifying fatigue as one of the most disabling and persistent symptoms in MS, often independent of physical disability.



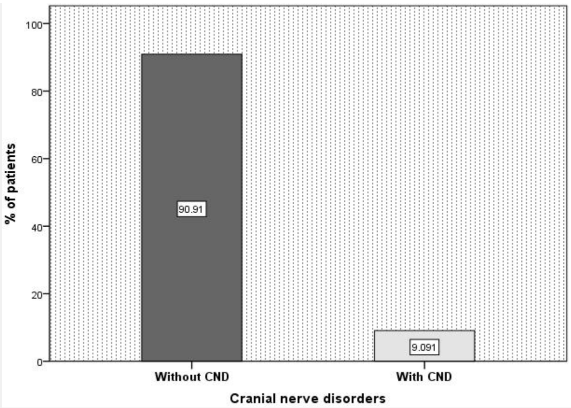
Prevalence of Motor Disorders in MS Patients.



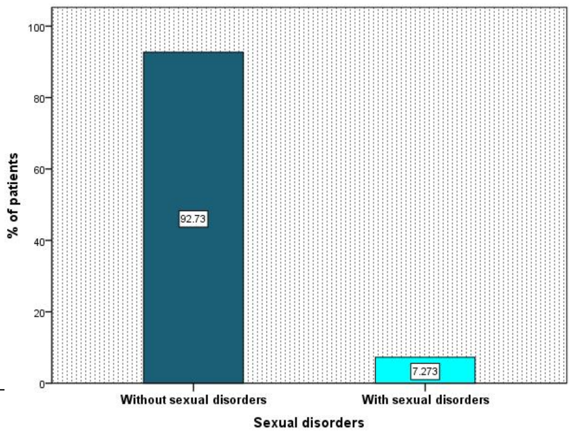
Frequency of Sensory Disturbances in the Study Population

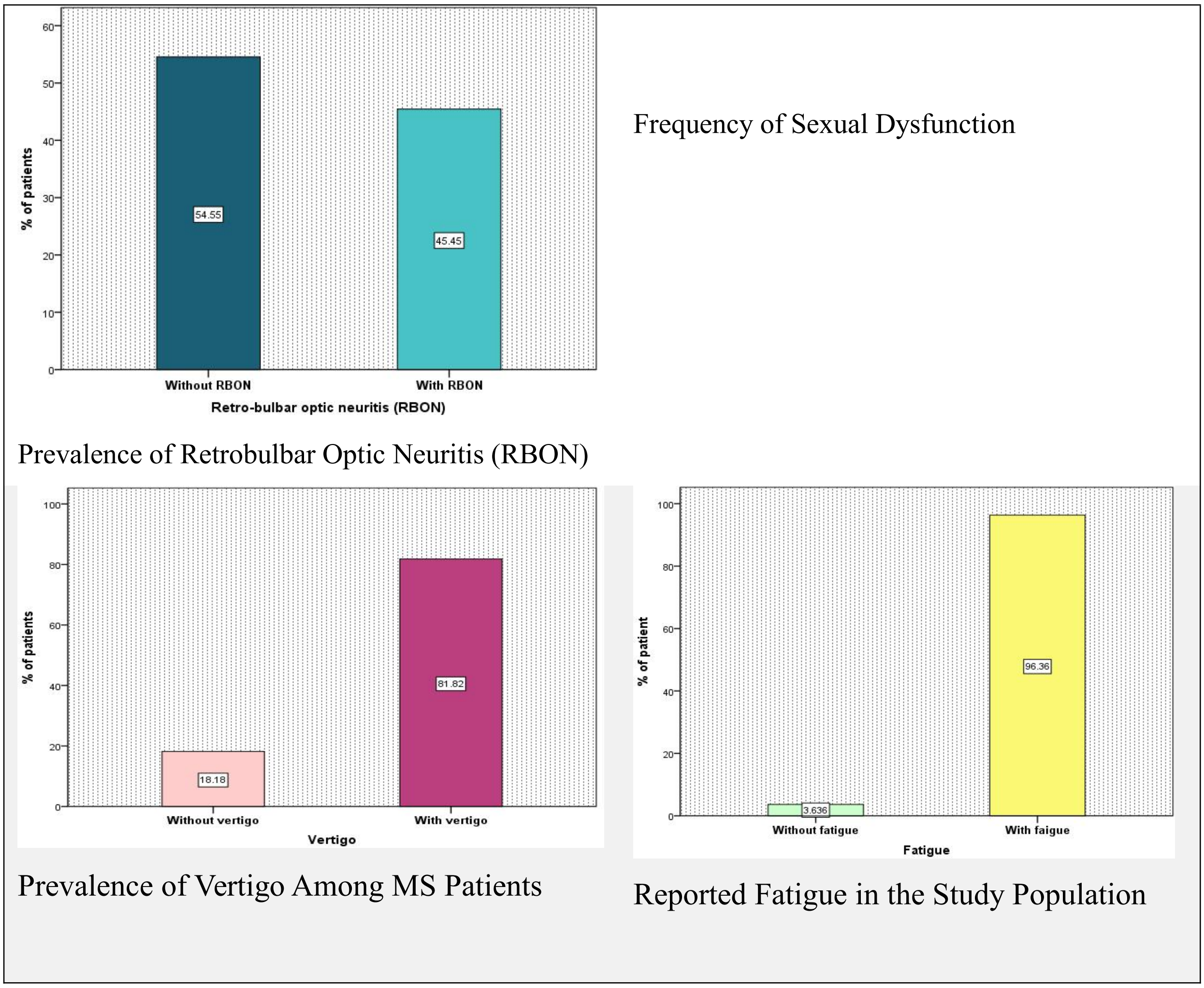


Occurrence of Cerebellar Disorders



Cranial Nerve Involvement Among MS Patients





Frequency of Sexual Dysfunction

Prevalence of Retrobulbar Optic Neuritis (RBON)

Prevalence of Vertigo Among MS Patients

Reported Fatigue in the Study Population

Figure 26 : Neurological and Functional symptomes in MS patients.

3.1.4. Disability Assessment

3.1.4.1. Initial Clinical Exam

Regarding initial motor function, 74.5% of patients had limited walking capacity and required assistance, while 23.6% could walk with some limitations, and only 1.8% could walk without restriction (**Figure 27**). These findings reflect a significant functional impact at or near the time of diagnosis, potentially related to diagnostic delays or multiple early relapses.

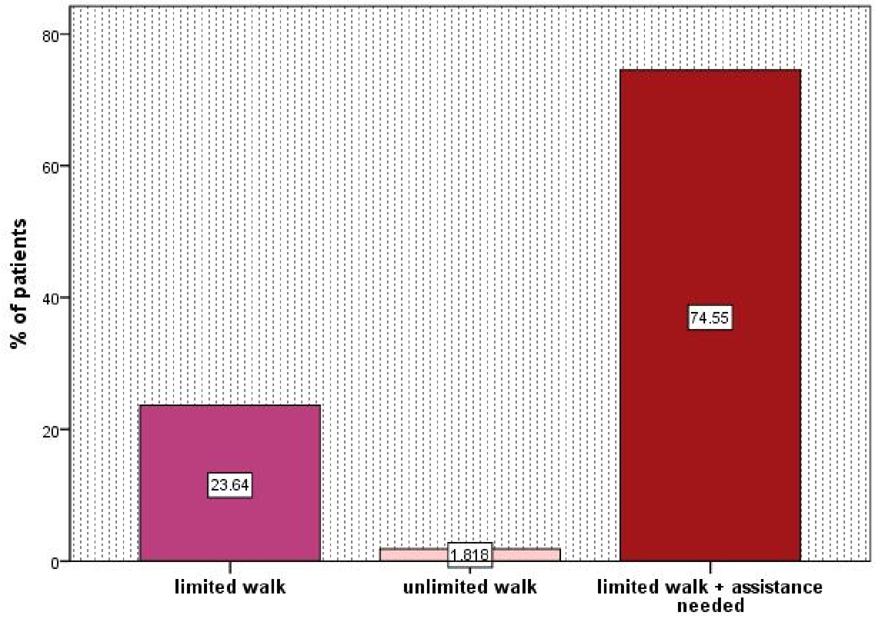


Figure 27 : Initial Walking Ability at Clinical Examination.

3.1.5. Biological and Laboratory Markers

3.1.5.1. C-Reactive Protein

Among the patients, 83.6% had normal CRP values, while 9.1% had elevated CRP, and 7.3% showed no detectable CRP (**Figure 29**). As MS is primarily a CNS disease, CRP being a marker of systemic inflammation is typically normal unless a concurrent infection or systemic inflammatory condition is present.

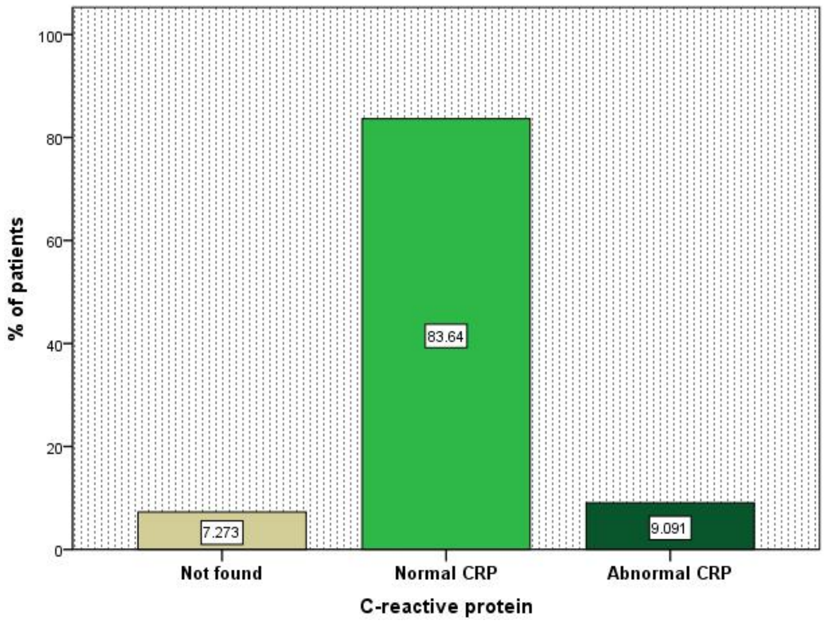


Figure 29 : C-Reactive Protein (CRP) Status in MS Patients.

3.1.5.2. Isoelectric Focusing Results

The isoelectric focusing of cerebrospinal fluid and serum revealed several distinct patterns. The most common result (52.7%) showed identical oligoclonal bands (OCBs) in CSF and serum, indicating a systemic rather than intrathecal origin (Type 4). A monoclonal band in CSF only was observed in 20% of cases, while the typical MS-specific pattern of CSF-restricted OCBs (Type 2) was present in 14.5%. Another 5.5% of patients exhibited CSF bands with partial matches in serum (Type 3), indicating both systemic and central synthesis. 7.3% of patients showed no OCBs (Type 1), which is less common in MS but possible, especially early in disease or in atypical forms (**Figure 30**). These findings highlight the immunological heterogeneity of MS, and the importance of combining clinical, radiological, and biological data for accurate diagnosis.

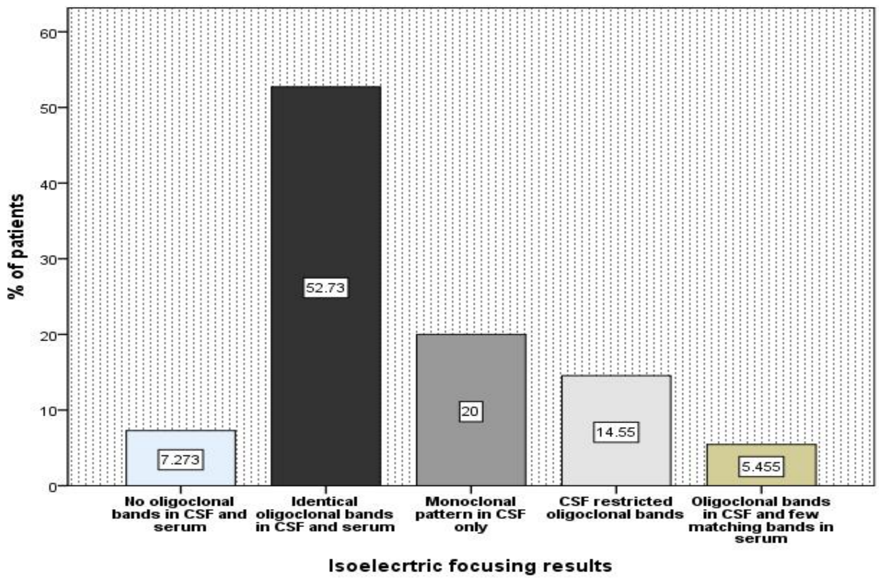


Figure 30 : Patterns of Oligoclonal Bands from Isoelectric Focusing.

3.1.6. Therapeutic Management of muliple sclerosis

3.1.6.1. Treatment of MS with Disease-Modifying Therapies (DMTs)

Among the 55 patients, the majority (81.8%) were treated with monoclonal antibodies, reflecting the growing use of high efficacy therapies in MS management. A smaller proportion (14.5%) received a combination of immunomodulators and monoclonal antibodies, while 1.8% were treated with immunosuppressants only. Notably, one patient (1.8%) received no DMT treatment at all (**Figure 31**). These data suggest a clear therapeutic shift toward monoclonal antibody-based regimens as first-line or escalation therapy in this population.

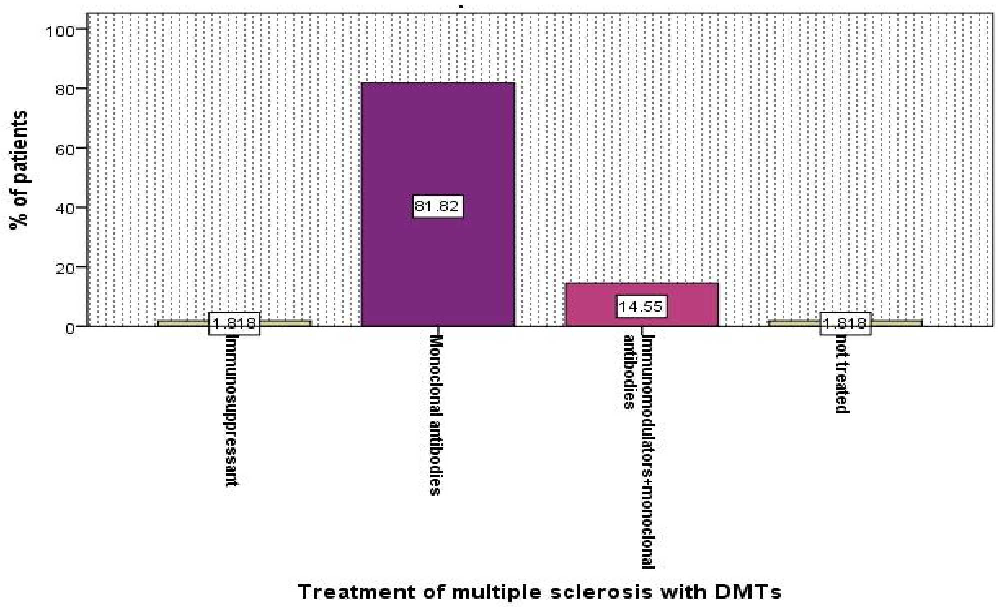


Figure 31 : Distribution of Patients According to the Type of DMTs Used.

- **Treatment with Monoclonal Antibodies**

Among monoclonal antibodies, Tysabri® (natalizumab) was the most commonly prescribed, used in 54.5% of patients, followed by Truxima® (rituximab) in 29.1%, and Ocrevus® (ocrelizumab) in 14.5%. Only one patient (1.8%) had not received monoclonal antibody treatment (**Figure34**). This distribution reflects the high reliance on second-generation monoclonal therapies, in line with their demonstrated efficacy in reducing relapse rates and slowing progression.

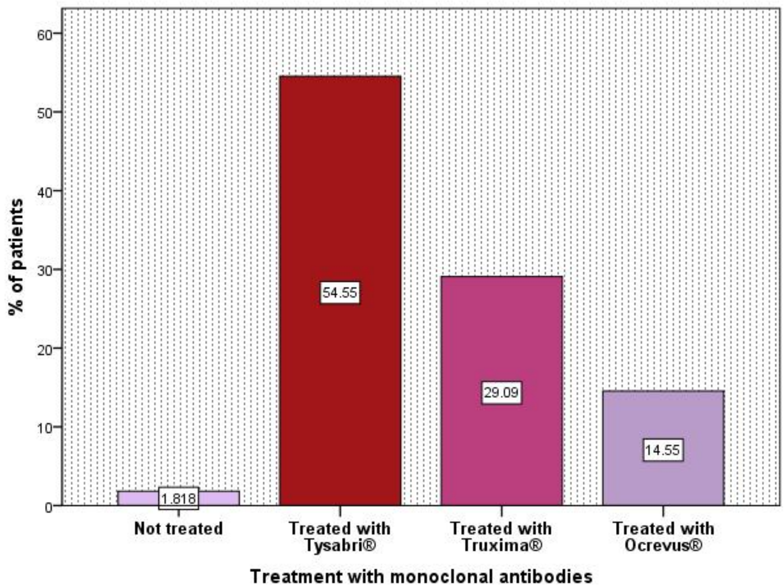


Figure 34: Prescription of Monoclonal Antibodies Among MS Patients.

The distribution of monoclonal antibody usage in our cohort aligns with these recommendations, confirming a therapeutic shift toward B cell depleting and targeted biologics in clinical practice.

3.1.6.2. Treatment of Relapses

All patients (100%) received chronic corticosteroid treatment for managing relapses, consistent with standard practice, where corticosteroids are used to shorten the duration and severity of acute MS attacks.

In our study, all patients (100%) received corticosteroid treatment for managing relapses, which aligns with current clinical guidelines for multiple sclerosis. Corticosteroids, particularly high-dose intravenous methylprednisolone, remain the standard approach for reducing the severity and duration of acute MS exacerbations. They act by dampening inflammation and stabilizing the blood-brain barrier during active demyelination. As highlighted by(**Minden *et al.*, 2009**), systemic corticosteroids are among the most widely validated interventions for acute MS attacks and are regularly used across various healthcare settings. Although corticosteroids do not influence the long term progression of MS, their timely use is critical for symptom relief and recovery from relapses. The universal administration of corticosteroids in our cohort reflects good clinical practice and reinforces their continued relevance in MS relapse management.

3.1.6.3. Symptom-Specific Treatments

- **Spasticity Treatment**

Among the cohort, 29.1% received treatment for spasticity, whereas 70.9% were not treated for this symptom (**Figure 35**). This may suggest that spasticity, although common in MS, was either mild or underdiagnosed in this population.

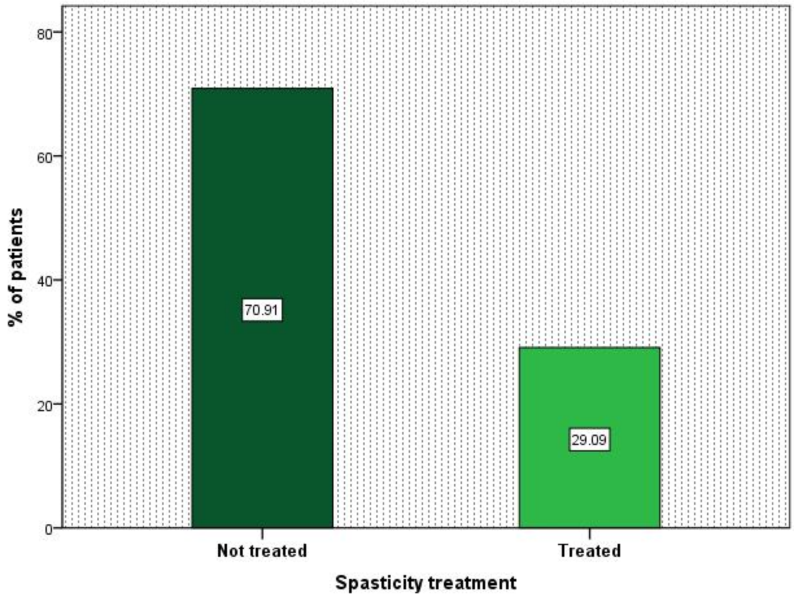


Figure 35: Use of Treatment for spacticity.

❖ Pain and Sensory Disturbance Treatment

58.2% of patients were treated for pain or sensory disturbances, while 41.8% were not (**Figure 36**). This aligns with the high prevalence of sensory symptoms (reported in previous sections), underlining the need for symptomatic relief in MS care.

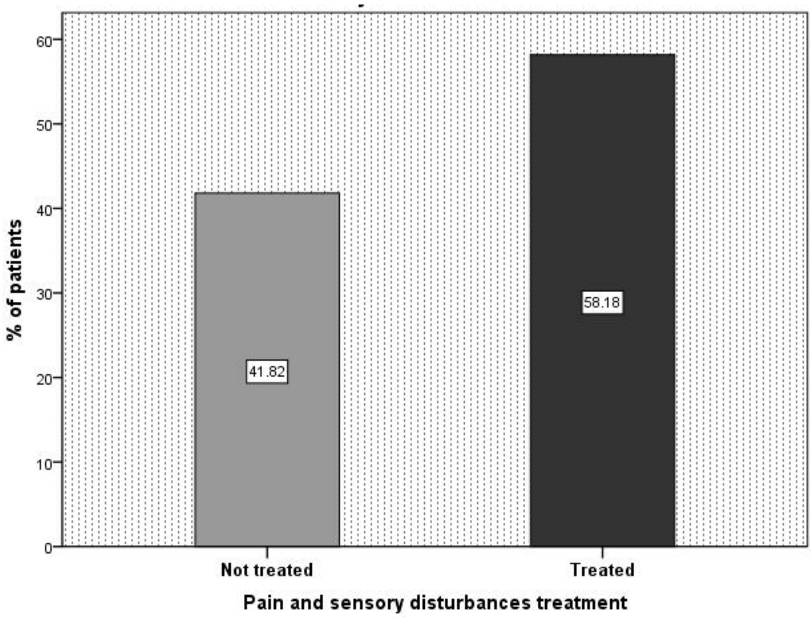


Figure 36 : Use of Treatment for Pain and Sensory Disturbances.

❖ Urinary Disorders Treatment

Only 10.9% of patients received treatment for urinary disorders, while the majority (89.1%) were not treated (**Figure 37**). This may reflect the relatively low incidence of sphincter dysfunction reported earlier, or underreporting of urological symptoms.

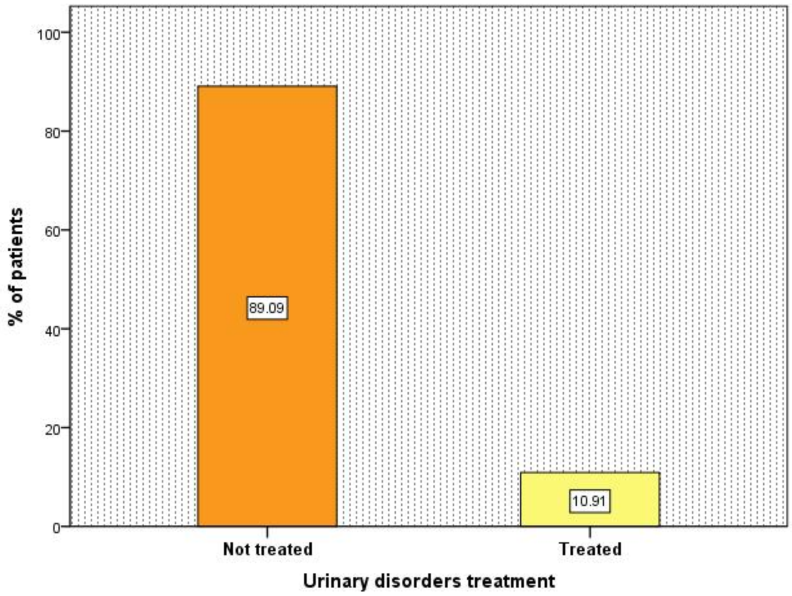


Figure 37 : Management of Urinary Disorders Among MS Patients.

❖ Anxiolytic Treatment

Anxiolytic medication was prescribed to 9.1% of the patients (**Figure 38**), suggesting a relatively low rate of pharmacological management for anxiety. Given that anxiety was reported by over 30% of patients in prior findings, this may indicate a gap in psychological care.

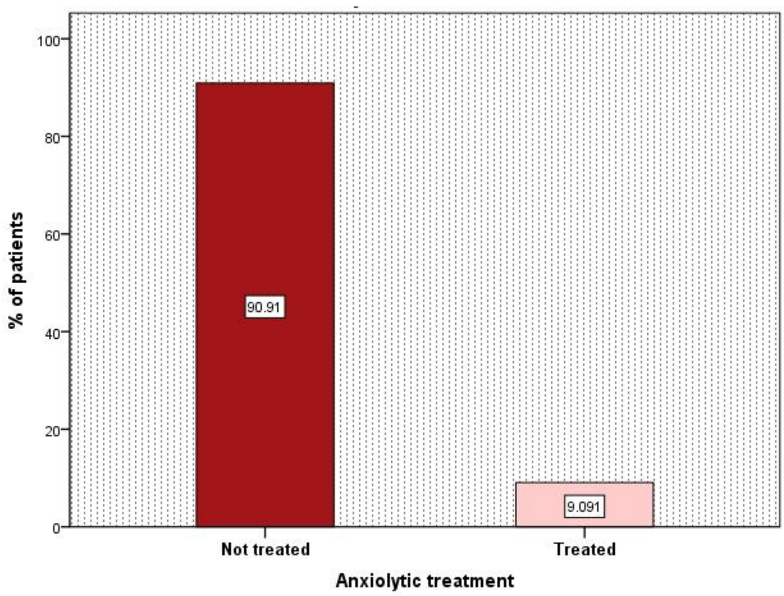


Figure 38: Anxiolytic Use for Psychological Support.

❖ **Fatigue Management**

All patients (100%) received vitamin D and multivitamin supplementation for fatigue management. This suggests systematic support for fatigue, the most frequently reported symptom in the study population.

CONCLUSION

CONCLUSION

This study aimed to assess the clinical and therapeutic management of multiple sclerosis (MS), with particular emphasis on the use of monoclonal antibodies:Natalizumab, Rituximab, and Ocrelizuma, among patients followed at the Neurology Department of CHU Frantz Fanon in Blida. The findings contribute to a better understanding of the real world effectiveness, safety, and impact of these therapies within the Algerian healthcare setting.

Multiple sclerosis remains a complex, multifactorial disease characterized by immune-mediated demyelination, neuroinflammation, and progressive axonal loss. As confirmed by our literature review and patient data, MS primarily affects young adults, with a notable predominance among women. These epidemiological features highlight the socioeconomic burden of the disease, particularly during individuals’ most productive years, with a substantial proportion of patients facing unemployment or job loss related to disease progression.

From a clinical perspective, most patients presented with RRMS, the most responsive form to immunomodulatory and immunosuppressive therapies. Comorbidities were relatively infrequent but important to note, as they can influence disease course, treatment choices, and patient quality of life. Parameters such as reproductive status, family history, and mental health factors were also documented to provide a holistic view of each patient's condition.

The therapeutic outcomes of monoclonal antibody use were promising. Natalizumab showed considerable efficacy in reducing annual relapse rates and improving neurological function, although its use requires strict monitoring due to the risk of PML, particularly in JC virus positive patients. Rituximab, despite being off label for MS in many countries, was widely used in our cohort due to its affordability and favorable efficacy profile. Ocrelizumab, the only anti CD20 agent formally approved for MS, was associated with consistent reductions in relapse rates and radiological activity, and it showed good tolerability.

In terms of treatment adherence and tolerance, the majority of patients tolerated therapy well, with only a minority reporting adverse events. Side effects were generally manageable, and treatment interruptions were rare. These results emphasize the feasibility of integrating monoclonal antibody therapies into routine clinical practice, even in resource constrained environments, provided that adequate follow up and risk assessment protocols are in place.

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Conclusion

The study also highlighted several challenges in MS care, including limited access to high cost therapies, the need for personalized treatment strategies, and the importance of long term patient monitoring. These issues underscore the necessity for national policies that promote early diagnosis, equitable access to innovative treatments, and the establishment of multidisciplinary care pathways.

In conclusion, the findings of this research underscore the transformative role that monoclonal antibodies can play in the management of MS. Their ability to significantly reduce disease activity, delay disability progression, and improve clinical and radiological outcomes makes them essential components of modern therapeutic protocols. However, their use must be balanced with appropriate risk evaluation, cost-effectiveness considerations, and individualized patient care. Continued research, including long-term and large-scale studies, is necessary to optimize treatment outcomes and adapt global guidelines to the specific needs of the Algerian patient population. With evolving scientific advances and increased awareness, the future of MS care in Algeria holds great potential for progress and innovation.

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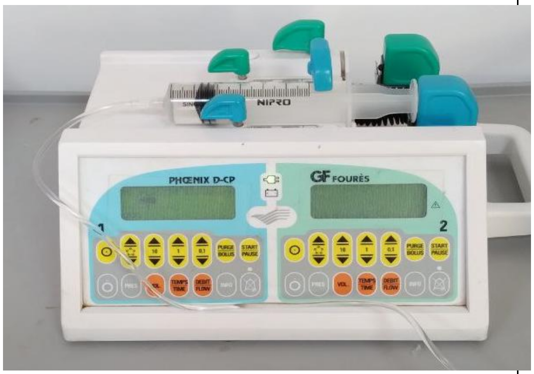
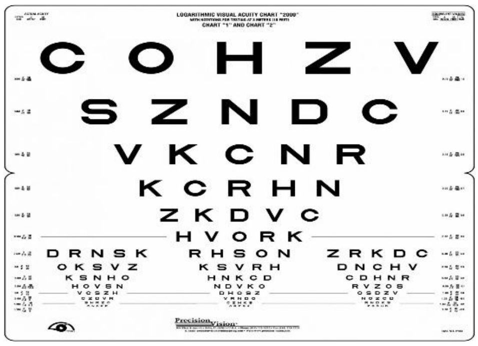
Appendices

Appendix 1 : Materials

Name	Role	Figure
Infusion Pumps (PHIZHIX D-CP / FOURSS)	Automatically deliver intravenous medications Natalizumab) at controlled rates, ensuring safety and precision.	
Brain MRI (with Gadolinium Contrast)	Assesses the presence and activity of demyelinating lesions in the central nervous system. Gadolinium highlights active inflammation.	
IV Drug Administration Sets	Allow safe infusion of medication into the bloodstream using sterile tubing, filters, and connectors.	

Reflex Hammer	Tools used to evaluate neurological function including reflexes	
Visual Acuity Chart (Sloan 100%)	Tools used to evaluate, vision	
Large Syringe (60 mL)	Used to dilute and prepare monoclonal antibody treatments (e.g., Natalizumab), then transfer the solution into the infusion pump reservoir for controlled intravenous administration.	
Chronometer	Used for the Timed 25-Foot Walk Test to measure walking speed in MS patients	

Treatments

Name	**Role**	**Figure**
NATALIZUBAM	Monoclonal antibody – Anti-α4-integrin	
OCREVUS	Monoclonal antibody – Anti-CD20	
RITUXIMAB	Monoclonal antibody – Anti-CD20	

Normal Saline NaCl 0.9%	Isotonic physiological solution – Used for drug dilution and infusion	

FICHE DE RENSEIGNEMENT POUR LE DIAGNOSTIC ET LE TRAITEMENT DE LA SCLÉROSE EN PLAQUES

1. Informations Générales du Patient

- Numéro de dossier médical : ___________________________

- Nom et prénom : ________________________________

- Date de naissance : ____ / ____ / _______ Age:

- Lieu de résidence:

- Sexe : ☐ Homme ☐ Femme

- Adresse : _______________________________________

- Téléphone : ___________________________

- État matrimonial : célibataire □ marié(e)□ divorcé(e)□ veuf (ve)□

- Profession: sans profession□ actif □ arrêt de travail □

2. Antécédents

2.1. Antécédents médicaux

Maladies auto-immunes: oui□ non □

ATCD infectieux : oui□ non □ si oui: □ Antécédents de LEMP

□ Antécédents de tuberculose

□ Autres

Diabète: oui□ non □

4. Historique de la SEP

Age de survenue des symptômes : -----------------------------

Symptômes révélateurs

1. Troubles moteurs : monoparésie □ paraparésie □ hémiparésie □

tétraparésie □

2. NORB : oui□ non □ 3. Troubles sensitifs :oui□ non□

4. Atteintes des nerfs crâniens : oui□ non□ 5. Atteinte cérébelleuse : oui □ non□

6. Troubles sphinctériens : oui□ non □ 7. Troubles sexuels: oui□ non□

8. Vertiges: oui□ non□ 9. Fatigue: oui□ non□

Age au diagnostic :…………………………………………………………

Durée d'évolution de la maladie avant le diagnostic …………………....

La symptomatologie actuelle

1. Troubles moteurs : oui□ non□ 2. NORB : oui□ non □ 3.Troubles sensitifs : oui□ non□

4. Atteintes des nerfs crâniens :oui□ non□ 5. Atteinte cérébelleuse :oui □ non□

6. Troubles sphinctériens :oui□ non □ 7.Troubles sexuels: oui□ non□

8. Vertiges: oui□ non□ 8. Fatigue

Évolution

-L'intervalle entre la première et la deuxième poussée :……………………

Maladies cardiovasculaire: oui□ non □

Affections respiratoires: oui□ non □

Affections neurologiques: oui□ non □

Hypersensibilité : oui□ non □ si oui: quelle classe/molécule:

Grossesse: oui□ non □

2.2. Habitudes toxiques

o Tabac : oui□ non□

o Alcool : oui□ non□

2.3. Antécédents chirurgicaux: oui □ non□

2.4. Antécédents gynéco-obstétricaux

Contraception: oui□ non □

2.5. Antécédents familiaux

Maladies neurologiques : ☐ Oui ☐ Non

3. Examens complémentaires

IRM initiale

date   /   /

Résultats: □ Pas de lésions □ Lésions en T1, nombre:......... □ Lésions en T2, nombre:.........
□ Lésions en T2/FLAIR, nombre:.........

-Le nombre de poussées avant le diagnostic :………………………………..

- Forme clinique : Forme RR □   Forme SP □   Forme PP □

5. Examen clinique

5.1. Evaluation clinique initiale

Capable de courir: oui□ non□

Périmètre de marche: illimité □ limité □ ==>

Aide nécessaire: unilatérale □ bilatérale □ chaise roulante □ chaise motorisée □

5.2. Examen neurologique actuel

Conclusion de l'examen neurologique complet (syndrome) :

Syndrome pyramidal : oui □ non □   Syndrome cérébelleux : oui □ non □

Syndrome vestibulaire : oui □ non □ Syndrome ataxospasmodique : oui □ non □
Syndrome cordonnal postérieur : oui □ non □ NORB : oui □ non □ Atteinte du TC : oui □ non □ Atteinte médullaire : oui □ non □

Degré d'handicap EDSS :………………………………………………..

Historique des traitements de fond de la SEP

	Nom du médicament	Date de début	Date d'arrêt	Motif d'arrêt 1,2,3....
Les traitements Immunomodulateurs (Interférons)	☐ Rebif 44	|__|__|___|	|__|__|___|	
	☐ Avonex	|__|__|___|	|__|__|___|	
	☐ Bétaféron	|__|__|___|	|__|__|___|	
Les traitements immunosuppresseurs	☐ Endoxan	|__|__|___|	|__|__|___|	
	☐ Elsep/ Mitoxantrone	|__|__|___|	|__|__|___|	
	☐ Azathioprine	|__|__|___|	|__|__|___|	
	☐ Méthotréxate	|__|__|___|	|__|__|___|	
Les biothérapies	☐ Tysabri	|__|__|___|	|__|__|___|	
	☐ Rituximab	|__|__|___|	|__|__|___|	
Autres	☐ Corticoides chroniques	|__|__|___|	|__|__|___|	
	☐ Immunoglobulines	|__|__|___|	|__|__|___|	

1-Arrêt programmé **2**– Intolérance **3**-Intolérance générale **4**-Intolérance biologique **5**-absence d'efficacité **6**-Convenance personnelle **7**-Effet indésirable grave **8**-Autres

Autres:

Les traitements symptomatiques

Symptômes	Le(s) traitements
Spasticité	
Troubles sensitifs, douleurs	
Troubles urinaires	
Constipation	
Troubles sexuels	
Fatigue	
Autres..	

Résultats biologiques

Date de la NFS |__ |___|___|

Leucocytes |_____|g/L

Polynucléaires neutrophiles |_____|g/L

Lymphocytes |_____|g/L

Hémoglobine |_____|g/L

Plaquettes |_____|g/L

VS |_____|

CRP |_____|

Numération de lymphocytes

CD4+ |____|

CD8+ |____|

B(CD19+) |____|

Dosage pondérale des immunoglobulines

IgA |____| g/L

IgG |____| g/L

IgM |____| g/L

L'analyse du LCR

Aspect	Le nombre et type des cellules présente	Protéines (g/l)	Glucose (g/l)	Chlore (g/l)	L'analyse virale	L'analyse bactériologique
☐ Clair ☐ Trouble purulent ☐ Jaune /rouge					☐Positif ☐Négatif	☐Positif ☐Négatif

Les résultats en isoélectrofocalisation

☐ Pas de bande oligoclonale IgG dans le LCR ni dans le sérum ==> négatif

☐ Bandes oligoclonales IgG à la fois dans le LCR et le sérum ==> négatif

☐ Bande monoclonale dans le LCR non retrouvée dans le sérum ==> douteux

☐ Au moins 2 bandes oligoclonales dans le LCR non retrouvées dans le sérum ==> évocateur d'une inflammatic du SNC

☐ Plus de bandes dans le LCR que dans le sérum ==> évocateur d'une inflammation du SNC

Nom:_______________ Prénom:_____________ date de naissance:_______________

Fiche de suivi patient sous Tysabri

Date de la dernière consultation:____________ Nombre de cures déjà recues:

I. Avant la cure de ce jour:

A. Le patient a-t-il présenté des effets indésirables:

1.Infections et infestations: ☐ Oui ☐ non

☐ Infection urinaire : ☐ Cystite ☐ Pyélonéphrite ☐ Infection rhinopharyngée ☐ Autres ; si oui précisez :

2.Affections du système immunitaire: ☐ Oui ☐ Non

☐ Hypersensibilité ☐ Réactions liées a la perfusion ; précisez:

3.Affections du système nerveux: ☐ Oui ☐ Non

☐ Céphalées ☐ Sensations vertigineuses ☐ LEMP

☐ Autres ; si oui précisez :

4.Affections gastro-intestinales : ☐ Oui ☐ Non

☐ Nausées ☐ Vomissements ☐ Autre ; si oui précisez:

B. Au cours d'une perfusion ou dans ses suites immédiates:

1.le patient a-t-il présenté un événement indésirable:

☐ **Non** ; si non ignorez la section suivante

☐ **Oui** ;si oui précisez la nature de cet ou ces effet(s) indésirable(s)

☐ Frissons	☐ Erythème, prurit	☐ Dyspnée
☐ Nausée	☐ Vomissement	☐ Etat de choc
☐ Sensations vertigineuses	☐ Céphalée	☐ Arrêt respiratoire
☐ Toux	☐ Œdème du visage	☐ Cyanose
☐ Diarrhée	☐ Malaise	☐ Arrêt circulatoire
☐ Autre; si oui précisez:		

Précisez le délai écoulé entre la perfusion et l'événement : heure _____ minute ______

2.Traitement correcteur :

☐ **Non** ☐ **Oui** ;si oui précisez la nature: ....

3.Quelle a été l'évolution de l'effet indésirable:

....

Y'a t-il eu un arrêt du traitement par ***Tysabri*** suite à la survenue de cet effe☐ **Oui** ☐ **Oui**

C. y'a-t-il eu une recherche d'anticorps anti-natalizumab:

☐ **Non** ☐ **Oui**

D. Y'a t'il eu une recherche d'anticorps anti virus JC

☐ **Non** ☐ **Oui** ; si oui quel a été le résultat:

E. Y'a-t-il une évaluation du traitement sous ***Tysabri*** à 6 mois après son instauration:

Efficacité:...

Sécurité et tolérance :..

II. Durant la cure de ce jour:

1.Décrire les modalités de préparation et reconstitution du médicament:

....

....

2.le malade reçoit-il un traitement avant la perfusion:

☐ **Non** ☐ **Oui** ;Si oui précisez lequel:

3.Durée de la perfusion:_____heure_____minutes

4.Au cours de la perfusion ou dans ses suites immédiates :

a. Le patient a t'il présenté un événement indésirable:

☐ **Non**

☐ **Oui** ;Si oui précisez la nature de l'évènement :

Précisez le délai écoulé entre la perfusion et l'évènement: _____heure_____minutes

b. Traitement correcteur:

☐ **Non** ☐ **Oui** ;Si oui précisez la nature :

c. Quelle a été l'évolution de l'effet indésirable:

....

III. Quel est le motif pour lequel ***Tysabri*** a-t-il été instauré :

☐ Inefficacité du traitement antérieur

☐ Intolérance; précisez quel type :

IV. 1. Le patient a-t-il présenté des poussées :

. Au cours des 12 derniers mois ;Si oui précisez: Le nombre:..................

La fréquence : ....

. Au cours des 24 derniers mois ;Si oui précisez: Le nombre:..................

La fréquence : ....

2. le patients a-t-il présenté des signes **d'amélioration/aggravation** après instauration du **Tysabri** :

a. Score EDSS:

. Score EDSS initial: ....

. Score EDSS après 12 mois de traitement: ....

. Score EDSS après 24 mois de traitement: ....

b. IRM (0-24mois):

.apparition de nouvelles lésions: ☐ **Non** ☐ **Oui** ;si oui: ☐ Lésions en T1, nombre:.......... ☐ Lésions en T2, nombre:............. ☐ Lésions en T2/FLAIR; nombre: nombre,.........

.volume médiane des lésions: ☐ Amélioration ☐ aggravation

3.Analyse du LCR : derniers résultats:

Nom:_______________ Prénom:_____________ date de naissance:_______________

Fiche de suivi patient sous **Rituximab**

Date de la dernière consultation:______________ Nombre de cures déjà recues:

I. Avant la cure de ce jour:

A.1.le patient a-t-il présenté des infections et infestations:☐ **Oui** ☐ **non**

☐ Infections bactériennes ☐ Pneumonie ☐ Infection des voies respiratoires
☐ Infections virales ☐ Bronchites ☐ LEMP
☐ Infections fongiques ☐ Hépatite b1 ☐ Infection fébrile
☐ septicémie ☐ Sinusite ☐ Autre ;si oui précisez :_

A.2.le patient a-t-il présenté des affections hématologiques et du système lymphatique :☐ **Oui** ☐ **Non**

☐ Neutropénie ☐ Anémie hémolytique ☐ Troubles de la coagulation et aplasie médullaire
☐ Leucopénie ☐ Pancytopénie ☐ Autres ; si oui précisez :
☐ Thrombopénie ☐ Granulocytopénie

A.3. le patient a-t-il présenté des affections du système immunitaire: ☐ **Oui** ☐ **Non**

☐ Hypersensibilité ☐ Réactions liées a la perfusion ; précisez:
☐ Angio-œdème ☐ Autres ; si oui précisez :

A.4.le patient a-t-il présenté des troubles de métabolisme et de nutrition : ☐ **Oui** ☐ **Non**

☐ Hyperglycémie ☐ Œdème périphérique ☐ Hypocalcémie
☐ Perte de poids ☐ Œdème du visage ☐ Autre ; si oui précisez:

A.5.le patient a-t-il présenté des affections du système nerveux: ☐ **Oui** ☐ **Non**

☐ Agitation ☐ Hypoesthésie ☐ Neuropathie crânienne
☐ Insomnie ☐ Paresthésie ☐ Autre ; si oui précisez:
☐ Anxiété ☐ Neuropathie périphérique

A.6.le patient a-t-il présenté des affections cardiaques: ☐ **Oui** ☐ **Non**

☐ Infarctus du myocarde ☐ Tachycardie ☐ Ischémie myocardique
☐ Arythmie ☐ Bradycardie ☐ Autre ; si oui précisez:
☐ Fibrillation auriculaire ☐ Insuffisance ventriculaire

A.7.le patient a-t-il présenté des affections vasculaires: ☐ **Oui** ☐ **Non**

☐ Hypertension ☐ Hypotension ☐ Autres ; si oui précisez :

A.8.le patient a-t-il présenté des affections oculaires: ☐ **Oui** ☐ **Non**

☐ Troubles lacrymaux ☐ Perte de la vision ☐ Autre ; si oui précisez:
☐ Conjonctivite ☐ Troubles lacrymaux

A.9.le patient a-t-il présenté des affections gastro-intestinales : ☐ **Oui** ☐ **Non**

☐ Nausées ☐ Douleurs abdominales ☐ Stomatite
☐ Vomissements ☐ Dysphagie ☐ Irritation laryngée
☐ Diarrhées ☐ Anorexie ☐ Autres ; si oui précisez :

A.10.le patient a-t-il présenté des affections de la peau et du tissu sous cutané : ☐ **Oui** ☐ **Non**

☐ Prurit ☐ Urticaire ☐ Syndrome de Stevens-Johnson
☐ rash ☐ Sudation ☐ Sueurs nocturnes
☐ Alopécie ☐ Autres ; si oui précisez :

II. Durant la cure de ce jour:

1.Décrire les modalités de préparation et reconstitution du médicament:

....

....

2.le malade reçoit-il un traitement avant la perfusion:

☐ **Non** ☐ **Oui** ;Si oui précisez lequel:

2.Durée de la perfusion:_____heure_____minutes

3.Au cours de la perfusion ou dans ses suites immédiates :

a. Le patient a t'il présenté un événement indésirable:

☐ **Non** ☐ **Oui** ;Si oui précisez la nature de l'évènement :

Précisez le délai écoulé entre la perfusion et l'évènement: _____heure_____minutes

b. Traitement correcteur:

☐ **Non** ☐ **Oui** ;Si oui précisez la nature :

c. Quelle a été l'évolution de l'effet indésirable:

....

Y'a-t-il eu un arrêt du traitement par ***Rituximab*** suite à la survenue de cet ☐ **Oui** ☐ **Non**

III. La patient a-t-il déjà reçu du ***Tysabri*** avant le ***Rituximab*** : ☐ **Non** ☐ **Oui**

Quel est le motif pour lequel ***Rituximab*** a-t-il été instauré :

☐ Inefficacité du traitement antérieur
☐ Intolérance; précisez quel type :

IV. 1. Le patient a-t-il présenté des poussées :

. Au cours des 12 derniers mois ;Si oui précisez: Le nombre:..............

La fréquence : ....

. Au cours des 24 derniers mois ;Si oui précisez: Le nombre:..............

La fréquence : ....

2. le patients a-t-il présenté des signes **d'amélioration/aggravation** après instauration du **Rituximab** :

a. Score EDSS:

. Score EDSS initial: ....

. Score EDSS après 12 mois de traitement: ....

. Score EDSS après 24 mois de traitement: ....

b. IRM (0-24mois):

.apparition de nouvelles lésions: ☐ **Non**

☐ **Oui** ;si oui: ☐ Lésions en T1, nombre:..........
☐ Lésions en T2, nombre:..............
☐ Lésions en T2/FLAIR; nombre: nombre,.........

.volume médiane des lésions: ☐ Amélioration
☐ aggravation

3.Analyse du LCR : derniers résultats:

PEOPLE'S DEMOCRATIC REPUBLIC OF ALGERIA

MINISTRY OF HIGHER EDUCATION AND SCIENTIFIC RESEARCH

UNIVERSITY OF BLIDA 1

Avis favorable
Dr Menacer A.

Faculty of nature and life sciences

Department of Biology

Dissertation

Dissertation Submitted to the Department of Biology as a Partial Fulfillment for the Requirement for the Degree of Master in the field of nature and life sciences

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Speciality : **Pharmacotoxicology**

Thème

Therapeutic management of multiple sclerosis in patients consulting the neurology department of the Frantz Fanon University Hospital.

Presented by:

Miss BELKHOUS Hidaya

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