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HANDBOOK OF CLINICAL NEUROLOGY

Series Editors:
MICHAEL J. AMINOFF, FRANÇOIS BOLLER,
DICK F. SWAAB

122

3rd Series

MULTIPLE SCLEROSIS AND RELATED DISORDERS

Edited by:
DOUGLAS S. GOODIN

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Volume Editor

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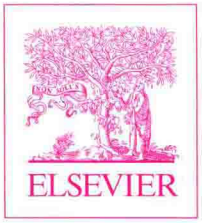

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Foreword

The *Handbook of Clinical Neurology*, founded by Pierre Vinken and George Bruyn in 1968, is a prestigious, multi-volume reference work covering all disorders of clinical neurology. Rapid progress in neurology necessitates regular updates. So when the first series was concluded in 1982, it was followed by a second one, edited again by Vinken and Bruyn. We took over as editors of the current third series, with volume 79 appearing in late 2003 and since then more than 40 volumes have appeared.

Multiple sclerosis (MS) was first distinguished clinically from Parkinson's disease in 1868 by Jean-Martin Charcot (1825–1893), and named by him *la sclérose en plaques*. Pathologic descriptions of the condition preceded its clinical description. For instance the Swiss pathologist Georg Eduard Rindfleisch (1836–1908) had 5 years earlier described the inflammation-associated lesions distributed around blood vessels and proposed a vascular etiology. Ever since such observations some 150 years ago, MS has been the focus of attention from clinical neurologists. MS and related inflammatory demyelinating disorders were covered in volumes 9 and 47 of the first and second series of the *Handbook*. Novel imaging procedures since then have changed the field dramatically. A new volume on this topic also became necessary because of the extremely rapid advances that have occurred in molecular biology, neuropathology, genetics, immunology, neurophysiology, and CSF analyses, by the development of experimental models of the disease and an emphasis on evidence-based treatments, and by the better insights in differential diagnosis, etiologic factors, clinical outcome measures, and prognosis that followed these other advances.

Dr. Douglas Goodin, director of the Multiple Sclerosis Center at the University of California Medical Center in San Francisco, is a neurologist and internationally renowned expert on this disease. He has assembled a truly international group of authors with acknowledged expertise and produced with them an authoritative, comprehensive, and up to date volume on MS. Its availability electronically on Elsevier's Science Direct site as well as in print format should ensure its ready accessibility and facilitate searches for specific information.

We are grateful to Dr. Goodin and to all the contributors for their efforts in creating such an invaluable resource. As series editors we read and commented each of the chapters with great interest. We are therefore confident that both, clinicians and researchers in many different disciplines will find much in these volumes to appeal to them.

As always it is a pleasure to thank Elsevier, our publishers – and in particular Tom Stone, Michael Parkinson, and Kristi Anderson – for their unfailing and expert assistance in the development and production of this volume.

Michael J. Aminoff
François Boller
Dick F. Swaab

Preface

Multiple sclerosis (MS) seems to be a modern illness that afflicts only humans. Thus, there are no known spontaneous conditions in animals that reliably mimic the human condition. Also, prior to the 14th century, there are no reports of conditions that bear any resemblance to modern-day cases of MS. Indeed, some authors identify, as the index case, that of Lidwina the Virgin from Schiedam (Holland) who, at age 15 years, in 1395, fell while ice-skating and fractured a rib. Subsequent to this fall, Lidwina developed a progressive neurologic condition, which included a paralysis in her legs and right arm, blindness in one eye, and severe pain. Lidwina's history is often taken for an example of a progressive form of MS. Nevertheless, her repeated visions of God, the ecstasies that she experienced, and the religious fervor that surrounded descriptions of her illness make the diagnosis of MS less convincing. A more reliable index case is that of Augustus d'Este (1794–1848), the grandson of King George III (England) who, beginning in 1822, documented the course of his illness in a diary and, almost certainly, had the condition that we refer to today as relapsing/remitting MS.

During the 19th century, our understanding of the disease MS accumulated only slowly. The first descriptions of the pathology of MS by Richard Carswell (1838) and Jean Cruvelhier (1841) lagged behind this index case by approximately two decades and the first clinical description of the illness by Jean-Martin Charcot (1868) only appeared 2 to 3 decades thereafter (Charcot named the condition: *la sclérose en plaques*). However, beginning in the 20th century, the pace of advances in our understanding increased dramatically. The animal model, experimental autoimmune encephalomyelitis (EAE), was introduced in the 1930s; a scale to measure disability in MS patients was first introduced in 1955; the characteristic oligoclonal IgG bands were described in the spinal fluid of MS patients in the 1960s; various clinical neurophysiologic techniques (evoked potentials) were introduced for diagnostic purposes in the 1970s; the first randomized, multicenter, controlled clinical trial of a therapy in MS was published in 1970; the first MS-susceptibility gene (*DRB1*) was unequivocally identified on the short arm of chromosome 6 in the 1970s; magnetic resonance imaging (MRI), which revolutionized our ability to visualize (*in vivo*) the pathology of MS, was introduced to medicine in the 1980s; and the modern era of disease modifying therapy for MS was launched with the approval of interferon beta-1b therapy in 1993.

Nevertheless, despite the considerable progress made during the 20th century, the 21st century (now little more than a decade old) has seen an exponential expansion in our knowledge about the pathophysiology, epidemiology, immunology, genetics, molecular mechanisms, neurophysiology, and treatment of MS. We have steadily improved the design and conduct of our clinical trials and our statistical methods such that eight different, proven-effective, therapeutic agents for MS are now commercially available and several more are in the late stages of drug-development. Using both modern MRI and modern spinal fluid analysis, we now have the ability to diagnose MS in its very earliest (even pre-clinical) stages and can begin to think about the possibility of therapies, used at the very beginning of the illness, that might arrest the further course of disability progression.

We have tentatively identified two important environmental factors (vitamin D deficiency and Epstein-Barr viral infections) that contribute to disease development and, thus, can begin to contemplate potential methods of primary disease prevention. And finally, we have now identified approximately 100 MS-associated genes and can envision utilizing this kind information to guide future therapeutic innovations, to assess who, within a population of individuals, is at risk of developing this illness, and to determine the most appropriate therapy for a specific patient-based on individual genetic make-up.

However, inevitably, with such rapid advances in knowledge, it becomes increasingly difficult for individual practitioners to keep abreast of the relevant developments in widely diverse fields of study. It is the purpose of this volume to collect in one place the necessary information for physicians to both understand and appreciate the significance of the latest developments in our understanding of the disease we call MS. To this end, this volume includes 30 chapters

devoted to covering in depth various subject areas relevant to our current understanding of MS. Thus, several chapters are devoted to covering the important clinical aspects of MS. For example, the epidemiology of MS, its presentation in adults and children, its clinical course, and its prognosis are all considered at length. Other chapters are devoted to diagnostic considerations, including the clinical criteria and the appropriate use of ancillary testing (spinal fluid analysis, neurophysiology, and neuroimaging) for making the correct diagnosis. The differential diagnosis of MS is discussed in detail, both generally and also with a focus placed on those conditions with an uncertain relationship to MS (e.g., acute disseminated encephalomyelitis, neuromyelitis optica, and the acute inflammatory myelopathies). Because of the current importance of MRI both in the diagnosis of MS and in monitoring disease activity, special emphasis is placed on the use of this technique.

Several chapters are devoted to the pathology, pathophysiology, genetics, and immunology of MS. These include discussions of immune function and its regulation in MS, the genetic basis of MS in both its relapsing and progressive forms, the potentially causative role of infectious agents and autoimmunity in MS pathogenesis, the good and bad aspects of inflammation in the nervous system, and the pathophysiology of injury to the myelin and the axons and the use of animal models in elucidating these mechanisms. Finally, the treatment of MS (both now and in the future) is considered, including the use of disease-modifying therapies, corticosteroids, symptomatic management strategies, and the treatment of acute attacks. Moreover, consideration is also given to how the design of clinical trials and certain key design concepts (e.g., validity, reliability, replicability, and outcome assessment) affect, or should affect, our evaluation of the efficacy and safety for the different therapies now available and how we can appropriately incorporate this clinical trial data into clinical practice.

It is hoped that, with this volume, both the interested reader and the busy practitioner will find a useful, thorough, readily accessible, and easily understandable guide to the breadth of our most recent, but rapidly expanding, knowledge about MS.

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