Nutritional Neurosciences

Hamdan Hamdan *Editor*

Exploring the Effects of Diet on the Development and Prognosis of Multiple Sclerosis (MS)

Springer

Nutritional Neurosciences

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Preface

This book offers an insightful exploration into the relationship between diet and multiple sclerosis (MS), aiming to address a crucial question: Can dietary interventions serve as effective preventative and therapeutic measures for patients with MS? Delving into this question, this book examines various dietary components and regimens, shedding light on their potential impacts on the progression, relapse rate, and development of MS. It offers readers valuable insights into how dietary choices can influence the management of this condition.

Backed up by evidence gathered from review and clinical trial papers, this book discusses the role of vitamins such as A, B, and D, as well as dietary supplements like caffeine, carnitine, and lipoic acid in benefiting patients with MS. Particular attention is given to the significance of vitamin D in lowering the risk of developing MS and its immunomodulatory effects on the inflammatory processes associated with the disease.

In parallel, this book also addresses the detrimental effects of diets such as the Western or high salt diet (HSD) on MS prognosis, emphasizing how these dietary regimens can harm the gut microbiome and exacerbate inflammatory responses, ultimately promoting demyelination of the central nervous system (CNS). This book then explores alternative dietary approaches that confer a protective effect to the gut microbiome and the CNS, including whole grain, fasting, Mediterranean, and ketogenic diets.

In order to represent MS holistically, this book delves into the epidemiology, pathogenesis, and epigenetics of MS. It offers a thorough examination of the underlying pathophysiology of the disease, driven by the activation of inflammatory markers and the impairment of the immune system, with a particular focus on the role of CD4 T cells and their Th1 and Th17 subtypes. Finally, the current and emerging therapeutic regimens for the treatment of MS are discussed.

This comprehensive resource is an essential read for patients with MS seeking to understand the potential impacts of diet on their overall health, as well as healthcare professionals and researchers interested in exploring dietary interventions for MS management.

Abu Dhabi, United Arab Emirates — Hamdan Hamdan

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Contents

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About the Editor

Hamdan Hamdan an Assistant Professor at Khalifa University and Visiting Professor at Baylor College of Medicine, specializes in neurodegenerative diseases and autism spectrum disorders. His laboratory aims to understand the mechanisms by which the axon initial segment (AIS) and the nodes of Ranvier are assembled and maintained in their normal health and during injury or their role in neurodegenerative diseases. Any therapeutic intervention of the nervous system must involve proper maintenance and assembly of the node of Ranvier and the AIS. He is part of a pioneering team from Khalifa University, the first in the MENA region to reach the semifinals of the Longitude Prize on Dementia. In addition to his research, he is an expert in designing different serotypes of viruses, leveraging viral vectors as vehicles for delivering therapeutic genes into cells; he utilizes gene editing CRISPR/Cas9 techniques, designs transgenic animal models, and focuses on advancing our understanding and treatment of neurological disorders. His proficiency in this area and his expertise in gene editing using CRISPR/Cas9 position him at the forefront of innovative approaches for studying and potentially treating neurological disorders.

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Chapter 1
Introduction to Multiple Sclerosis

Maitha M. Alhajeri, Rayyah R. Alkhanjari, Sara Aljoudi, Nadia Rabeh, Zakia Dimassi, and Hamdan Hamdan

Abstract Multiple sclerosis (MS) is a chronic demyelinating central nervous system disease caused by acquired autoimmune inflammation, demyelination, and axonal degeneration. It is primarily a disease of young adults. Various genetic and environmental factors have been identified as possible contributors to the disease pathogenesis, diet being a key factor. We hypothesize that diet can serve as a preventive and therapeutic target for patients with MS. This book is dedicated to collect the available evidence that establishes a relationship between diet and MS, thus exploring dietary interventions as a potential avenue for the prevention and treatment of the disease that is accessible across various cultural and socioeconomic backgrounds.

Keywords Multiple sclerosis (MS) · McDonald's Criteria · Immune-mediated Demyelination · Oligodendrocytes · Disease-modifying therapies (DMTs) · Diet

Abbreviations

APC	Antigen-presenting cells
BBB	Blood-brain barrier
CNS	Central nervous system

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CSF	Cerebrospinal fluid
DMTs	Disease-modifying therapies
EAE	Experimental allergic encephalomyelitis
GWAS	Genome-wide association studies
HLA	Human leukocyte antigen
HSD	High salt diet
IFN-γ	Interferon-gamma
IL-17	Interleukin-17
IL-22	Interleukin-22
IL-23	Interleukin-23
IL-6	Interleukin-6
MHC class I	Major histocompatibility complex class I
MPO	Myeloperoxidases
MRI	Magnetic resonance imaging
MS	Multiple Sclerosis
NHS	Nurses' Health Study
NMSS	National Multiple Sclerosis Society
NO	Nitric oxide
PP	Primary Progressive
PPMS	Primary Progressive MS
RCTs	Randomized control trials
ROS	Reactive oxygen species
RRMS	Relapsing-remitting MS
S1P	Sphingosine 1 phosphate
SPMS	Secondary-Progressive MS
Th1	T helper 1
Th17	T helper 17
TNF-α	Tumor necrosis factor-alpha
TYK2	Tyrosine kinase 2
UV	Ultraviolet
VDR	Vitamin D receptor
WBCs	White blood cells

Learning Objectives

- Define MS and its underlying pathology involving demyelination and axonal degeneration.
- Classify MS into its main subtypes: Relapsing-Remitting, Secondary Progressive, Primary Progressive, and Progressive Relapsing.
- Explain the diagnostic criteria for MS, focusing on the Revised McDonald's Criteria.

- Explore the inflammatory cascade and cellular interactions leading to demyelination and neurodegeneration.
- Evaluate environmental factors like vitamin D deficiency, obesity, and smoking in the development and progression of MS.

1.1 What Is Multiple Sclerosis, and How Does It Present?

Multiple Sclerosis (MS) is an acquired, immune-mediated disease characterized by the demyelination of the central nervous system (CNS). It commonly begins in adulthood, peaking between 20 and 40, with a female:male of 3:1 or greater female predominance (Ford 2020). It is known for its broad spectrum of clinical presentation and severity, radiological appearance, involved gene loci, and response to therapy (Lucchinetti et al. 2000). Among the classical symptoms seen in most patients are sensory deficits, including paresthesia (e.g., tingling, prickling, or "pins and needles" sensation) and hypesthesia (e.g., reduced sensation or numbness). Patients may develop unpleasant sensory experiences like *Lhermitte's symptom,* an electric shock sensation radiating to the lower extremities, usually triggered by neck flexion. MS can also manifest as motor symptoms resulting from upper motor neuron lesions, including limb weakness accompanied by increased spasticity, hyperreflexia, and positive Babinski signs (Doshi and Chataway 2016; Kasper et al. 2018).

MS can also affect the optic nerve, which is embryologically derived from the prosencephalon and myelinated by the oligodendrocytes, resulting in optic neuritis, a subacute, unilateral, painful vision loss, accompanied by periorbital pain aggravated by eye movement and relative afferent pupillary defect. Internuclear ophthalmoplegia is another ocular sign usually encountered in MS, whereby the immune-mediated demyelination damages the medial longitudinal fasciculus, impairing ipsilateral adduction and causing nystagmus of the contralateral abducting eye (Kasper et al. 2018; Nij Bijvank et al. 2019; Petzold et al. 2014). Interestingly, some patients' neurological symptoms can result from or worsened by an increase in the core body temperature, such as in cases of fever, strenuous physical activity, and hot showers. This phenomenon, known as *Uhthoff's phenomenon*, predominantly manifests as temporary painful vision loss, albeit it can occur with any symptom of MS (Kasper et al. 2018; Opara et al. 2016).

1.2 Classification of MS

Based on the natural history of the disease, MS can be divided into several subtypes. Here we will discuss the main four (Fig. 1.1) according to the classification of the US National Multiple Sclerosis Society (NMSS) Advisory Committee (Polman et al. 2011). In relapsing-remitting MS (RRMS), patients experience discrete, gradual-onset attacks evolving over several days and interspaced with periods of

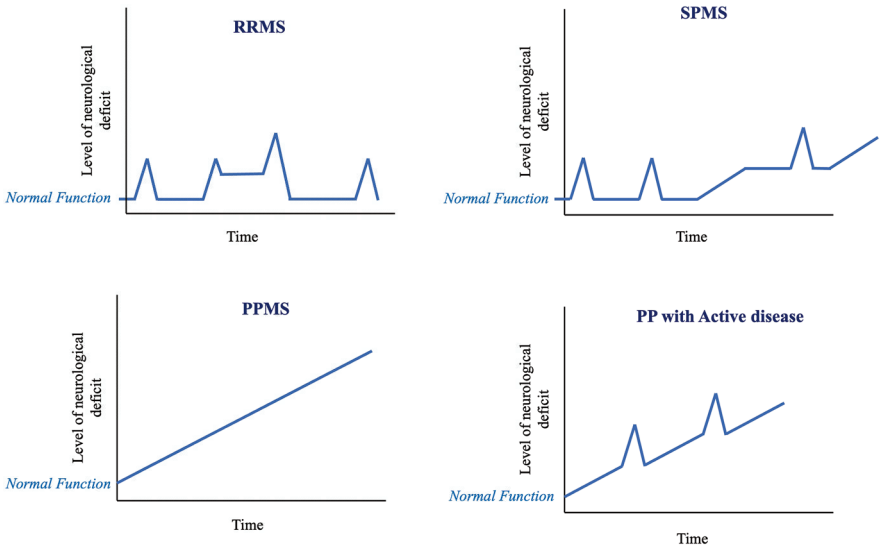

Fig. 1.1 Classification of MS. Each graph represents a disease subtype based on its clinical course. The peaked portion of the graph represents an acute attack. *RRMS* - Relapsing-Remitting MS, *SPMS* - Secondary Progressive MS, *PPMS* - Primary Progressive MS, and *PP with Active disease* - Primary Progressive with Active disease. Adapted from "Clinical presentation and diagnosis of multiple sclerosis," by H. Ford 2020, Clin Med (Lond), 20(4), 380–383. Copyright 2020 by the Royal College of Physicians

neurological stability. The NMSS specifies that symptoms in the RRMS subtype do not develop suddenly and last at least 24 h without signs of fever or infectious process. In secondary progressive MS (SPMS), some patients experience incomplete recovery between the attacks while concomitantly developing gradual worsening of the symptoms after a relapsing-remitting course. SPMS is often diagnosed retrospectively based on the patient's history. Almost 10% of cases present with the primary progressive MS (PPMS) subtype, which is characterized by a gradual, steady decline in neurological function rather than presenting with acute episodic attacks. The fourth subtype of MS is progressive relapsing (PRMS), where the patient demonstrates a steady progressive neurological disability with apparent acute attacks. However, the MS committee recommends categorizing patients with PRMS as Primary Progressive (PP) patients with active disease (Ford 2020; Kasper et al. 2018; Lublin et al. 2014).

1.2.1 MS Diagnosis

Until now, a definitive diagnosis of MS cannot be made based on the results of a single test. A diagnosis is facilitated by the amalgamation of clinical signs and symptoms with various supporting investigations, namely, magnetic resonance

imaging (MRI), cerebrospinal fluid (CSF) analysis, and evoked potentials (Doshi and Chataway 2016; Ford 2020). The hallmark feature that the clinical, paraclinical, or both types of investigations must demonstrate to diagnose MS is the spatiotemporal dissemination of the pathologic lesions (Ford 2020; Polman et al. 2011). Based on the most recent Revised McDonald's Criteria, there are various constellations of signs and symptoms that aid in the diagnosis of MS. One approach to reach a diagnosis is to confirm the occurrence of two or more attacks, each lasting for more than 24 h and separated by at least 1 month, and an associated pathology in two or more anatomically unrelated areas in the CNS white matter. Another approach is only a clinical dissemination in time and radiological evidence of dissemination in space that are characteristic for MS. An example of radiological evidence that would support a diagnosis of MS would need to show at least one T2 lesion in at least two out of four CNS areas: periventricular, juxtacortical, infratentorial, or spinal cord. Those are only some of the possibilities that have been identified in patients with a likely diagnosis of MS (refer to Table 1.1 for more information) (Ford 2020; Kasper et al. 2018; Polman et al. 2011).

1.3 Is MS an Autoimmune Disease?

As mentioned previously, MS is an immune-mediated disease driven by a pathological immune response directed against the myelin found in the CNS. Whether it can be classified as an autoimmune disease remains inconclusive. Currently available evidence is not compelling enough to confirm MS as an autoimmune condition. In fact, MS fails to meet several characteristics of the autoimmunity criteria (Lemus et al. 2018; Wootla et al. 2012). Although various studies succeeded in identifying antibodies directed against different CNS antigens such as myelin protein, carbohydrates, and lipids, evidence confirming the presence of specific MS autoantigens is still lacking. Even with autoantibodies recognized, such as those against myelin oligodendrocyte glycoprotein, myelin basic protein, alu repeats, alpha-B-crystalline, and myelin-associated glycoprotein, there is no consistency or consensus among the published studies (Kasper et al. 2018; Lemus et al. 2018). In addition, attempts to induce MS lesions in animal models using the identified antibodies or T cells yielded contrasting findings. For the purpose of lab research in MS, we can generate similar demyelinating disease in animal models using Theiler's murine encephalomyelitis virus, coronavirus, and Semliki Forest virus or through utilizing multiple candidate antigens together (Lemus et al. 2018).

1.4 Pathophysiology of MS

A series of pathophysiological events, including localized immune mononuclear cells infiltration, microglia activation, demyelination, axonal damage, and gliosis, are identified in the pathogenesis of MS (Ciccarelli et al. 2014; Kasper et al. 2018).

Table 1.1 2017 McDonald criteria for the diagnosis of MS in patients with an attack at onset. Adapted from "Clinical presentation and diagnosis of multiple sclerosis," by H. Ford 2020, Clin Med (Lond), 20(4), 380–383. Copyright 2020 by the Royal College of Physicians

Number of attacks at clinical presentation	Number of lesions with objective clinical evidence	Additional data needed for diagnosis of multiple sclerosis
≥2	≥2	None [a]
≥2	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location)	None [a]
≥2	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site
		Or by MRI
1	≥2	Dissemination in time demonstrated by an additional clinical attack
		Or by MRI
		Or demonstration of CSF-specific oligoclonal bands
1	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site
		Or by MRI
		And dissemination in time demonstrated by an additional clinical attack
		Or by MRI
		Or demonstration of CSF-specific oligoclonal bands

[a] = no additional tests are required to demonstrate dissemination in space and time. However, unless MRI is not possible, brain MRI should be obtained in all patients in whom the diagnosis of multiple sclerosis is being considered. In addition, spinal cord MRI or CSF examination should be considered in patients with insufficient clinical and MRI evidence supporting multiple sclerosis, with a presentation other than a typical clinically isolated syndrome, or with atypical features. If imaging or other tests (e.g. CSF) are undertaken and are negative, caution needs to be taken before making a diagnosis of multiple sclerosis, and alternative diagnoses should be considered
CNS central nervous system, *CSF* cerebrospinal fluid, *MRI* magnetic resonance imaging

Among the major immune cells involved are $CD4^+$ (helper) T cells, which have been shown to recognize myelin basic protein based on the experimental allergic encephalomyelitis (EAE) animal model (Choi et al. 2016). Acute inflammation precipitating endothelial-lymphocyte interactions and disrupting the blood-brain barrier (BBB) facilitate the lymphocytic, localized invasion of the CNS seen in MS, as seen in Fig. 1.2. Endothelial-lymphocyte interactions are enabled through the upregulation of endothelial ligands, such as P-selectin and VCAM-1, that bind to

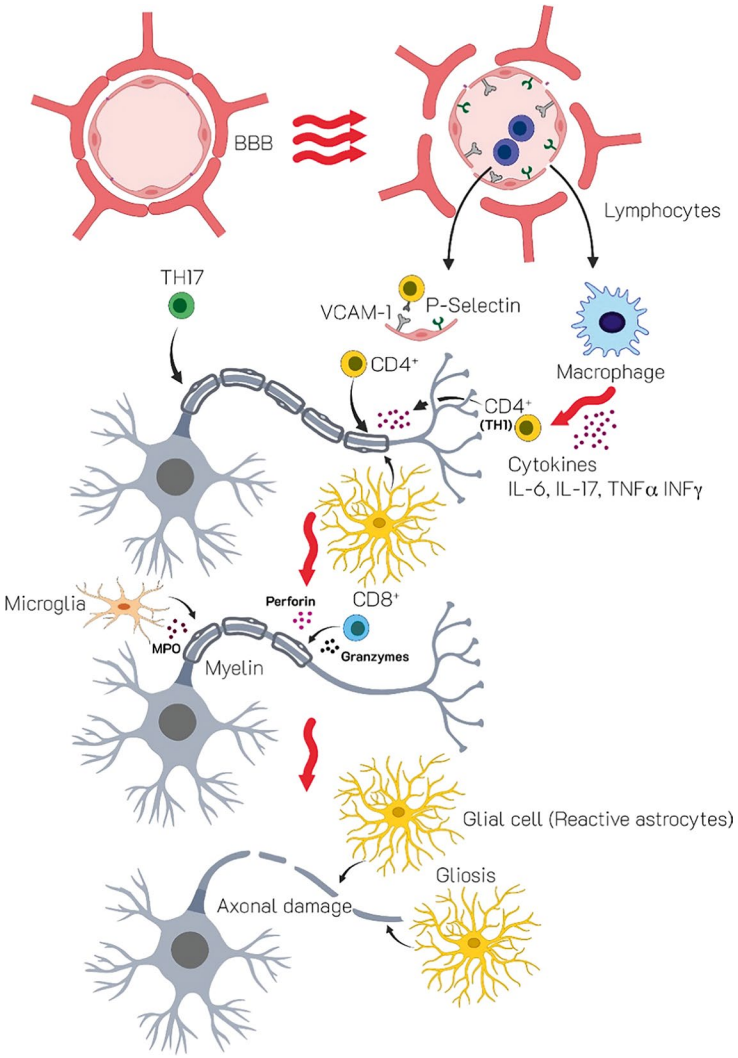

Fig. 1.2 Pathophysiology of MS. Axonal degeneration and demyelination in MS are the combined result of inflammatory reactions from the innate and adaptive immune system. The release of various cytokines, granzymes, perforins, and MPO are the key constituents that drive this process.*A disruption in BBB integrity facilitates the inflammatory process seen in MS. Initially, white blood cells (WBCs) migrate and adhere to cell adhesion molecules, such as VCAM-1 and P-selectin, to reach the CNS and start the sequence of inflammation. Once in the CNS, macrophages, CD4+ T cells, and Th17 release their inflammatory mediators and cytokines. CD8+ T cells also play a role in demyelination by releasing perforins and granzymes, while microglia contribute to this inflammatory cascade by releasing MPO. The consequence of these reactions is myelin sheath deterioration. Scarring of tissue, or gliosis, ensues and is mediated by reactive astrocytes in the CNS

integrins expressed on the surface of lymphocytes. Once lymphocytes cross the BBB, different helper T cells groups, namely type 1 (Th1) and 17 (Th17), their cytokines and inflammatory mediators, such as interleukin-6 (IL-6), IL-17 and IL-22, tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ) contribute to demyelination—a pathological hallmark of MS (Ciccarelli et al. 2014; Kasper et al. 2018). B cell lymphocytes also act as follicle-like aggregates in the meninges of SPMS patients, leading to a younger age of onset and contributing to inflammatory mediators associated with profound cortical pathology. In addition to the lymphocytes role in MS, microglial cells contribute to the disease as their activation is triggered by pervasive inflammation and injury in the brain parenchyma. Consequently, they produce myeloperoxidases (MPO) that further fuel the inflammatory response and exacerbate tissue damage. Interestingly, current research suggests the applicability of MPO as a biomarker and therapeutic target (Ciccarelli et al. 2014).

MS pathology encompasses not only myelin damage but also axonal and neuronal degeneration, contributing significantly to the neurological disability seen in the clinical course of the disease. A variety of mechanisms have been identified that explain the neuronal injury seen in MS. By interacting with the major histocompatibility complex class I (MHC class I), $CD8^+$ cytotoxic T cells target demyelinated axons and damage them through the action of perforin and granzymes. Perforin mediates cellular toxicity and apoptosis by creating membranous pores that enable the delivery of granzymes. Studies of neuronal motor function found that MS mice models deficient in perforin demonstrated larger-diameter axons with improved neuronal function (Lemus et al. 2018). Other factors that mediate axonal damage and neuronal loss include reactive oxygen species (ROS) and nitric oxide (NO) released by the activated microglia, infiltrated macrophages, and lymphocytes. Despite the various mechanisms of neuronal injury, damage is mainly caused by mitochondrial dysfunction and reduction in ATP synthesis, leading to oligodendrocytes apoptosis and axon degeneration (Kasper et al. 2018; Lemus et al. 2018). Secondary to this cellular loss and damage, a gliotic response is initiated, manifesting as the proliferation of reactive astrocytes that are detected within and at the border of the inflammatory lesions and in normal-appearing white matter. These reactive astrocytes are hypothesized to be the main contributors to the chronic symptoms of MS as they can interfere with remyelination (Lemus et al. 2018). The overarching pathophysiology of MS is outlined in Fig. 1.2.

1.5 MS from a Genetic Perspective

The heritability of MS has been extensively explored, and it was found that 15% of MS patients have affected family members, with a disease risk approaching 1 in 25 if a sibling having the disease (Goris et al. 2022; Kasper et al. 2018). Genome-wide association studies (GWAS) concluded that MS heritability is governed by many genetic factors rather than a single, isolated mutation, with the majority of those

genes associated with factors that play a role in the adaptive immunity (Goris et al. 2022). One of the earliest MS genetic risk factors identified is the HLA-DRB1*15:01, which increases the risk of the disease by threefold. HLA-DRB1 is expressed as antigen-presenting proteins on antigen-presenting cells (APC) that specifically present myelin and EBV peptides (Parnell and Booth 2017). Other recently recognized genes are those that translate into the IL-7 receptor (CD127), IL-2 receptor (CD25), T cell costimulatory molecule LFA-3 (CD58), and tyrosine kinase 2 (TYK2). Additional genes implicated in MS include EOMES and TBX21 encoding eomesodermin and T-bet, respectively. These genes are transcription factors regulating natural killers, $CD8^+$ memory cells, and $CD4^+$ differentiation. (Couturier et al. 2011; Goris et al. 2022; Kasper et al. 2018; McKay et al. 2016; Parnell and Booth 2017).

1.6 Environmental Factors

Research suggests that the development and progression of MS are influenced by a multifaceted interplay between genetic predisposition and distinct environmental factors, collectively elevating susceptibility. In this section, we will provide a concise overview of various environmental factors based on existing literature, with a more comprehensive exploration in Chap. 2 of the book. Broadly, studies have identified environmental risk factors that interact with human leukocyte antigen (HLA) risk genes and may play a role in the development or exacerbation of MS. These factors include inadequate sun exposure and low vitamin D levels, obesity, smoking, and infection with the Epstein-Barr virus. For a more detailed exploration, readers are encouraged to refer to Chap. 2 of this book.

While a comprehensive discussion of the role of vitamin D is addressed in Chap. 8, we will briefly touch upon key aspects in this section. Vitamin D deficiency and reduced sunlight exposure have long been associated with an elevated risk of MS, prompting investigations into the potential impact of vitamin D supplementation on disease progression. Having anti-inflammatory properties, vitamin D plays a crucial role as an immunomodulator and potentially reducing inflammation in MS. It also plays a vital role in bone metabolism. Notably, its synthesis primarily relies on exposure to ultraviolet (UV) radiation from sunlight. Numerous studies have assessed vitamin D levels in the MS population, revealing correlations between low serum vitamin D levels and an increased risk of MS (Michel 2018; Touil et al. 2023). Some research suggests that vitamin D deficiency in MS patients could stem from issues with the vitamin D receptor (VDR), which is essential for activating the VDR pathway, thereby enabling vitamin D to initiate an anti-inflammatory cascade (Touil et al. 2023). Adequate vitamin D levels support neuronal health by affecting neurotrophic factor secretion and enhancing neuronal survival (Touil et al. 2023). Vitamin D supplementation and appropriate sun exposure hold promise in managing MS risk and potentially impacting disease progression. Several randomized control trials (RCTs) investigating the effect of vitamin D supplementation found

that they were only beneficial when patients had an existing vitamin D deficiency. Unfortunately, investigations on the impact of vitamin D on MS are limited by their small sample sizes and short durations. Additional research is needed to elucidate the utility of vitamin D and its implication on the pathophysiology of MS (Waubant et al. 2019).

Obesity has gained recognition as a significant risk factor in the pathophysiology of MS. Observational studies consistently demonstrate an approximate two-fold increased risk of developing pediatric and adult MS in individuals with obesity since adolescence and early adulthood, compared to individuals with normal weight (Alfredsson and Olsson 2019; Waubant et al. 2019). One crucial mechanism linking obesity and MS progression is inflammation. Obesity triggers inflammation by elevating levels of IL-17 and IL-23, thereby promoting the presence of pro-inflammatory Th17 T cells. Furthermore, obesity has been associated with elevated levels of the inflammatory mediator leptin, primarily produced by adipose tissue, which influences immune responses and can exacerbate inflammation in individuals with obesity. Studies have also demonstrated that increased body weight is related to decreased levels of vitamin D availability. Vitamin D deficiency in individuals with obesity can exacerbate inflammation in the body, potentially worsening the course of MS (Touil et al. 2023). Cumulatively, chronic inflammation associated with obesity could potentially impact the progression of MS, which makes addressing it part of the comprehensive management of MS patients.

Cigarette smoke is a well-established risk factor for MS, contributing to the onset and exacerbation of the disease. Even the slightest lung irritation through secondhand smoke is associated with a comparable increased risk for MS as first-hand smoking. This increased risk is primarily attributed to the irritation of lung tissues (Alfredsson and Olsson 2019; Waubant et al. 2019). Some research proposes that smoking may activate immune cells near the airways or may trigger the aryl hydrocarbon receptor, known to influence the immune response (Waubant et al. 2019). Alternative mechanisms have been suggested where smoking has direct effects on the CNS, including the production of NO which can lead to axonal damage, and the potential to directly affect the permeability of the BBB (Correale et al. 2013). The evidence points to a clear and proportional relationship between smoking and the risk of developing MS (Alfredsson and Olsson 2019; Waubant et al. 2019). A study conducted in 2001 involving over 100,000 American women in the Nurses' Health Study (NHS) and NHS II underscored the association between active smoking and a 1.6 times higher incidence of MS compared to non-smokers. This risk escalates with cumulative exposure to tobacco. Additionally, it has been observed that sustained smoking can expedite the progression of MS, particularly toward SPMS, as well as increase disease severity and accelerated progression to disability (Michel 2018). What is intriguing is that smoking heightens the risk of MS regardless of the age at which one is exposed, with both the duration and intensity of smoking contributing independently to this risk (Correale et al. 2013; Michel 2018). Furthermore, individuals who carry the major MS risk allele HLA-DRB1*15:01, without the protective HLA-A2 variant, have an elevated risk of MS. This risk is further magnified in the presence of smoking, underscoring the intricate interplay between genetic

susceptibility and smoking in the context of MS (Alfredsson and Olsson 2019; Michel 2018). Importantly, studies have shown that this risk of MS associated with smoking is reversible, such that if a smoker quits smoking for approximately 10 years, their risk of developing MS can return to a level comparable to that of non-smokers (Michel 2018; Waubant et al. 2019), thus making smoking cessation a promising therapeutic avenue in MS.

1.7 Managing MS

Managing MS requires a multifaceted approach. This includes managing symptoms, providing physiotherapy, and addressing MS relapses. The treatment strategies for MS typically encompass two main approaches. The first approach is a 'gradual escalation' strategy, where treatment begins with a relatively mild or less potent therapy and is adjusted, as needed, based on the patient's response and disease progression. The second approach is a 'higher initial intensity' strategy, which involves starting treatment with a more potent therapy from the outset, with the possibility of reducing its intensity if the patient's condition stabilizes (Travers et al. 2022). For a comprehensive understanding of the current treatments and their implications, a detailed explanation will be available in Chap. 16 of this book.

At the core of MS treatment are disease-modifying therapies (DMTs), which play a pivotal role by reducing relapses and slowing disease progression (Charabati et al. 2023; Travers et al. 2022). This class of medications are categorized into three subgroups: Personalized Medicine, Novel Mechanisms of Action, and Emerging Oral and Infusion Therapies (Robertson and Moreo 2016). Ongoing clinical trials aim to improve the effectiveness, safety, and overall impact of these therapies on the quality of life for individuals with MS (Claflin et al. 2018).

Personalized Medicine tailors treatment based on individual attributes, offering a patient-centered, customized approach to treatment. Tailored treatments can be synthesized through an understanding of the patient's genetic profile, biomarkers, personal preferences, comorbidities, and adherence to therapy (Giovannoni 2017). Novel Mechanisms of Action explore various avenues for targeting the immune system, including therapies that focus on B cells, CD20, sphingosine 1 phosphate (S1P), and alpha-4 integrin interactions (Cross and Naismith 2014; Subei and Cohen 2015).

Emerging oral and infusion therapies, exemplified by monoclonal antibodies, like Ocrelizumab, Ofatumumab, Ublituximab, and immunomodulators, namely Fingolimod, offer promising approaches for managing MS. These treatments selectively target various immune system components to reduce relapses and impede disease progression. Some therapies combat inflammation and impede demyelination, while others focus on restraining lymphocyte activity, preventing their detrimental infiltration into the central nervous system, thereby alleviating inflammation. Additionally, certain treatments modify immune cell trafficking, collectively

working towards more effective MS management (Castro-Borrero et al. 2012; Cross and Naismith 2014; Subei and Cohen 2015).

1.8 Multiple Sclerosis and the Role of Diet

Dietary components and regimens are associated with the progression, relapse rate, and development of MS. Several studies investigated the various regimens and supplements that can modulate the pathogenesis of MS both positively and negatively. Vitamins, such as A and D, and dietary supplements, including caffeine and carnitine, can benefit MS patients (Jakimovski et al. 2019; Nunes and Piuvezam 2019; Tryfonos et al. 2019). Additionally, the literature emphasizes the importance of vitamin D in lowering the risk of developing MS. Vitamin D has been implicated in several studies as an immunomodulator with regulatory effects on the inflammatory processes of MS (Chang et al. 2010; Muthian et al. 2006; Staeva-Vieira and Freedman 2002). In fact, lower vitamin D serum levels have been associated with a poor prognosis (Tryfonos et al. 2019).

Similarly, diets such as the Western or high salt diet (HSD) can negatively impact the prognosis of MS patients. A regimen of dietary components high in salt, saturated fats, and carbohydrates damages the gut microbiome, increasing intestinal permeability and triggering an escalated inflammatory response that promotes demyelination of the CNS (Jayasinghe et al. 2022). The chapters in this book will shed light on the potential role of diet in the development and progression of MS, discuss some of the mechanistic pathways involved in regulating its pathogenesis, and consider the effects of dietary components and regimens on the inflammatory markers linked to MS.

1.9 Summary

This chapter explores MS a chronic central nervous system disease characterized by autoimmune inflammation, demyelination, and axonal degeneration, primarily affecting young adults, especially women. MS presents diverse symptoms like sensory deficits, motor issues, and optic neuritis. Diagnosis involves clinical signs, MRI, cerebrospinal fluid analysis, and evoked potentials. It is classified into relapsing-remitting, secondary progressive, primary progressive, and progressive relapsing subtypes. MS pathophysiology involves immune cells, microglia activation, and inflammatory mediators. Genetic factors, particularly the HLA-DRB1*15:01 allele, and environmental factors such as vitamin D deficiency, obesity, smoking, and Epstein-Barr virus infection contribute to its development. Management includes symptom control, physiotherapy, and DMTs. The chapter also highlights diet as a potential preventive and therapeutic target. Vitamins A and D, caffeine, and carnitine can benefit MS patients, while high-salt, high-fat diets