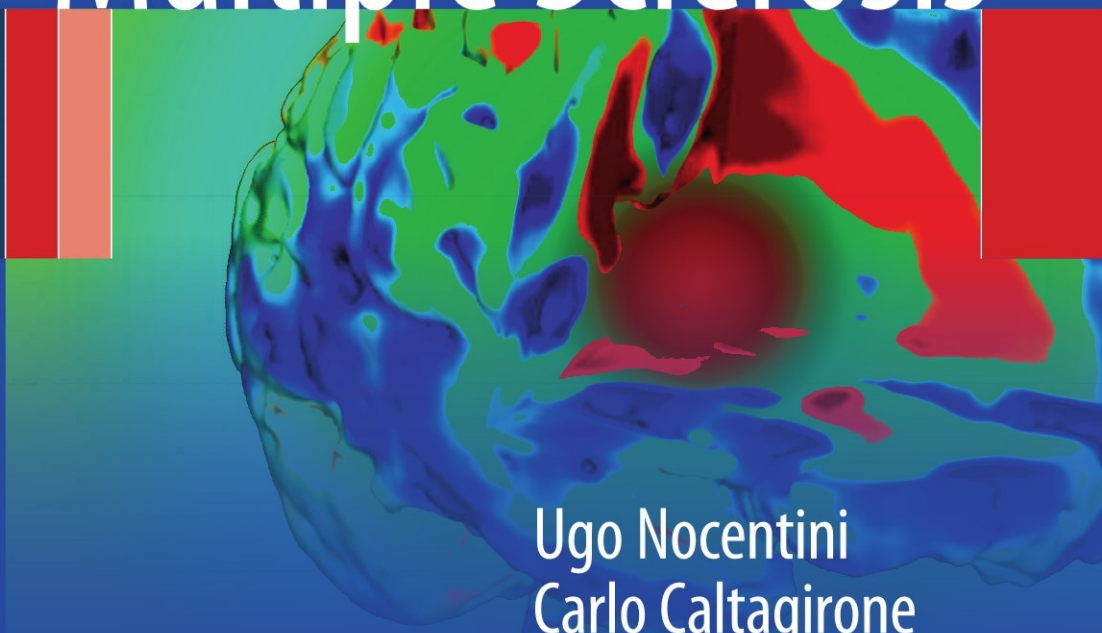
Neuropsychiatric Dysfunction in Multiple Sclerosis



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Foreword

Multiple Sclerosis (MS) is a disease of the nervous system which has profound effects on everyday life of not only the person who is diagnosed, but her/his family and close friends. MS is among the most common cause of neurological disability among young adults, and affects about 2.5 million people worldwide. In the United States, a new person is diagnosed with MS about every hour. Fortunately, we are in the midst of an intellectual explosion in understanding the underlying neurobiology of this disease. This is largely due to the rapid and significant advances in neuroimaging over the last decade, in addition to considerable new knowledge concerning the basic neuropathology of MS. For example, while classically viewed as a white matter disease involving myelin in the central nervous system (CNS), we now know that MS also involves CNS gray matter, and that pathology is also found in the cerebral cortex where it was previously delimited to "subcortical" regions. These advances in neurobiology have led to new and improving treatments for persons with MS. In fact, work over the past two decades is a testament to a translational approach to clinical science, whereby basic knowledge results in new treatment in clinical practice. These treatments almost exclusively involve slowing the progression of the disease. Although modest in effectiveness, it represents a significant leap forward in our approach to the disease and holds promise for new and more effective therapies in the near future. On the other hand, symptomatic treatment in MS seems to have lagged behind, especially involving the neuropsychiatric consequences of MS. For example, there are no approved pharmacological treatments for cognitive impairment, and behavioral approaches have been mixed, limited, and marred by significant methodological limitations, which haunt any potential applicable benefits. One very significant void in the work on MS to date is the lack of evidence-based treatment for progressive forms of the disease. Therefore, despite the significant advances in our knowledge of the neurobiology of MS, little transfer of this knowledge toward treatment of progressive MS has resulted, and it is an area that requires immediate attention.

Despite the significant advances made over the last decade in understanding the pathophysiology of MS through work in neuroimaging, we also have become increasingly aware about the lack of a one to one relationship between MS

symptoms and MS pathology. For instance, the majority of studies involving cognition show that pathology observed via neuroimaging account for less than 50% of the variance, and oftentimes considerably less. There are clearly individual differences that account for the less-than-desired relationship between neuroimaging parameters and behavior, which are both genetic and environmentally determined. We are only beginning to understand this relationship. For instance, it is only recently, that we have found that lifetime intellectual enrichment of the MS patient has a profound impact on the expression of cognitive symptoms, a concept referred to as "cognitive reserve." That is, persons with a high degree of lifetime intellectually challenging experiences are significantly less likely to display cognitive impairments relative to those with less fortunate intellectual stimulation, even when both have the same degree of brain atrophy on MRI. Clearly, the impact of environmental and genetic factors that mediate the expression of the disease itself, as well as our ability to assess these symptoms through existing and future instruments, is a critical area of future research.

Even with the recent advances that have come with neuroimaging, relatively little is known about the neuropsychiatric consequences of the disease. There is a paucity of comprehensive publications integrating the vast spectrum of the disease's behavioral consequences, ranging from cognitive, behavioral, personality, and psychopathology, that exist. This new volume, *Neuropsychiatric Dysfunctions in Multiple Sclerosis*, edited by Nocentini, Caltagirone, and Tedeschi, fills this void. Not only does it provide detailed and current knowledge on numerous aspects of the disease itself (e.g., epidemiology, pathophysiology, diagnostic and clinical manifestations, therapy, and rehabilitation) but it provides a detailed overview of the neuropsychiatric consequences of MS. This is a very unique contribution to the MS discussion. Clinicians are often faced with very complicated behavioral and psychiatric complications in an MS patient, and they have limited resources to reference other than a time-consuming literature review that is often selective and lacks integration. This new book provides an up-to-date and comprehensive presentation, which will be extremely helpful for the clinician. Its focus on neuropsychiatric manifestation of the disease provides the MS student a single volume in which comprehensive knowledge on the topic is contained and the MS scholar the appropriate tools necessary to envision future directions in this critically important area of MS research.

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Acknowledgments

First, we would like to sincerely thank the patients we have encountered during our professional activity. As a matter of fact, their lives are intertwined with ours. Even if at times their suffering affected us quite much, we hope we have always shown them our humanity as well as our professional skills. We are grateful to the patients and their families because we learned from them much more than from books, scientific journals, and conferences.

Still, with regard to what we have learned, we would like to thank our teachers for imparting their knowledge to us and providing an example of dedication to the values of life. In any case, we will all be gratified if in the future we are esteemed in the same way as we consider those who have supported us during the years of our training.

We also wish to thank our families for their patience when we had to sacrifice moments of life we wished we could share with them.

Furthermore, special thanks goes to the institutions where we work for providing material and moral support for our clinical and research work.

In addition, we would like to thank our readers in advance for choosing this book; we hope that they will find it useful and enlightening.

Last but not least, we would like to thank the publisher, Springer, for supporting our initiative. Above all we would like to thank those people working in Springer-Verlag Italia for helping us complete this work. In particular, we thank Catherine Mazars, Juliette Kleemann, Roberto Garbero, and those who work in the administration offices and typography. We believe that being able to speak of a good result is only due to the efforts of all those who contributed to making this book available to the readers.

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Part I

Multiple Sclerosis: General Clinical Aspects

Introduction

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Silvia Romano, Carlo Caltagirone, and Ugo Nocentini

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating and degenerative disease of the central nervous system (CNS) with a highly variable course. The exact cause of inflammation remains unclear, but an autoimmune response directed against CNS antigens is suspected. MS is the second most common neurologic cause of disability of young adults, after head trauma [1] (about 2.5 million people affected worldwide, 350,000 in Europe alone).

During the course of the disease a wide range of functional impairments and disabilities may develop, leading to a significant impact on the quality of life of patients, their family members and on employment (unemployment rates are higher for people with MS) [2]. According to the World Health Organization (WHO), MS is one of the most expensive diseases, with an annual social cost of 1 billion 600 million euros in Italy alone and an average annual cost per person of about 32,000 euros.

MS is classified in the group of CNS demyelinating diseases. This is a heterogeneous group of neurologic disorders characterized by a relatively selective damage of the CNS myelin. Demyelinating diseases may be classified as primary, characterized by direct damage of myelin, or secondary, in which the damage to the myelin results from neuronal or axonal injury. The spectrum of primary forms includes MS, acute disseminated encephalomyelitis (ADEM), optic neuritis and a group of diseases considered as particular variants of MS (Balo's concentric sclerosis, Schilder's diffuse cerebral sclerosis, Marburg's disease, neuromyelitis optica or Devic's disease).

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A precise clinical description of MS was given for the first time by Jean Cruveilhier in 1835 [3], but it was not until some years later (1868) that the first scientific definition of clinical and neuro-pathological characteristics was provided when, in three lectures on disseminated sclerosis (lectures V, VI and VII) at the Hôpital de la Salpêtrière, Charcot clearly delineated the main features of the disease. He identified three distinct forms (spinal, cephalic and bulbar), characterized by the triad of symptoms intention tremor, nystagmus and scanning speech (now known as Charcot's triad) and described the neuro-pathological damage with loss of myelin, glial scar formation and consequent axonal injury [4]. However, the first description of a case suggestive of MS dates from the fourteenth century, in the biography of St Ludwina of Schiedam. The extremely detailed documentation of the saint's life preserved in the Vatican Archives records that St Ludwina's disease began at the age of 16 years with remitting motor disorders followed by a slowly progressive course.

All autoimmune diseases such as MS are thought to be caused by dysregulation of the immune system, with the formation of immune cells specifically activated against CNS components; these cells are able to adhere to vessel walls, extravasate and migrate into nervous tissue, where they attack the myelin sheaths that preserve nerve fibers.

It is well known that the main feature of this disease is an inflammatory process resulting in the loss of the myelin sheath and subsequent axonal degeneration, with onset of symptoms/signs of focal CNS injury. The demyelinating process mainly involves white-matter long tracts and periventricular white matter, the optic nerve, the spinal cord, the brainstem and the cerebellum. The symptoms of the acute phase (first episode and relapses) tend initially to regress spontaneously, but over time they cause permanent neurological deficits. The acute clinical episodes are characterized by focal inflammatory lesions, identified as contrast-enhancing lesions on magnetic resonance imaging (MRI); in more advanced stages, when the neurologic deficits remain clinically stable, MRI shows signs of neurodegeneration characterized by diffuse atrophy in addition to the hyperintense white matter lesions. Although MS is considered a demyelinating disease, in recent years neuro-pathological and neuro-imaging studies have demonstrated the widespread involvement of not only the white matter but also the gray matter of the CNS [5, 6].

There is currently no cure for this disease, but the introduction of drugs that can change its course (interferons and glatiramer acetate) has resulted in a reduction of disease activity on clinical (number of clinical relapses) and MRI measures and a delay in disability progression [7]. In recent years, moreover, new drugs such as monoclonal antibodies (e.g., natalizumab) or selective, orally administered, immune-suppressors (e.g., fingolimod) have become available, and several phase III trials with new drugs are in progress.

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Epidemiology

2

Silvia Romano, Carlo Caltagirone, and Ugo Nocentini

MS has been described in various populations and geographical regions with different frequencies.

Generally, the most commonly used frequencies in epidemiological studies of diseases are prevalence and incidence.

As described in the next subsection (etiopathogenesis), regional differences in MS prevalence and incidence have contributed to formulating a hypothesis on its pathogenesis.

Prevalence is traditionally defined as a measurement of the proportion of "events" in a population at a given point of time. "Event" is defined as the occurrence of any phenomenon that can be discretely characterized, for example: infection, presence of antibodies, pregnancy. In epidemiology, diseases or infections are the most commonly used events, and therefore prevalence can be defined as the proportion of people in a population (of a state, region, province) that, at any given time, are affected by the disease. Incidence, on the other hand, measures the number of new cases of a disease occurring during a given period (for example, in a month or a year) and identifies the risk (i.e. probability) of developing the disease in the considered population. Since incidence indicates a change in a quantity (new people affected) compared with the change in another quantity (time), it is considered to be a dynamic measure.

Epidemiological studies, as well as other studies, are made difficult by the particular nature of MS. In fact, epidemiological researches aimed at formulating and testing etiopathogenetic hypotheses demand levels of diagnostic accuracy

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