Mimics and Red Flags of Multiple Sclerosis

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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-aquaporine-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