

Mimics and Red Flags of Multiple Sclerosis

Tomas Uher

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“Life is like riding a bicycle. To keep your balance, you must keep moving.” (A. Einstein)

I dedicate my work to my patients, colleagues, friends, my family, and all good people. I would also like to express my gratitude to Professor Andrew J. Solomon for his valuable suggestions and for writing the foreword.

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This book has been written entirely by the author. ChatGPT, an AI language model, was utilized solely for correcting English grammar. The content, concepts, and ideas presented in this book remain the original work of the author.

The figures were created with Zoner Photo Studio X.

Foreword

The clinical and radiological heterogeneity of multiple sclerosis (MS) is widely acknowledged, and an accessible, highly sensitive and specific biomarker for MS remains an unmet need in clinical practice. Consequently, accurate diagnosis of MS relies upon clinical acumen that requires a breadth of knowledge for its differential diagnosis. Although MS diagnostic criteria have evolved over the last 60 years, each has relied upon the concept of “no better explanation” as a key element: disorders that may mimic MS must be considered and ruled out in order to diagnose MS.

Advancement in knowledge, particularly over the last decade, has required changes in clinical approaches to MS differential diagnosis. There has been increased recognition of neuroinflammatory disorders that may present with syndromes typical of MS. Newly identified clinical, laboratory, and radiological findings increasingly aid differentiation of these and other disorders from MS. In tandem, data from an expanding spectrum of clinical and radiological presentations previously considered atypical or insufficient for diagnosis challenge the boundaries of MS diagnostic criteria. Importantly, in this context, recent data also increasingly suggest that MS misdiagnosis is prevalent and associated with unnecessary medical risk and morbidity. In some cohorts, misdiagnosis has been identified in approximately one in seven patients who carry a diagnosis of MS. In sum, these recent developments inform optimal and nuanced approaches to MS differential diagnosis that necessitate greater expertise than was required in the past.

Mimics and Red Flags of Multiple Sclerosis by Dr. Tomáš Uher is a new and essential resource that will help inform the clinical care of patients where diagnosis of MS is being considered. This impressive accomplishment systematically and thoughtfully tackles the often daunting breadth of MS differential diagnosis. Comprehensive yet easy to navigate, its practical organization allows readers to quickly find disorders of interest. Each entry is accompanied by an efficient description of key clinical, laboratory, and radiological findings to facilitate accurate diagnosis. These findings are further enriched by a differential diagnosis provided for each disorder. Enhanced figures helpfully highlight MRI features that point to specific diagnoses. Updated data surrounding disease epidemiology, pathobiology, prognosis, and treatment complement diagnostic considerations to further aid

clinical care. This exceptionally detailed and thoroughly cited compendium will serve as a principal reference for clinicians navigating MS differential diagnosis in practice for many years to come.

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Preface

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) presenting with a wide spectrum of clinical and radiological phenotypes. In clinical practice, many patients with MS are initially misdiagnosed with other medical conditions (false-negative diagnosis). Furthermore, patients with various medical conditions are incorrectly diagnosed with MS (false-positive diagnosis). Additionally, in some patients, when an alternative diagnosis is suspected, neither a comprehensive assessment nor observing the disease course over time provides any clues for an alternative diagnosis to MS. The relatively high frequency of MS misdiagnosis is due to the challenging differential diagnosis, which is mainly caused by the following reasons:

- MS has no specific biomarkers, and the diagnosis is made when no other explanations are found for the patient's neurological manifestations (diagnosis per exclusionem).
- The spectrum of alternative diagnoses that mimic MS is very broad.
- MS mimics include several very rare diagnoses, which may be unknown to clinicians owing to their rarity. Diagnosing these conditions may require complex and detailed genetic or metabolic assessments that may not be routinely available.
- There is increasing pressure to diagnose MS early because early treatment initiation is associated with better disease outcomes. However, the growing number of patients seen in practice, decreasing consultation times, and the urgency to start immuno-modulatory treatment (DMT) as soon as possible may lead to limited time for observing the disease course and thorough evaluation by physicians, potentially increasing the risk of misdiagnosis.
- The MS patient population is heterogeneous, and it is possible that a proportion of patients with atypical phenotypes diagnosed with MS have yet undefined or undiscovered diseases. Advances in research may result in discoveries of new diagnoses in the future, like how anti-aquaporin-4 (AQP4) IgG was identified 20 years ago and anti-myelin oligodendrocyte glycoprotein (MOG) IgG approximately 10 years ago.
- Incorrect application of the McDonald diagnostic criteria for MS.
- Geographically variable awareness of MS manifestations among the public and healthcare professionals, along with a shortage of neurologists with adequate

training and limited access to diagnostic equipment in some low- and middle-income countries.

Misdiagnosis of MS is a significant issue because it is associated with potential serious consequences:

- **False-Negative Diagnosis:** This leads to either late initiation or non-initiation of immunomodulatory treatment, which is associated with poorer prognosis of MS.
- **Untargeted Treatment:** Misdiagnosis prevents targeted treatment of the underlying medical condition, which may lead to disease progression and worse disease outcomes (e.g., not using enzyme replacement therapy in Fabry disease or biotin supplementation in patients with biotinidase deficiency).
- **Missed Genetic Counseling:** Patients with unrecognized or late-diagnosed inherited genetic diseases may miss opportunities for genetic counseling, aiding in family planning or prenatal diagnosis.
- **Negative Impact of MS Treatments:** Some treatments used for MS in patients with alternative diagnoses may have serious adverse effects (e.g., alemtuzumab, dimethyl-fumarate, glatiramer-acetate, interferons, natalizumab or S1P inhibitors in neuromyelitis optica spectrum disorder [NMOSD]; interferons in Susac's syndrome; immunosuppressive drugs in infectious diseases; natalizumab causing progressive multi-focal leukoencephalopathy [PML]; or alemtuzumab triggering autoimmune diseases).
- **High Financial Burden:** MS treatments are associated with high medical costs [1–7].

Neurologists may not frequently encounter patients with MS who present with atypical clinical courses, imaging findings, or biochemical abnormalities. However, managing these patients—who may have suspected alternative diagnoses to MS—can be extremely time-consuming. This is due to the lack of treatment response and the need for comprehensive assessments to rule out a wide range of potential diagnoses, often resulting in negative findings.

Given the wide range of MS mimickers, it is intellectually challenging to consider all alternative diagnoses and choose a rational diagnostic algorithm that is supported by red flags, rather than resorting to an expensive “fishing expedition” of examining everything. To address these concerns, my goal was to investigate further the differential diagnosis of MS. This investigation resulted in the creation of the book, where I have summarized contemporary knowledge on the manifestations and diagnosis of the most important MS mimickers in a structured manner.

The main aim of this work is to provide an inspiration for alternative diagnoses of MS when managing difficult or atypical cases of patients with potential diagnosis of MS and related demyelinating disorders.

This book has some limitations:

- **Scope:** The field is vast; therefore, only essential information on the clinical and paraclinical features of various conditions is provided. For a more in-depth understanding of specific diagnoses, consulting specialized literature is recommended.
- **Illustrations:** Real magnetic resonance scans have been replaced with scan-cartoon hybrid illustrations to enhance clarity and educational value.
- **Author's Experience:** This work is not based on extensive personal experience with patients diagnosed with the full spectrum of rare MS mimickers. Some of the diagnoses included are known to the author solely from the literature.
- **Consequently,** this work may contain inaccuracies, particularly when presenting information from non-neurological specialties such as radiology, genetics, and biochemistry. I sincerely apologize for any potential errors and encourage readers to share their feedback (tomas.uher@vfn.cz or tomauher@gmail.com).

Despite these limitations, I hope this work inspires clinicians to carefully consider differential diagnoses in complex cases and proves valuable in their clinical practice.

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Competing Interests

The author has no competing interests to declare that are relevant to the content of this manuscript.

Contents

1	Multiple Sclerosis (MS)	1
1.1	Epidemiology	1
1.2	Etiology and Definition	1
1.3	Clinical Features	2
1.4	Disease Course	3
1.5	Brain Imaging	4
1.6	Spinal Cord Imaging	8
1.7	Blood Work	10
1.8	Examination of CSF	10
1.9	Kappa Free Light Chain	11
1.10	Fundoscopy	11
1.11	OCT	12
1.12	Electrophysiological Studies	12
1.13	Diagnosis of Relapsing-Remitting MS	14
1.14	Diagnosis of Radiologically Isolated Syndrome (RIS)	15
1.15	Diagnosis of Clinically Isolated Syndrome (CIS)	16
1.16	Diagnosis of Primary Progressive MS (PPMS)	17
1.17	The McDonald 2024 Diagnostic Criteria	17
1.18	Treatment	18
1.19	Prognosis	19
	References	19
2	Autoimmune Demyelinating Diseases of Central Nervous System (CNS)	25
2.1	Acute Disseminated Encephalomyelitis (ADEM)	25
2.1.1	Epidemiology	25
2.1.2	Etiology and Definition	25
2.1.3	Clinical Features	26
2.1.4	Disease Course	26
2.1.5	Brain Imaging	27
2.1.6	Spinal Cord Imaging	28
2.1.7	Blood Work	29
2.1.8	Examination of CSF	29
2.1.9	Electrophysiology	30

2.1.10	Diagnosis	30
2.1.11	Differential Diagnosis	30
2.1.12	Treatment and Prognosis	30
2.2	Acute Hemorrhagic Leukoencephalitis (AHLE)	31
2.2.1	Synonyms.	31
2.2.2	Epidemiology	31
2.2.3	Etiology and Definition	31
2.2.4	Clinical Features	31
2.2.5	Brain and Spinal Cord Imaging	31
2.2.6	Blood Work	31
2.2.7	Examination of CSF.	31
2.2.8	Diagnosis	32
2.2.9	Differential Diagnosis	32
2.2.10	Treatment and Prognosis	32
2.3	Autoimmune Glial Fibrillary Acidic Protein (GFAP) Astrocytopathy	33
2.3.1	Epidemiology.	33
2.3.2	Etiology and Definition	33
2.3.3	Clinical Features	33
2.3.4	Disease Course.	34
2.3.5	Brain Imaging	34
2.3.6	Spinal Cord Imaging	34
2.3.7	Blood Work	35
2.3.8	Examination of CSF.	35
2.3.9	OCT	36
2.3.10	Electrophysiology	36
2.3.11	Diagnosis	36
2.3.12	Differential Diagnosis	36
2.3.13	Treatment and Prognosis	37
2.4	Baló Concentric Sclerosis	37
2.4.1	Epidemiology.	37
2.4.2	Etiology and Definition	37
2.4.3	Clinical Features	38
2.4.4	Disease Course.	38
2.4.5	Brain Imaging	38
2.4.6	Spinal Cord Imaging	39
2.4.7	Blood Work	39
2.4.8	Examination of CSF.	40
2.4.9	Diagnosis	40
2.4.10	Differential Diagnosis	40
2.4.11	Treatment and Prognosis	40
2.5	Combined Central and Peripheral Demyelination	40
2.5.1	Synonyms.	40
2.5.2	Epidemiology.	41
2.5.3	Etiology and Definition	41

2.5.4	Clinical Features	41
2.5.5	Disease Course.	41
2.5.6	Brain Imaging	42
2.5.7	Spinal Cord Imaging	42
2.5.8	Blood Work	42
2.5.9	Examination of CSF.	42
2.5.10	OCT	42
2.5.11	Electrophysiology	42
2.5.12	Diagnosis	42
2.5.13	Differential Diagnosis	43
2.5.14	Treatment and Prognosis	43
2.6	Idiopathic Acute Transverse Myelitis	43
2.6.1	Epidemiology	43
2.6.2	Etiology and Definition	43
2.6.3	Clinical Features	44
2.6.4	Brain Imaging	44
2.6.5	Spinal Cord Imaging	44
2.6.6	Blood Work	45
2.6.7	Examination of CSF.	45
2.6.8	Diagnosis	46
2.6.9	Differential Diagnosis	46
2.6.10	Treatment and Prognosis	46
2.7	Marburg’s Variant of Multiple Sclerosis	47
2.7.1	Epidemiology	47
2.7.2	Etiology and Definition	47
2.7.3	Clinical Features	47
2.7.4	Disease Course.	47
2.7.5	Brain Imaging	47
2.7.6	Spinal Cord Imaging	48
2.7.7	Blood Work	48
2.7.8	Examination of CSF.	48
2.7.9	Diagnosis	48
2.7.10	Treatment and Prognosis	48
2.8	Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease (MOGAD)	48
2.8.1	Epidemiology	48
2.8.2	Etiology and Definition	49
2.8.3	Disease Course.	49
2.8.4	Optic Neuritis (Clinical and Imaging Features).	49
2.8.5	Transverse Myelitis (Clinical and Imaging Features)	51
2.8.6	ADEM (Clinical and Imaging Features)	52
2.8.7	Cerebral Cortical Encephalitis	53
2.8.8	Brain Parenchymal Manifestations	53
2.8.9	Blood Work	55
2.8.10	Examination of CSF.	57

2.8.11	OCT	57
2.8.12	Electrophysiology	58
2.8.13	Diagnosis	58
2.8.14	Differential Diagnosis	58
2.8.15	Treatment and Prognosis	59
2.9	Neuromyelitis Optica Spectrum Disorders (NMOSD)	59
2.9.1	Synonyms.	59
2.9.2	Definition	59
2.9.3	Epidemiology	59
2.9.4	Etiology	60
2.9.5	Clinical Features	60
2.9.6	Disease Course.	62
2.9.7	Optic Nerve Imaging	62
2.9.8	Brain Imaging	63
2.9.9	Spinal Cord Imaging	64
2.9.10	Imaging Red Flags for NMOSD	67
2.9.11	Blood Work	67
2.9.12	Examination of CSF.	68
2.9.13	Laboratory Red Flags for NMOSD	69
2.9.14	OCT	69
2.9.15	Electrophysiological Studies	69
2.9.16	Diagnosis	69
2.9.17	Differential Diagnosis	71
2.9.18	Treatment.	77
2.9.19	Prognosis	78
2.10	Post- and Para-Infectious Myelitis and Optic Neuritis	78
2.11	Schilder’s Disease	78
2.11.1	Synonym	78
2.11.2	Epidemiology.	78
2.11.3	Etiology and Definition	78
2.11.4	Clinical Features	79
2.11.5	Disease Course.	79
2.11.6	Brain Imaging	79
2.11.7	Spinal Cord Imaging	79
2.11.8	Blood Work	80
2.11.9	Examination of CSF.	80
2.11.10	Diagnosis	80
2.11.11	Differential Diagnosis	80
2.11.12	Treatment and Prognosis	81
2.12	Solitary Sclerosis	81
2.12.1	Epidemiology	81
2.12.2	Etiology and Definition	81
2.12.3	Clinical Features	81
2.12.4	Disease Course.	81
2.12.5	Brain and Spinal Cord Imaging	82

2.12.6	Blood Work	82
2.12.7	Examination of CSF.	83
2.12.8	Electrophysiology	83
2.12.9	Diagnosis	83
2.12.10	Differential Diagnosis	83
2.12.11	Treatment and Prognosis	83
2.13	Tumefactive Multiple Sclerosis	84
2.13.1	Epidemiology	84
2.13.2	Etiology and Definition	84
2.13.3	Clinical Features	84
2.13.4	Brain Imaging	84
2.13.5	Spinal Cord Imaging	85
2.13.6	Examination of CSF.	86
2.13.7	Diagnosis	86
2.13.8	Differential Diagnosis	87
2.13.9	Treatment and Prognosis	87
	References.	87
3	Autoimmune Non-demyelinating Diseases of Nervous System.	99
3.1	Atopic Myelitis	99
3.1.1	Synonym	99
3.1.2	Epidemiology.	99
3.1.3	Etiology and Definition	99
3.1.4	Clinical Features	100
3.1.5	Disease Course.	100
3.1.6	Brain Imaging	100
3.1.7	Spinal Cord Imaging	100
3.1.8	Blood Work	101
3.1.9	Examination of CSF.	102
3.1.10	Diagnosis	102
3.1.11	Differential Diagnosis	102
3.1.12	Treatment and Prognosis	102
3.2	Autoimmune Encephalitis with Antibodies Against Neuronal Surface	103
3.2.1	Epidemiology.	103
3.2.2	Etiology and Definition	103
3.2.3	Clinical Features	103
3.2.4	Disease Course.	104
3.2.5	Brain and Spinal Cord Imaging	105
3.2.6	Blood Work	106
3.2.7	Examination of CSF.	107
3.2.8	Biopsy	108
3.2.9	Diagnosis	108
3.2.10	Differential Diagnosis	108
3.2.11	Treatment and Prognosis	109

3.3	Bickerstaff’s Brainstem Encephalitis.	109
3.3.1	Epidemiology	109
3.3.2	Etiology and Definition	109
3.3.3	Clinical Features	110
3.3.4	Disease Course.	110
3.3.5	Brain Imaging	111
3.3.6	Spinal Cord Imaging	111
3.3.7	Blood Work	112
3.3.8	Examination of CSF.	112
3.3.9	Electrophysiology	112
3.3.10	Diagnosis	112
3.3.11	Differential Diagnosis	112
3.3.12	Treatment and Prognosis	113
3.4	Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS)	113
3.4.1	Epidemiology.	113
3.4.2	Etiology and Definition	113
3.4.3	Clinical Features	113
3.4.4	Disease Course.	114
3.4.5	Brain Imaging	114
3.4.6	Spinal Cord Imaging	115
3.4.7	Blood Work	115
3.4.8	Examination of CSF.	115
3.4.9	Diagnosis	116
3.4.10	Differential Diagnosis	116
3.4.11	Treatment and Prognosis	117
3.5	Hashimoto Encephalopathy	117
3.6	Myasthenia Gravis	118
3.6.1	Epidemiology.	118
3.6.2	Etiology and Definition	118
3.6.3	Clinical Features	118
3.6.4	Brain and Spinal Cord Imaging	118
3.6.5	Blood Work	118
3.6.6	Examination of CSF.	118
3.6.7	Electrophysiology	119
3.6.8	Diagnosis	119
3.6.9	Differential Diagnosis	119
3.6.10	Treatment and Prognosis	119
3.7	Primary Angiitis of the CNS (PACNS)	119
3.7.1	Synonyms.	119
3.7.2	Epidemiology.	119
3.7.3	Etiology and Definition	120
3.7.4	Clinical Features	120
3.7.5	Disease Course.	120

3.7.6	Brain Imaging	120
3.7.7	Spinal Cord Imaging	122
3.7.8	Clinico-radiological Phenotypes of the PACNS	122
3.7.9	Blood Work	123
3.7.10	Examination of CSF.	123
3.7.11	OCT and Ophthalmological Assessment	124
3.7.12	Diagnosis	124
3.7.13	Differential Diagnosis	124
3.7.14	Treatment and Prognosis	126
	References.	126
4	Autoimmune and Inflammatory Multisystem Diseases.	131
4.1	Anti-phospholipid Syndrome.	131
4.1.1	Epidemiology.	131
4.1.2	Etiology and Definition	131
4.1.3	Subtypes.	131
4.1.4	Non-neurological Clinical Features.	132
4.1.5	Neurological Clinical Features	132
4.1.6	Ocular Features	133
4.1.7	Brain Imaging	133
4.1.8	Spinal Cord Imaging	134
4.1.9	Blood Work	135
4.1.10	Examination of CSF.	135
4.1.11	Electrophysiology	135
4.1.12	Diagnosis	135
4.1.13	Differential Diagnosis	136
4.1.14	Treatment and Prognosis	137
4.2	Behçet's Disease	137
4.2.1	Epidemiology.	137
4.2.2	Etiology and Definition	138
4.2.3	Non-neurological Clinical Features.	138
4.2.4	Neurological Clinical Features	138
4.2.5	Disease Course.	140
4.2.6	Brain Imaging	140
4.2.7	Spinal Cord Imaging	141
4.2.8	Blood Work	141
4.2.9	Examination of CSF.	142
4.2.10	OCT	143
4.2.11	Electrophysiology	143
4.2.12	Diagnosis	143
4.2.13	Differential Diagnosis	143
4.2.14	Treatment and Prognosis	144
4.3	Celiac Disease	144
4.3.1	Epidemiology.	144

4.3.2	Etiology and Definition	144
4.3.3	Non-neurological Clinical Features	144
4.3.4	Neurological Clinical Features	145
4.3.5	Brain Imaging	145
4.3.6	Spinal Cord Imaging	145
4.3.7	Blood Work	145
4.3.8	Examination of CSF.	146
4.3.9	Electrophysiology	146
4.3.10	Diagnosis	146
4.3.11	Differential Diagnosis	147
4.3.12	Treatment and Prognosis	147
4.4	Churg–Strauss Syndrome.	147
4.4.1	Synonyms.	147
4.4.2	Epidemiology.	147
4.4.3	Etiology and Definition	147
4.4.4	Clinical Features	148
4.4.5	Brain Imaging	149
4.4.6	Spinal Cord Imaging	149
4.4.7	Blood Work	150
4.4.8	Examination of CSF.	150
4.4.9	Diagnosis	150
4.4.10	Differential Diagnosis	150
4.4.11	Treatment and Prognosis	150
4.5	Cogan’s Syndrome.	151
4.5.1	Epidemiology.	151
4.5.2	Etiology and Definition	151
4.5.3	Clinical Features	151
4.5.4	Disease Course.	152
4.5.5	Brain Imaging	152
4.5.6	Spinal Cord Imaging	152
4.5.7	Blood Work	152
4.5.8	Examination of CSF.	152
4.5.9	Diagnosis	153
4.5.10	Differential Diagnosis	153
4.5.11	Treatment and Prognosis	153
4.6	Cytotoxic T Lymphocyte Antigen 4 (CTLA-4) Haploinsufficiency.	154
4.6.1	Epidemiology.	154
4.6.2	Etiology and Definition	154
4.6.3	Non-neurological Features.	154
4.6.4	Neurological Features	154
4.6.5	Disease Course.	155
4.6.6	Brain Imaging	155
4.6.7	Spinal Cord Imaging	155
4.6.8	Blood Work	155

4.6.9	Examination of CSF.	156
4.6.10	Diagnosis	156
4.6.11	Treatment and Prognosis	156
4.7	IgG4-Related Disease	157
4.7.1	Epidemiology	157
4.7.2	Etiology and Definition	157
4.7.3	Non-neurological Features.	157
4.7.4	Neurological Features	157
4.7.5	Disease Course.	158
4.7.6	Brain and Spinal Cord Imaging	159
4.7.7	Blood Work	159
4.7.8	Examination of CSF.	159
4.7.9	Diagnosis	159
4.7.10	Differential Diagnosis	160
4.7.11	Treatment and Prognosis	160
4.8	Inflammatory Bowel Disease.	160
4.8.1	Epidemiology.	160
4.8.2	Etiology and Definition	160
4.8.3	Intestinal Features	161
4.8.4	Extraintestinal Non-neurological Features	161
4.8.5	Neurological Features	161
4.8.6	Brain Imaging	161
4.8.7	Spinal Cord Imaging	162
4.8.8	Examination of Blood and CSF.	162
4.8.9	Diagnosis	162
4.8.10	Differential Diagnosis	163
4.8.11	Treatment.	163
4.9	Rheumatoid Arthritis	163
4.9.1	Epidemiology.	163
4.9.2	Etiology and Definition	163
4.9.3	Joint and Systemic Features.	164
4.9.4	Neurological and Imaging Features Related to RA.	164
4.9.5	Neurological and Imaging Features Unrelated to RA	165
4.9.6	Neurological and Imaging Features Related to Anti-TNF Drugs.	165
4.9.7	Blood Work	166
4.9.8	Examination of CSF.	166
4.9.9	Diagnosis	166
4.9.10	Treatment and Prognosis	166
4.10	Sarcoidosis.	167
4.10.1	Epidemiology	167
4.10.2	Etiology and Definition	167
4.10.3	Non-neurological Clinical Features.	167
4.10.4	Cranial Neuropathy	168
4.10.5	Aseptic Meningitis.	169

4.10.6	Hypothalamic/Pituitary Infiltration	170
4.10.7	Brain Parenchymal Lesions	170
4.10.8	Encephalopathy	171
4.10.9	Vascular Disease	171
4.10.10	Myelopathy	171
4.10.11	Peripheral Involvement	172
4.10.12	Disease Course.	174
4.10.13	Blood Work	174
4.10.14	Examination of CSF.	174
4.10.15	Diagnosis	175
4.10.16	Differential Diagnosis	175
4.10.17	Treatment and Prognosis	176
4.11	Sjogren’s Syndrome.	176
4.11.1	Synonyms.	176
4.11.2	Epidemiology.	176
4.11.3	Etiology and Definition	177
4.11.4	Subtypes.	177
4.11.5	Glandular Features.	177
4.11.6	Extra-glandular Systemic Features	178
4.11.7	Neurological Features	178
4.11.8	Disease Course of Neurological Manifestations	180
4.11.9	Brain Imaging	180
4.11.10	Spinal Cord Imaging	180
4.11.11	Ultrasonography.	180
4.11.12	Blood Work	180
4.11.13	Examination of CSF.	181
4.11.14	OCT	181
4.11.15	Electrophysiology	182
4.11.16	Diagnosis	182
4.11.17	Differential Diagnosis	183
4.11.18	Treatment.	184
4.11.19	Prognosis	184
4.12	Susac’s Syndrome	185
4.12.1	Synonyms.	185
4.12.2	Epidemiology.	185
4.12.3	Etiology and Definition	185
4.12.4	Clinical Features	185
4.12.5	Disease Course.	187
4.12.6	Brain Imaging	187
4.12.7	Spinal Cord Imaging	188
4.12.8	Blood Work	189
4.12.9	Examination of CSF.	189
4.12.10	OCT	189
4.12.11	Histology	189

4.12.12	Diagnosis	189
4.12.13	Differential Diagnosis	190
4.12.14	Treatment and Prognosis	191
4.13	Systemic Lupus Erythematosus (SLE)	191
4.13.1	Epidemiology	191
4.13.2	Etiology and Definition	192
4.13.3	Non-neurological Systemic Features	192
4.13.4	Neurological Features	192
4.13.5	Disease Course.	194
4.13.6	Brain Imaging	194
4.13.7	Spinal Cord Imaging	195
4.13.8	Blood Work	195
4.13.9	Examination of CSF.	195
4.13.10	Examination of Blood and CSF in Different Subtypes of Demyelinative NPSLE.	196
4.13.11	Diagnosis of SLE.	197
4.13.12	Diagnosis of NPSLE	197
4.13.13	Differential Diagnosis	198
4.13.14	Treatment.	199
4.13.15	Prognosis	199
4.14	Other Autoimmune Multisystem Diseases.	199
4.14.1	Ankylosing Spondylitis	199
4.14.2	Relapsing Polychondritis.	200
4.14.3	Sneddon's Syndrome	200
4.14.4	Systemic Sclerosis and Localized Scleroderma.	201
	References.	201
5	Infectious Diseases	215
5.1	Brain Abscess.	215
5.1.1	Epidemiology.	215
5.1.2	Etiology and Definition	215
5.1.3	Clinical Features	216
5.1.4	Brain Imaging	216
5.1.5	Blood Work	217
5.1.6	Examination of CSF.	217
5.1.7	Diagnosis	218
5.1.8	Differential Diagnosis	218
5.1.9	Treatment and Prognosis	218
5.2	Brucellosis	218
5.2.1	Synonyms.	218
5.2.2	Epidemiology.	218
5.2.3	Etiology and Definition	219
5.2.4	Disease Course.	219
5.2.5	Systemic Clinical Features.	219
5.2.6	Neurological Features	219

5.2.7	Brain Imaging	220
5.2.8	Spinal Cord Imaging	220
5.2.9	Blood Work	220
5.2.10	Examination of CSF.	221
5.2.11	Diagnosis	221
5.2.12	Differential Diagnosis	221
5.2.13	Treatment and Prognosis	221
5.3	COVID-19	222
5.3.1	Etiology and Definition	222
5.3.2	Respiratory Disease	222
5.3.3	Neurological Involvement	222
5.3.4	Diagnosis	223
5.3.5	Differential Diagnosis:	223
5.3.6	Treatment and Prevention	224
5.4	Epstein–Barr Virus (EBV)	224
5.4.1	Etiology	224
5.4.2	Non-neurological Features of Acute Infection.	224
5.4.3	Neurological Clinical, Imaging, and Laboratory Features	224
5.4.4	Diagnosis	225
5.4.5	Treatment	226
5.5	Hepatitis C (HCV)	226
5.5.1	Epidemiology	226
5.5.2	Etiology	226
5.5.3	Hepatic Clinical Features.	226
5.5.4	Extrahepatic Non-neurological Clinical Features	227
5.5.5	Neurological Clinical Features and Imaging	227
5.5.6	Blood Work	229
5.5.7	Examination of CSF.	229
5.5.8	Diagnosis	229
5.5.9	Treatment and Prognosis	229
5.6	Herpes Simplex Virus (HSV) Infections	229
5.6.1	Epidemiology	229
5.6.2	Cause and Definition	230
5.6.3	Clinical Features	230
5.6.4	Brain Imaging in HSV Encephalitis	230
5.6.5	Spinal Cord Imaging	231
5.6.6	Blood Work	231
5.6.7	Examination of CSF.	232
5.6.8	Diagnosis	232
5.6.9	Differential Diagnosis	232
5.6.10	Treatment and Prognosis	232
5.7	Human Immunodeficiency Virus (HIV).	233
5.7.1	Epidemiology	233
5.7.2	Etiology and Definition	233
5.7.3	Clinical Features	233

5.7.4	Brain Imaging	235
5.7.5	Spinal Cord Imaging	236
5.7.6	Blood Work	236
5.7.7	Examination of CSF.	236
5.7.8	Electrophysiological Studies	237
5.7.9	Diagnosis	237
5.7.10	Differential Diagnosis	237
5.7.11	Treatment and Prognosis	237
5.8	Human T-Lymphotropic Virus Type I (HTLV-1) Myelopathy.	238
5.8.1	Synonyms.	238
5.8.2	Epidemiology.	238
5.8.3	Etiology and Definition	238
5.8.4	Clinical Features	238
5.8.5	Disease Course.	239
5.8.6	Brain Imaging	239
5.8.7	Spinal Cord Imaging	239
5.8.8	Examination of Blood and CSF.	240
5.8.9	Electrophysiology	240
5.8.10	Diagnosis	240
5.8.11	Differential Diagnosis	241
5.8.12	Treatment and Prognosis	241
5.9	Lyme Neuroborreliosis.	241
5.9.1	Etiology and Definition	241
5.9.2	Epidemiology.	241
5.9.3	Stage 1 (Early Localized Lyme disease; After 1–4 Weeks from Infection).	242
5.9.4	Stage 2 (Early Disseminated Lyme Disease; After Weeks to 4 Months from Infection)	242
5.9.5	Stage 3 (Late disseminated Lyme Disease; After >4 Months from Infection).	244
5.9.6	Brain Imaging	245
5.9.7	Spinal Cord Imaging	245
5.9.8	Blood Work	245
5.9.9	Examination of CSF.	245
5.9.10	Electrophysiology	247
5.9.11	Diagnosis	247
5.9.12	Differential Diagnosis	248
5.9.13	Treatment and Prognosis	248
5.10	Progressive Multifocal Leukoencephalopathy (PML).	249
5.10.1	Epidemiology.	249
5.10.2	Etiology and Definition	249
5.10.3	Clinical Features	250
5.10.4	Brain Imaging	251
5.10.5	PML Subtypes According to Brain MRI	253
5.10.6	Spinal Cord Imaging	253
5.10.7	Blood Work	253

5.10.8	Examination of CSF	254
5.10.9	Diagnosis	254
5.10.10	Differential Diagnosis	254
5.10.11	Treatment and Prognosis	255
5.11	Syphilis	255
5.11.1	Epidemiology	255
5.11.2	Etiology and Definition	256
5.11.3	Disease Course.	256
5.11.4	Asymptomatic Neurosyphilis.	256
5.11.5	Clinical Features of Early Neurosyphilis.	256
5.11.6	Clinical Features of Late Neurosyphilis	257
5.11.7	Brain Imaging	257
5.11.8	Spinal Cord Imaging	258
5.11.9	Blood Work	259
5.11.10	Examination of CSF.	260
5.11.11	Diagnosis	261
5.11.12	Differential Diagnosis	261
5.11.13	Treatment and Prognosis	261
5.12	Tuberculosis.	262
5.12.1	Epidemiology.	262
5.12.2	Etiology and Definition	262
5.12.3	Tuberculosis Subtypes	262
5.12.4	Tuberculous Meningitis	262
5.12.5	Brain Parenchymal Tuberculosis	263
5.12.6	Spinal Cord Tuberculosis.	263
5.12.7	Blood Work	264
5.12.8	Examination of CSF.	265
5.12.9	Diagnosis	265
5.12.10	Treatment and Prognosis	265
5.13	Varicella Zoster Virus (VZV) Infection	266
5.13.1	Epidemiology	266
5.13.2	Cause	266
5.13.3	Clinical Features and Imaging	266
5.13.4	Blood Work	268
5.13.5	Examination of CSF.	269
5.13.6	Diagnosis	269
5.13.7	Treatment and Prognosis	270
5.14	Whipple Disease	270
5.14.1	Epidemiology	270
5.14.2	Etiology and Definition	270
5.14.3	Systemic Clinical Features.	270
5.14.4	Neurological Clinical Features	270
5.14.5	Disease Course.	271
5.14.6	Brain Imaging	271
5.14.7	Spinal Cord Imaging	272

5.14.8	Examination of CSF	272
5.14.9	Diagnosis	272
5.14.10	Differential Diagnosis	272
5.14.11	Treatment and Prognosis	272
5.15	Other Bacterial, Parasitic, and Fungal Infections	273
5.15.1	Cat Scratch Disease	273
5.15.2	Chagas Disease (American Trypanosomiasis).	274
5.15.3	Cryptococcal Meningitis	275
5.15.4	Cysticercosis	276
5.15.5	Leptospirosis	276
5.15.6	Listeria Monocytogenes.	277
5.15.7	Mediterranean Spotted Fever	279
5.15.8	Mycoplasma Pneumonia Infection	279
5.15.9	Schistosomiasis	281
5.15.10	Toxocarosis	282
5.16	Other Viral Infections.	284
5.16.1	Acute Flaccid Myelitis.	284
5.16.2	Cytomegalovirus (CMV) Infection	285
5.16.3	Dengue Fever	286
5.16.4	Enterovirus 71	288
5.16.5	Hepatitis A (HAV) and B (HBV).	288
5.16.6	Hepatitis E (HEV)	289
5.16.7	Human Herpesvirus 6 (HHV-6).	290
5.16.8	Human Parvovirus (B19V)	291
5.16.9	Subacute Sclerosing Panencephalitis (SSPE)	292
5.16.10	West Nile Virus	293
	References.	295
6	Acquired Metabolic and Nutritional Diseases	311
6.1	Central Pontine Myelinolysis.	311
6.1.1	Epidemiology	311
6.1.2	Etiology and Definition	311
6.1.3	Clinical Features	312
6.1.4	Brain Imaging	312
6.1.5	Spinal Cord Imaging	313
6.1.6	Blood Work	313
6.1.7	Examination of CSF.	313
6.1.8	Diagnosis	313
6.1.9	Differential Diagnosis	313
6.1.10	Treatment and Prognosis	314
6.2	Cobalamin and Folate Deficiency	314
6.2.1	Epidemiology	314
6.2.2	Etiology	314
6.2.3	Non-neurological Clinical Features.	314
6.2.4	Neurological Clinical Features	315

6.2.5	Brain Imaging	315
6.2.6	Spinal Cord Imaging	315
6.2.7	Electrophysiology	315
6.2.8	Blood Work	316
6.2.9	Examination of CSF.	316
6.2.10	Diagnosis	316
6.2.11	Treatment and Prognosis	317
6.3	Cooper Deficiency and Zinc Overload.	317
6.3.1	Etiology	317
6.3.2	Clinical Features	317
6.3.3	Brain Imaging	317
6.3.4	Spinal Cord Imaging	317
6.3.5	Blood Work	318
6.3.6	Examination of CSF.	318
6.3.7	Treatment and Prognosis	318
6.4	Lathyrism.	318
6.5	Marchiafava–Bignami Disease	318
6.5.1	Epidemiology.	318
6.5.2	Etiology and Definition	319
6.5.3	Clinical Features	319
6.5.4	Brain Imaging	319
6.5.5	Spinal Cord Imaging	320
6.5.6	Examination of Blood and CSF.	320
6.5.7	Diagnosis	321
6.5.8	Differential Diagnosis	321
6.5.9	Treatment and Prognosis	321
6.6	Nitrous Oxide-Induced Myeloneuropathy	321
6.6.1	Synonyms.	321
6.6.2	Epidemiology.	321
6.6.3	Etiology and Definition	321
6.6.4	Clinical Features	322
6.6.5	Brain Imaging	322
6.6.6	Spinal Cord Imaging	322
6.6.7	Blood Work	322
6.6.8	Examination of CSF.	323
6.6.9	Electrophysiology	323
6.6.10	Diagnosis	323
6.6.11	Treatment and Prognosis	323
6.7	Vitamin E Deficiency.	323
6.7.1	Etiology	323
6.7.2	Clinical Features	324
6.7.3	Disease Course.	325
6.7.4	Brain Imaging	325
6.7.5	Spinal Cord Imaging	325
6.7.6	Electrophysiology	325

6.7.7	Blood Work	325
6.7.8	Examination of CSF.	325
6.7.9	Diagnosis	326
6.7.10	Treatment and Prognosis	326
6.8	Wernicke Encephalopathy	326
6.8.1	Epidemiology	326
6.8.2	Etiology and Definition	326
6.8.3	Clinical Features	326
6.8.4	Brain Imaging	327
6.8.5	Spinal Cord Imaging	328
6.8.6	Blood Work	328
6.8.7	Examination of CSF.	328
6.8.8	Diagnosis	328
6.8.9	Differential Diagnosis	329
6.8.10	Treatment and Prognosis	329
	References.	329
7	Inherited Metabolic Diseases	333
7.1	Biotinidase Deficiency	333
7.1.1	Epidemiology.	333
7.1.2	Etiology and Definition	333
7.1.3	Clinical Features	333
7.1.4	Brain Imaging	334
7.1.5	Spinal Cord Imaging	334
7.1.6	Blood Work	334
7.1.7	Urine Analysis	335
7.1.8	Examination of CSF.	335
7.1.9	OCT	335
7.1.10	Electrophysiological Studies	336
7.1.11	Diagnosis	336
7.1.12	Differential Diagnosis	336
7.1.13	Treatment and Prognosis	336
7.2	Cerebrotendinous Xanthomatosis	336
7.2.1	Epidemiology.	336
7.2.2	Etiology and Definition	337
7.2.3	Non-neurological Clinical Features.	337
7.2.4	Neurological Clinical Features	338
7.2.5	Disease Course.	338
7.2.6	Brain Imaging	338
7.2.7	Spinal Cord Imaging	339
7.2.8	Blood Work	339
7.2.9	Examination of CSF.	340
7.2.10	Electrophysiological Studies	340
7.2.11	Diagnosis	340
7.2.12	Differential Diagnosis	341

7.2.13	Treatment and Prognosis	341
7.3	Fabry Disease	341
7.3.1	Epidemiology	341
7.3.2	Etiology and Definition	341
7.3.3	Subtypes	342
7.3.4	Neurological Clinical Features	342
7.3.5	Non-neurological Clinical Features	342
7.3.6	Brain Imaging	343
7.3.7	Spinal Cord Imaging	343
7.3.8	Blood Work	344
7.3.9	Examination of CSF	344
7.3.10	Electrophysiology	344
7.3.11	Diagnosis in Males	344
7.3.12	Diagnosis in Females	345
7.3.13	Differential Diagnosis	345
7.3.14	Treatment and Prognosis	346
7.4	Homocysteine Remethylation Disorders	346
7.4.1	Etiology	346
7.4.2	Clinical Features	346
7.4.3	Brain Imaging	347
7.4.4	Spinal Cord Imaging	347
7.4.5	Electrophysiology	347
7.4.6	Blood Work	348
7.4.7	Examination of Urine	348
7.4.8	Examination of CSF	348
7.4.9	Diagnosis	348
7.4.10	Treatment and Prognosis	348
7.5	Hyperornithinemia-Hyperammonemia-Homocitrullinuria (HHH) Syndrome and Other Disorders of Glutamate and Urea Cycle Metabolism	348
7.5.1	Epidemiology	348
7.5.2	Etiology and Definition	349
7.5.3	Clinical Features	349
7.5.4	Disease Course	349
7.5.5	Brain Imaging	349
7.5.6	Spinal Cord Imaging	350
7.5.7	Examination of Blood and CSF	350
7.5.8	Electrophysiology	350
7.5.9	Diagnosis	351
7.5.10	Differential Diagnosis	351
7.5.11	Treatment and Prognosis	351
7.6	Lysosomal Storage and Peroxisomal Function Disorders	351
7.6.1	Epidemiology	351
7.6.2	Cause and Definition	352
7.6.3	X-Linked Adrenoleukodystrophy (X-ALD)	352

7.6.4	Krabbe Disease	354
7.6.5	Metachromatic Leukodystrophy	355
7.6.6	Fabry Disease	356
7.6.7	Niemann–Pick Disease Type C	357
7.6.8	Chédiak–Higashi Disease	358
7.6.9	Tay-Sachs Disease	359
7.6.10	Pompe Disease	359
7.6.11	Blood Work (in General)	360
7.6.12	Examination of CSF (in General)	360
7.6.13	Diagnosis (in General)	360
7.6.14	Treatment and Prognosis (in General)	361
7.7	Mitochondrial Disorders	361
7.7.1	Epidemiology	361
7.7.2	Cause and Definition	361
7.7.3	Subtypes	361
7.7.4	Non-neurological Clinical Features	362
7.7.5	Neurological Clinical and Imaging Features	363
7.7.6	Disease Course	364
7.7.7	Brain Imaging	364
7.7.8	Spinal Cord Imaging	366
7.7.9	Other Organ Systems Imaging	366
7.7.10	Blood Work	367
7.7.11	Examination of CSF	368
7.7.12	OCT	368
7.7.13	Electrophysiology	368
7.7.14	Diagnosis	368
7.7.15	Differential Diagnosis	369
7.7.16	Treatment and Prognosis	369
7.8	Wilson’s Disease	369
7.8.1	Epidemiology	369
7.8.2	Etiology	369
7.8.3	Clinical Features	369
7.8.4	Brain Imaging	370
7.8.5	Spinal Cord Imaging	370
7.8.6	Blood Work	370
7.8.7	Urine	371
7.8.8	Liver Biopsy	371
7.8.9	Examination of CSF	371
7.8.10	Treatment and Prognosis	371
7.9	Other Rare Inherited Metabolic Diseases	371
7.9.1	Acute Intermittent Porphyria	371
7.9.2	Alpha-Methylacyl-CoA Racemase Deficiency	371
7.9.3	Adult Polyglucosan Body Disease	372
7.9.4	Aicardi–Goutières Syndrome	372
7.9.5	Arginase 1 Deficiency	373