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Neurodegeneration in Multiple Sclerosis

M. Filippi, M. Rovaris, and G. Comi, eds. New York: Springer; 2007, 236 pages, \$119.00.

Although multiple sclerosis (MS) is considered primarily an inflammatory demyelinating disease of the central nervous system, in the last decade evidence has accumulated that axonal injury accompanies the initial inflammatory pathologic process in white matter, that gray matter including cortical injury patterns without extensive inflammation can be recognized in the early pathologic stages, and that the disease in its primary or secondary-progressive clinical stages is not well explained by the concurrent inflammatory pathologic process. As a result of this more modern understanding of MS, many new avenues for MS research have emerged including those exploring the neurodegenerative aspects of the disease, which entails rethinking of treatment options for the more advanced progressive disease on the basis of neuronal salvage and protection. As imaging has become established as an essential tool in the diagnosis of MS, in following the course of the disease, and in therapeutic trials, there is now expanded interest and enthusiasm in imaging the neurodegenerative aspects of MS, which are only poorly and indirectly evaluated through conventional MR imaging techniques such as focal-enhancing lesion counts and techniques based on T2-hyperintense lesion burden of disease.

The book being reviewed, *Neurodegeneration in Multiple Sclerosis*, is a compilation of material derived from an international workshop held in Milan, Italy, in June 2005, with material updated through subsequent discussions by the authors. The stated goal of this book is to “provide a complete and up-to-date overview of the technical, methodological, and clinical issues related to the application of MR imaging in MS trials of neurodegeneration.”

This concise book includes 17 chapters and 236 pages with contributions by 39 authors with expertise in MS, MS imaging and pathologic processes, and statistical methodologies for clinical trials.

Chapter 1 sets the stage for subsequent discussions with an overview of key aspects of the pathologic processes of MS as concurrently understood. The authors include a brief and interesting discussion of axonal pathologic features, cortical and other gray matter lesions, and oligodendrocyte apoptosis. They also provide a more detailed discussion of the inflammatory pathologic process, including the role and increasingly recognized importance of the B lymphocytes, and microglial activation. At this point, it might be

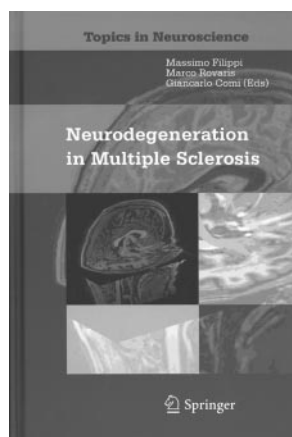
disconcerting to the reader that the emphasis of the chapter remains with the inflammatory rather than degenerative processes. This is not so much the fault of the authors but that of the state of the art of this investigative field, which is limited currently by great gaps in our understanding of the degenerative processes in MS. Nevertheless, an introductory chapter with an emphasis on the clinical problem (eg, progressive stages of disease) and factors thought to underlie the degenerative process would have been beneficial.

In Chapter 2, “Neurophysiological Methods,” primarily evoked potentials are reviewed. As the classic neurophysiologic methods provide information underlying function, they complement the anatomic-oriented imaging methodologies. In addition, the continued failure of imaging to predict clinical dysfunction or disability, or both, has fueled interest in exploring novel electrophysiologic approaches and, as discussed in Chapter 9, investigations on the basis of functional MR imaging.

Chapters 3 through 9 concern MR imaging methodology as it applies to MS. Leading this overview in Chapter 3 is an appropriately detailed review of the rationale and state of atrophy studies in MS. Brain and spinal cord atrophy are considered to be secondary manifestations of the pathologic processes in MS that destroy axons and neurons, remove or fragment myelin, and destroy the structural framework of the tissue. So although atrophy may be initiated by the inflammatory process as well as purer forms of the degenerative process in MS, this measure has assumed great importance in MS because it reports the overall slow, mostly irreversible, and potentially degenerative components of the disease. Chapter 4 is really 2 unrelated chapters, including the areas of T1 “black holes” (T1-hypointense lesions) and gray matter damage. Chapter 5 introduces magnetization transfer (MT) imaging, including a review of its use for focal disease in brain white matter, gray matter, the spinal cord, and the optic nerve. MT imaging has provided important insight into the microscopic pathologic features of MS in healthy-appearing tissues, and although it has emerged as a technique for evaluating nonspecific structural change, its importance lies in its potential for measuring myelin in MS. The chapter would have benefited from inclusion of consideration of the more modern quantitative MT methodology.

Chapter 6 introduces a new and important field of research in MS related to microvascular and ischemic pathologic processes, an area in its infancy, currently feasible on the basis of more sophisticated implementations of perfusion MR imaging methodologies. The authors introduce the ischemic hypotheses and their relevance to MS or subgroups of patients with MS, for example, those characterized as neuropathologic processes by pattern III (distal dying-back oligodendrogliaopathy), which mimics the pathologic process of non-MS early white matter ischemia. Chapter 7 is entitled “Diffusion-Weighted Imaging” but might be better entitled “Diffusion Imaging” because it is based predominantly on measures such as diffusivity and fractional anisotropy derived from diffusion tensor imaging.

The interpretation of MR spectroscopy studies in MS, specifically those concerned with *N*-acetylaspartate as a neuronal marker, contributed to many of the new ideas and central hypotheses responsible for supporting MS as a neurodegen-



erative disease. ^1H -MR spectroscopy is reviewed in Chapter 8, with an emphasis on studies using MR spectroscopy to date in MS and a well-balanced discussion of the strengths and limitations of the methodology in clinical trials. Concluding the MR methodologic section, Chapter 9 discusses functional MR imaging (fMRI), with an emphasis on technical aspects, measuring injury, and how it is noteworthy that fMRI may be providing insight into cortical reorganization after MS-related tissue injury.

Chapters 10 through 12 entail background material for the evaluation of MR imaging outcomes, including discussions relevant to defining (treatment) responders and nonresponders, statistical modeling, and validation of MR imaging surrogates. Chapters 13 and 14 present material emphasizing imaging in related areas of the more classic neurodegenerative disorders of Alzheimer, Huntington, and Parkinson diseases. Potential biomarkers for neurodegenerative diseases are reviewed in Chapter 15. Chapter 16 provides a brief overview of clinical trials in progressive MS.

Chapter 17, the final chapter, addresses the design of future trials of neurodegeneration in MS. Unfortunately, the workshop does not seem to provide any novel suggestions for studying the neurodegenerative process in MS as a conclusion

but merely discusses an extension of known strategies, which include those based on evolution of MT values (emphasis on myelin rather than axons), evolution of focal lesions to T1 black holes (emphasis on focal rather than diffuse disease), and yet unfulfilled hopes for whole-brain ^1H -MR spectroscopy and brain atrophy. This disappointing conclusion underscores the state of the field and imaging limitations rather than lack of insight by the expert authors.

Overall, the strength of this compact book would be its value as a compilation of material that is not so much novel as it is difficult to find in a single volume. Much of the material in this book can be found in recent reviews and articles. It will provide a convenient reference resource for MS investigators interested in the current status of neurodegeneration imaging studies in MS because the field of interest is covered comprehensively. Many chapters are better designed as a basis for discussion rather than as stand-alone entities. Perhaps the field of imaging neurodegeneration in MS is not yet mature enough to support a comprehensive text. The material will be of only limited value for neuroradiologists, fellows, and radiology residents.

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