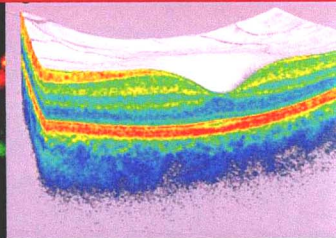
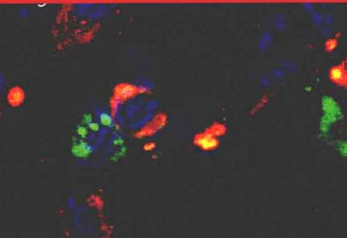
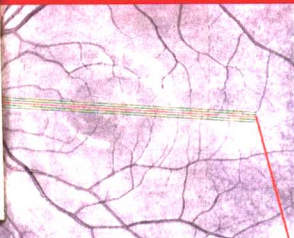


MULTIPLE SCLEROSIS

A Mechanistic View



Edited by
Alireza Minagar



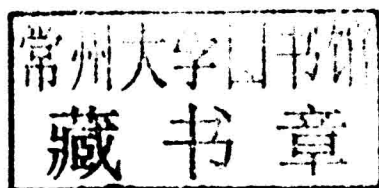
MULTIPLE SCLEROSIS

A MECHANISTIC VIEW

Edited by

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Preface

Multiple sclerosis (MS) is presumably an immune-mediated and neurodegenerative disease of the human central nervous system (CNS), which generally causes irreversible neurologic disability in young adults. As an incurable disease, MS imposes significant medical and financial burdens on patients, their family members, and society, which often leads to devastating outcomes. Despite major leaps in our understanding of the pathophysiology of MS since the 1980s, it remains largely unknown as to why individuals initially develop MS. Such lack of insight into the exact cause of MS translates into our inability to cure MS and, at best, we can only offer certain treatments to slow down disease progression and postpone the beginning the inevitable disability that such a rapidly progressive neurologic ailment creates.

Numerous textbooks and monographs about MS have been published, and the majority of these publications are clinically oriented and target, mainly, clinicians. Few textbooks exist to discuss the fundamental mechanisms involved in MS pathophysiology. The present textbook differs from other traditional books in the sense that it addresses what we know up to now about mechanisms of disease formation and progression in MS. Except for one chapter which briefly addresses the clinical manifestations of MS, the rest of this textbook focuses on pathophysiologic mechanisms involved in MS. The editor and contributors of this unique textbook have intentionally and significantly eliminated the clinical and therapeutic aspects of MS and have concentrated on molecular pathophysiology of this complex and fascinating disease. A panel of brilliant, well-published, and internationally known authors have kindly contributed their magnificent chapters on various aspects of MS pathophysiology. Each chapter addresses a different component of MS pathophysiology and discusses the latest achievements and findings in that field. I am eternally grateful and indebted to these phenomenal neurologists, neuroimagers, neuropathologists, and neuroscientists who made this book a reality.

During the course of preparation of this textbook, we lost a great neurologist and neuroscientist, Dr Istvan Pirko. Dr Pirko was a brilliant neuroimmunologist from the Mayo Clinic, Rochester, MN, USA, whose area of research was imaging of the animal models of MS. After a courageous battle against cancer, he eventually succumbed to this devastating disease. However, during his short life, he achieved much and improved our understanding of MS pathophysiology. I dedicate this book to his

name and memory. To a man who devoted his life to a great cause and for years after his untimely death, the scientific world will benefit from his achievements.

I would like to acknowledge Mrs April Farr, Mr Timothy Bennette, and their production team at Elsevier, Inc. for their dedication, hard work, time, and energy which they spent on this book. Thank you for all of your efforts.

At the end, the editor and the contributors to this interesting book wish that our effort will stimulate the scientific curiosity of other younger colleagues to continue the research on the pathophysiology of MS and find a cure for this progressive disease.

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Contents

Contributors	xi
Preface	xv

1. Clinical Manifestations of Multiple Sclerosis: An Overview

VIJAYKUMAR JAVALKAR, JEANIE MCGEE AND ALIREZA MINAGAR

Introduction	1
Motor and Sensory Manifestations	1
Fatigue	2
Cognitive Decline	3
Psychiatric Manifestations	3
Optic Neuritis and Other Neuroophthalmologic Manifestations	4
Uveitis	4
Uhthoff Phenomenon	5
Pulfrich Phenomenon	5
Brain Stem Involvement in MS	5
Transverse Myelitis	7
Cerebellar Involvement and Tremor in MS	7
Seizures and Other Paroxysmal Features of MS	8
Painful Syndromes	8
Bowel and Bladder Dysfunction	9
Movement Disorders	9
References	10

2. Novel Therapies for Multiple Sclerosis: A Mechanistic View

EMILY V. STEVENSON, JEANIE MCGEE, JONATHAN S. ALEXANDER AND ALIREZA MINAGAR

Introduction	13
Laquinimod	14
Monoclonal Antibodies as Novel Therapies for MS	14
Alemtuzumab	16
Daclizumab	17
Ocrelizumab	17
Ofatumumab	18
Rituximab	18
The Concept of Remyelination as Therapy for MS	18
AntiLINGO-1	19
rHlgM22	19
References	20

3. Role of B Cells in the Pathogenesis of Multiple Sclerosis: Mechanisms of Action

BEHROUZ NIKBIN, MANDANA MOHYEDDIN BONAB, FATEMEH TALEBIAN
AND YADOLLAH SHAKIBA

Introduction	23
Evidence of B Cell Involvement in the Pathogenesis of MS and Factors Pointing to the Limits of T Cell Action	25
The Mechanism of B Cell Action in the Development and Progress of MS	26
The Role of Clonally Expanded B Cells	27
Role of B Cells in Priming/Activating T Cells	27
Regulatory B Cells (Bregs)	29
Memory B Cells	31
The Role of MHC in Triggering MS	32
Conclusion	33
List of Abbreviations	33
References	34

4. Role of CD4⁺ T Cells in the Pathophysiology of Multiple Sclerosis

FUMITAKA SATO, SEIICHI OMURA, S.L. JAFFE AND IKUO TSUNODA

Summary	41
Traditional CNS Inflammation versus "Neuroinflammation"	42
Etiology of MS	44
Physiological and Pathological Roles of CD4 ⁺ T Cell Subsets	46
Classical Th1/Th2 Immunoregulatory Axis in MS and its Animal Models	48
Novel Th17/Treg Immunoregulatory Axis in MS and its Animal Models	51
Do "Gain-of-Function" Changes Affect Susceptibility to MS?	54
"T Cell Exhaustion" as a Protective Mechanism against Immunopathology	56
Protective Roles of PD-1 and TIM-3 in MS and its Animal Models	58
Conclusions	60
Acknowledgments	60
References	60

5. Granulocyte-Macrophage Colony-Stimulating Factor in Central Nervous System Autoimmunity

BOGOLJUB CIRIC, JAVAD RASOULI AND ABDOLMOHAMAD ROSTAMI

Introduction	71
The Role of GM-CSF in EAE	73
GM-CSF Production by T Cells in MS	87
Conclusion	93
References	93

6. Role of Cytokine-Mediated Crosstalk between T Cells and Nonimmune Cells in the Pathophysiology of Multiple Sclerosis

DAISUKE KAMIMURA, YASUNOBU ARIMA, TORU ATSUMI, JIE MENG,
LAVANNYA SABHARWAL, HIDENORI BANDO, HIDEKI OGURA, JING-JING JIANG,
ERIC S. HUSEBY AND MASAOKI MURAKAMI

Introduction	101
Pathogenic Roles of CD4 ⁺ T Cells	103

Pathogenic Roles of CD8 ⁺ T Cells	106
T Cell Subsets with Suppressive Functions	108
Pathogenic Role of Nonimmune Cells: The Inflammation Amplifier	109
The Mechanism of Autoreactive T Cell Invasion into the CNS	113
Conclusion	118
References	118

7. Vitamin D: Role in Pathogenesis of Multiple Sclerosis

VASU SAINI, MOHAMMED NADEEM, CHANNA KOLB, STEVEN GANGLOFF,
ROBERT ZIVADINOV, MURALI RAMANATHAN AND BIANCA WEINSTOCK-GUTTMAN

Introduction	127
Vitamin D and Genetic Susceptibility to MS	134
Vitamin D Deficiency as a Risk Factor for MS	135
Experimental Autoimmune Encephalitis	141
Role of Vitamin D in Disability Progression and Relapses in MS	142
Supplementation of Vitamin D	143
Therapeutic Potential of Vitamin D	144
Closing Remarks	144
References	146

8. Role of Genetic Factors in Pathophysiology of Multiple Sclerosis

AN GORIS, BÉNÉDICTE DUBOIS AND KELLY HILVEN

A Genetic Component to Multiple Sclerosis	153
Identification of Genetic Risk Variants	154
Missing Heritability	159
Association with Disease Phenotype and Therapy Outcome	164
From Gene to Function	168
Concluding Remarks	171
References	171

9. Neuropathology of Multiple Sclerosis

BOGDAN E. GH. POPESCU AND CLAUDIA E. LUCCHINETTI

Introduction	181
Plaque Types	182
Mechanisms of White Matter Demyelination	186
The Pathological Substrate of MS Progression	188
Cortical Demyelination in Early MS	193
Remyelination	195
Conclusion	196
References	197

10. Pathophysiology of Acute Disseminated Encephalomyelitis

RAVINDRA KUMAR GARG, HARDEEP SINGH MALHOTRA AND NEERAJ KUMAR

Introduction	201
Epidemiology	201
Immunopathogenesis of ADEM	202

Pathology of ADEM	228
Do ADEM and MS Represent a Part of Immune-Mediated Spectrum of Demyelinating Disorders?	229
Conclusion	230
References	230
11. Pathophysiology of Experimental Autoimmune Encephalomyelitis	
ALEKSANDAR DENIC, BHARATH WOOLLA, ISTVAN PIRKO AND ASHUTOSH MANGALAM	
Introduction	249
Experimental Autoimmune Encephalomyelitis	250
Immunopathogenesis of EAE	256
Monocytes/Macrophages	269
Concluding Remarks	271
References	272
12. Pathophysiology of Optic Neuritis	
OMAR AL-LOUZI AND SHIV SAIDHA	
Introduction	281
ON in Relation to the Risk of MS	282
Epidemiology of ON in MS	283
The Afferent Visual Pathway	284
Clinical Features of Optic Neuritis	286
Inflammation in Optic Neuritis	288
Demyelination in Optic Neuritis	290
Axonal and Neuronal Degeneration in Optic Neuritis	292
Imaging and Electrophysiologic Correlates of Optic Neuritis	294
Conclusions	302
Disclosures	302
References	302
13. Neurodegeneration and Remyelination in Multiple Sclerosis	
BARDIA NOURBAKSH AND EMMANUELLE WAUBANT	
Introduction	311
Inflammation and Neurodegeneration	315
Conclusion	334
Further Reading	335
14. Mechanisms of Action of Glatiramer Acetate in the Treatment of Multiple Sclerosis	
WILLIAM SHEREMATA AND YESICA CAMPOS	
Section 1	339
Introduction	339
Section 2	343
Impact on Adaptive Immune Responses	343

Section 3	349
Glatiramer Acetate as a Neuroprotective Agent	349
Conclusion	358
References	358

15. Mechanism of Action of Interferon Beta in Treatment of Multiple Sclerosis

ZOHREH HOJATI, MARYAM KAY AND FARIBA DEHGHANIAN

Introduction	365
IFN β Signaling Pathway	366
Association between Molecular Defects in IFN β Signaling and MS Pathogenesis	368
Modifying the Immune Response due to Effects on Multiple Cell Types	369
Therapeutic Effects of IFN β through Targeting B Cells' Functions	370
Effects of IFN β on DCs	370
IFN β Blocks T Cell Activation	371
Downregulation of MHC II Expression	372
Inhibition of Coactivators Interaction	374
Upregulation of Death Receptors and CTLA4 on the T Cell Surface	375
The Effect of IFN β in Cytokine Shift	377
The BBB in the Pathogenesis of MS	379
Mechanisms of Action of IFN β at the BBB	381
ECAMs and Junctional Proteins	381
Chemokines and Chemokines Receptors	382
MMPs and CD73 Protein	383
The Effect of IFN β in the CNS	384
MS and miRNAs	387
Vitamin D and IFN β Treatments in MS	389
References	390

16. Mechanisms of Blood–Brain Barrier Disintegration in the Pathophysiology of Multiple Sclerosis

EMILY V. STEVENSON, JONATHAN S. ALEXANDER, J. WINNY YUN, FELIX BECKER, EDUARDO GONZALEZ-TOLEDO AND ALIREZA MINAGAR

The Blood–Brain Barrier: Normal Anatomy and Physiology	393
BBB Disintegration in MS: A Mechanistic Picture	397
Chemokines and Cytokines in MS	402
Role of Cell-Derived Microparticles in the Pathogenesis of MS	406
MRI and Blood–Brain Disintegration in MS	406
Conclusion	407
References	407

17. Mechanisms and Potentials of Stem Cells in the Treatment of Multiple Sclerosis: The Unpaved Path

MANDANA MOHYEDDIN BONAB, YADOLLAH SHAKIBA, FATEMEH TALEBIAN AND BEHROUZ NIKBIN

Introduction	415
Neural Progenitor/Stem Cells (NP/SCs): Mechanism of Function	417

Mesenchymal Stem Cells: Mechanisms of Function	420
Hematopoietic Stem Cells	424
Embryonic Stem Cells and Induced Pluripotent Stem Cells	427
Allogenic Stem Cell Therapy	429
Conclusion	430
List of Abbreviations	430
References	431

18. Role of Neuroimaging in Multiple Sclerosis

ROBERT ZIVADINOV

Introduction	443
Conventional MRI Techniques	445
Nonconventional MRI Techniques	457
Conclusions	467
List of Abbreviations	468
References	469

19. Pathophysiology of Lymphatic Drainage of the Central Nervous System: Implications for the Pathophysiology of Multiple Sclerosis

ROY O. WELLER, ROXANA O. CARARE, CHERYL A. HAWKES AND
IAN GALEA

Introduction	479
Lymphatic Drainage of CSF	482
Lymphatic Drainage of ISF from the Brain Parenchyma	484
Evidence for Lymphatic Drainage of the Human Brain	486
Age-Related Deterioration of Perivascular Lymphatic Drainage of the Brain	487
Motive Force for Perivascular Lymphatic Drainage	489
Temporary Impairment of Perivascular Drainage by Immune Complexes	489
Pathophysiology of Perivascular Macrophages	490
Interrelationship between CSF and ISF	491
Immunological Significance of Lymphatic Drainage of the Brain and Implications for MS	493
Conclusions	496
References	496

Index	503
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Clinical Manifestations of Multiple Sclerosis: An Overview

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INTRODUCTION

Multiple sclerosis (MS) is a presumably immune-mediated, demyelinating, and neurodegenerative disease of the human central nervous system, which usually affects young adults and causes significant irreversible neurological disability. Up to 85% of newly diagnosed MS patients have relapsing–remitting (RR) disease which is characterized by periods of development of new or worsening of older neurological deficits followed by complete or partial improvement. In most cases, MS manifests between the ages of 20 and 40, with a peak age of 29 and females being predominantly affected, at least in the most common form of MS. MS lesions develop in various areas of the brain and spinal cord which, in turn, lead to the development of a wide array of clinical manifestations. In many cases the neurologic manifestations of MS present episodically and then advance to a progressive phase with steady accumulation of neurologic deficits. In many patients the severity and complexity of clinical manifestations of MS are severe and devastating and significantly compromise the patient's quality of life. The present chapter presents an overview of MS clinical features.

MOTOR AND SENSORY MANIFESTATIONS

Weakness is a common finding in MS patients and significantly stems from the involvement of corticospinal tract. Patients describe their weakness as heaviness, stiffness, or giving way under their weight of their

extremities. The lower extremities are more commonly and usually earlier affected than the upper extremities. Weakness begins in one lower extremity; however, both lower extremities eventually are affected. The weakness is usually associated with hyperactive reflexes and increased tone in the lower extremities, and many patients present with spastic paraparesis. Clonus is present at the ankle, and examination of these patients also reveals extensor plantar responses. Spasticity of the upper, lower, or four extremities is also a significant finding and may interfere with the patient's gait and other physical activities.

Sensory symptoms, including numbness, pins and needles sensation, dysesthetic pain, tingling, and burning, are among the most common complaints of MS patients and often present early in its clinical course. These sensory presentations may be more indicative of the demyelination of the posterior columns than spinothalamic tracts. Neurologic examination of these patients may reveal impairment and decrease in feeling of the vibration and abnormalities in fine touch and joint position senses. Pinprick and temperature sensations are less commonly affected over the course of MS. An interesting sensory symptom of MS is Lhermitte's sign wherein the patient experiences an acute feeling of electric shock sensation which travels down the spine and the extremities. This event occurs when the individual bends the neck forward. A number of painful sensory experiences in MS patients include persistent and painful dysesthesia, burning pain, and painful cramps and spasms of the muscles, particularly in the lower extremities.

FATIGUE

Mental and physical fatigue constitutes the most common problem voiced by MS patients. Many report an increase of their fatigue prior to and during the clinical exacerbation. During pathophysiology of MS, the demyelination of the axons leads to tardy and desynchronized transmission of nervous impulses to the point that the impulse conduction may completely cease. Interestingly, exposure to heat intensifies the fatigue in MS patients. They describe fatigue as an unusual and overwhelming feeling of mental and physical exhaustion, which is worse with heat exposure and may slightly improve with rest and sleep. Fatigue significantly restricts patients' mental and physical activity and adversely affects their performance on neuropsychological evaluations. Fatigue is worse during relapses of MS and does not show any meaningful correlations with brain magnetic resonance imaging (MRI) parameters such as gadolinium-enhancing lesions, lesion load, or any known inflammatory biomarkers. Primary mechanisms for fatigue in MS include pro-inflammatory cytokines, endocrine influences, axonal loss, and altered patterns of cerebral