

Contemporary Clinical Neuroscience

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Gülin Öz
Editor

Magnetic Resonance Spectroscopy of Degenerative Brain Diseases

 Springer

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Foreword

Nuclear magnetic resonance (NMR) was discovered by physicists, exploited by chemists and swiftly commandeered as magnetic resonance imaging (MRI) by medical radiologists for its diagnostic value. Magnetic resonance spectroscopy (MRS), the chemical analytical counterpart, has thus largely become a stepchild of diagnostic MRI – and is included as a minor after-thought, if at all, in prevailing neurology textbooks. The present volume is an innovation and corrects the prior omission. True to its roots as a non-destructive tool for chemical and biochemical analysis, MRS has its adherents in neurology and the neurosciences. Biochemistry, they reason, must to a greater rather than a smaller extent underlie brain ‘function’; MRS may therefore unlock the secrets of brain, cognition and even mind. Neurodegenerative diseases attack all of these normal functions. The present volume assembles many of the ‘keys’ that have been discovered by a quarter-of-a century of dedicated investigation and presents them in a readable, coherent and convenient form, for the coming generations of neurologists, psychiatrists, neuroscientists and biomedical engineers who will one day reap that harvest. Confronted by a virtual epidemic of neurodegenerative disorders and an ageing population, the potential for MRS as a new diagnostic tool has become compelling.

The achievement of editor and author, Dr. Gülin Öz and the 15 other contributors to the new volume “Magnetic Resonance Spectroscopy of Degenerative Brain Disorders” is timely and significant. It makes accessible to the expert and novice alike, the excitement of 25 years of research and development of MRS as metabolic imaging of the living, functioning human brain. Thanks to the success of MRI as a first-line diagnostic tool in neurology and latterly also in psychiatry, these expensive and ungainly machines are universally available and have become familiar and well-tolerated by patients. MRI has migrated from the Clinic to become available to an entire generation of physicians and scientists interested in brain function, dysfunction and disease previously confined to exploring their subjects indirectly, through post-mortem tissue or secondary tests on blood and cerebrospinal fluid. Latterly, and in a variant of reverse-engineering, MRI and MRS ‘scanners’ based on successful human applications, but suited to the 1000-fold smaller brain of the

mouse, have been designed to take advantage of the revolution in genetics and animal modeling of human degenerative brain diseases. This continuous iteration of preclinical with clinical research is another special feature of the present volume. But the real value of MRS, explored through the medium of human degenerative brain disorders, lies in the non-invasive access to neurochemistry that this technology provides: while we should not forget that the major innovation in 'structural MRI', which distinguishes it from computerized X-ray tomography, comes from its power to image neurochemistry of brain water in all its myriad forms, one metabolite N-acetyl aspartate, NAA, dramatically advances the role of MRS in the brain. Largely as a consequence of the industry of many of the Authors assembled in this new volume, NAA can now safely be viewed as a 'neuronal marker'. MRS of NAA, deserves its place as the new 'tendon-hammer' (invented in 1841 and still going strong) for diagnostic neurologists by defining the 'number' of viable neurons and axons in any pre-selected region of the human brain. In this Volume we are informed how NAA predicts (pre-clinical diagnosis), documents progression, and gives early warning of response in most, if not all neurodegenerative diseases.

But this Volume takes us well beyond NAA, demystifying previously unfamiliar MR 'spectra' to reveal an additional dozen brain metabolites, each the potential 'biomarkers' of some feature of pathobiology. The concept of neurodegeneration itself is explained in an Introductory chapter by the Editor, touching on the genetic, biochemical, intracellular and apoptotic origins of diseases as various as Alzheimer's, Huntington's, Parkinson's, motor neuron disease (Lou Gehrig's disease) and a handful of cerebellar diseases epitomized by Friedreich's ataxia. Technical details crucial to credible clinical MRS – and often ignored in more general "MRI" tomes devoted principally to the butterfly collection of disease-specific images – are here stressed to allow explorers to evaluate their reliability as tools in the broader endeavor of the entire field of now broadly recognized as neurospectroscopy. Armed with these skills, the reader is then offered detailed evaluation of neurospectroscopy as a harbinger of degenerative disease and a bell-weather of successful diagnosis by a succession of specialists in each of disorders included in that concept. Although the Editor and some of the authors of individual Chapters call for 'standardization' in MRS technique, for future multi-center clinical trials this may be premature for two reasons; the two Chapters devoted to MRS technique illustrate that a considerable diversity of MRS methods may be necessary if the analytical depths of magnetic resonance are to be plumbed: we should recall that is precisely the path taken by diagnostic MRI where every new technique is incorporated. Next, with the increased recognition and reliance on biomarkers, not least those revealed through MRS itself, the era of massive clinical trials may itself be evolving into personalized medicine. Might not diversity in MRS-methodology become a strength? In any event, the authors of the Chapters which follow have not heeded the 'siren-call' of standardization nor have they been restricted by any Editorial limitation on the MRS techniques they describe – and, as befits a work of scholarship, we are offered everything available under the heading of proton (^1H) MRS, provided that it contributes to the central purpose of explaining neurodegenerative disorder. The real pleasure in reading this compelling volume comes with

the carefully considered Chapters each by experts in their field as the richness of MRS plays out to explore the commonalities and the differences between the disorders classified here as ‘neurodegenerative’.

While they may be ‘linked’ by loss of NAA there is much more to the story. Alzheimer’s disease, with the longest track record, more than 20 years of MRS study, is yielding to careful cross-sectional and longitudinal studies with added-value in the taxonomy of a once-uniform diagnosis. MRS is well positioned to become a meaningful biomarker for this dominant group of dementias, when therapeutic option(s) finally emerge. In successive Chapters on the key disorders of this spectrum – Huntington’s, Parkinson’s, Motor Neuron Disease and Ataxias the authors skillfully blend *in vivo* pre-clinical studies in an ever increasing cast of disease models, with copious clinical experience of the real disease permitting an excellent evaluation of the relevance of the model through their MRS patterns. Each Chapter is accompanied by References pruned to eliminate the irrelevant or frankly wrong (all too common in the published MRS literature), with inclusion of crucial lost literature from the ‘dark-age’ which preceded the Internet. The slimmest Chapter, that on prion disease highlights one of the limitations, even of so robust a tool as clinical MRS – confining a deteriorating patient within a monster tube – today’s MR scanner – can be an almost insurmountable challenge! Can we hope this is one that MR engineers will surmount?

Three Chapters not traditionally covered by the adjective ‘degenerative’ – on multiple sclerosis, HIV and epilepsy – are included. Here too the Editor’s decision was wise – each Chapter is authoritatively written and informative with the bonus that two, MS and HIV, unlike the classical degenerative disorders, have a number of efficacious treatments. Putative MRS biomarkers sometimes respond to treatments – as expected – thereby providing an opportunity to test their hypotheses of etiology, evolution and reversal of disease. The final chapter, that on epilepsy also more than earns its place, notably emphasizing that epilepsy syndromes may involve neural re-generation, rather than de-generation. So there might be ‘light at the end of the tunnel’ of MRS of ever-progressing degenerative brain diseases. Neural re-generation, through the medium of pluripotent stem cells, while not directly mentioned anywhere in this Volume, is believed by many to represent the future. MRS detection and monitoring of stem cell populations has been mooted and seems well-within the bounds of possibility. If so, this book represents an important milestone on the long road ahead in ridding Society of degenerative brain disorders. Because degenerative brain disease remains a poorly understood accumulation of historically distinct disorders, readers who stray beyond their disease of interest to read more widely about MRS in other diseases, challenges and answers, will be richly rewarded by the cross-fertilization of the neighboring Chapters.

Reading this Volume thoroughly is highly recommended.

Brian Ross: Division of Medical Engineering, California Institute of Technology, Pasadena.

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