Cerebral Microbleeds

Pathophysiology to Clinical Practice

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Edited by
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Foreword

Brain imaging shows us much more than we can understand. This book goes a long way in bridging the gap between seeing and knowing, regarding cerebral microbleeds.

The problem is put in perspective beginning with the classical studies of Charcot and Bouchard and then systematically describing and interpreting subsequent pathological studies. A geography of pathology is reaffirmed, but modified. Although cerebral microbleeds parallel the distribution of the two leading causes of intracerebral hemorrhage, namely hypertensive and cerebral amyloid pathology, their occurrence is not limited to their respective areas of prevalence. Hypertensive hemorrhages typically involve the pons, cerebellum, basal ganglia and thalamus, while vascular amyloid affects the meningeal and cortical vessels. Cerebral microbleeds are found more widely. One can imagine vessels stiffened by hypertension and weakened by amyloid outside the typical subcortical and cortical distribution of hypertensive and amyloid pathology, respectively, where one pathology alone would be asymptomatic but the combination puts the vessels over the threshold for bleeding. It is clear that we have much to learn about what, until recently, we could not see. In the age of falling rates of autopsies, their continuing relevance is heightened by the need to understand the origins and evolution of cerebral microbleeds.

This volume also deals with the occurrence of cerebral microbleeds in the general population, in patients with ischemic stroke and in relation to cognitive impairment. As the resolution and sophistication of brain imaging grows, we will increasingly face the challenge of deciding the clinical relevance of cerebral microbleeds in a given patient. The editors and authors have rendered a great service by collecting, reviewing and evaluating in this volume all that is known. This book will be useful and can be recommended to anyone who relies on brain imaging for diagnosis and decision making.

Vladimir Hachinski, CM, MD, FRCPC, DSc.
Distinguished University Professor

Preface

Cerebrovascular diseases (including symptomatic strokes and vascular cognitive impairment) are arguably the leading cause of death and disability worldwide. About one in three symptomatic strokes are caused by diseases of small perforating arteries, including most cases of spontaneous intracerebral hemorrhage, the most severe and lethal type of stroke. Despite the clear importance of small vessel diseases, many effective interventions (for example endovascular techniques) currently target only disease of large arteries, because small vessels are technically inaccessible and the underlying mechanisms of small vessel diseases remain relatively poorly understood. The importance of small vessel disease is yet further increased because it is the commonest cause of so-called "silent strokes": vascular damage to the brain seen on neuroimaging (or at autopsy) that does not cause an obvious acute stroke syndrome but may have important cumulative effects, particularly on behavior or cognition. Subclinical cerebrovascular disease is revealed by changes on MRI scans, including white matter changes (leukoaraiosis) and small, deep infarcts (lacunes). There is increasing evidence that such silent cerebrovascular disease signifies an increased risk of symptomatic stroke, and plays a key role in cognitive impairment and dementia – perhaps the biggest challenge of all facing aging societies.

Since the first reports, in the late 1990s, of small, black, rounded lesions on gradient-recalled echo MRI scans of patients suffering symptomatic large cerebral hemorrhage, cerebral microbleeds have emerged as an important new imaging manifestation of small vessel diseases. Although new to stroke clinics, the lesions that we now call cerebral microbleeds are probably similar to those described by histopathologists in hypertensive brains affected by macroscopic intracerebral hemorrhage well over a century ago. With the development of MRI techniques that are exquisitely sensitive to the products of bleeding, including gradient echo T_2^*-weighted and susceptibility-weighted sequences, cerebral microbleeds have been detected in ever-increasing numbers of patients in stroke and cognitive clinics, as well as in population-based samples of healthy older people (up to approximately 40% of healthy community-dwelling individuals over 80 years have microbleeds that are identified with an optimized MRI protocol). As imaging methods improve, with even higher field strength, thinner slices and better tissue contrast, there may come a time when more people have identified microbleeds than do not. There is, therefore, an urgent need to establish their pathophysiological and clinical significance, in all sorts of populations. For example, there is much interest in the concept of prevention and in treatment of high-risk individuals; could cerebral microbleeds have a role in identifying those who would benefit from intensive risk factor management or other new therapeutic approaches to small vessel diseases?

Despite their high prevalence, there remains uncertainty even about the basic question of whether cerebral microbleeds actually have any effect on brain function. So far, it is clear that cerebral microbleeds are common in all stroke populations (more so in intracererbal hemorrhage than ischemic stroke) and are closely linked to the commonest small vessel diseases: hypertensive arteriopathy and cerebral amyloid angiopathy (the latter usually identified in association with intracerebral hemorrhage or Alzheimer's disease). Cerebral microbleeds, therefore, seem likely to play a key role in increasing our understanding of small vessel disease mechanisms, and the link between cerebrovascular disease and neurodegeneration. Another key question is whether microbleeds are a useful tool to assess the risk of intracerebral hemorrhage prior to antithrombotic treatments. This question has particular urgency because intracerebral hemorrhage in older age groups is increasing in incidence compared with other stroke types, probably because of the increasing use of antithrombotic drugs in people with fragile small vessels prone to bleeding.

Preface

So, is the time right for a book about cerebral microbleeds? If the interest of a topic can be judged by the number of people writing and publishing articles, then the answer is a resounding "yes." The publication of papers on cerebral microbleeds is increasing at an exponential rate, indicating that cerebral microbleeds have truly captured the attention of cerebrovascular researchers; from the start of 2009 through to mid-2010, over 100 papers relating to cerebral microbleeds have been published. Many studies describe their prevalence and anatomical distribution, or association with clinical or imaging factors; some investigate the physical principles underlying detection, others their pathological basis, and still others describe experimental studies. Because of the diversity of research, studies on cerebral microbleeds have been published in many varied sources. And naturally, as with any emerging technology and its application to clinical medicine, there are areas of uncertainty, debate and sometimes confusion. Methods of detection and quantification are under active development. This book is an attempt to bring all of these sources of information together in a single volume to summarize current knowledge, and controversies, in the field. I have been lucky to be able to assemble a world-class team of authors, all distinguished in their research areas; the contributions of such a diverse team, across many countries and continents, will give different and valuable perspectives.

Each chapter is designed to stand alone, so some repetition between chapters is inevitable and necessary; because the field remains relatively well defined, there will be reference in many chapters to similar early papers and key findings. However, overlap has been minimized as far as possible, so that the book can also be used as a single volume. Although definitive answers to many questions cannot yet be provided, it is hoped that this volume will give a useful synthesis of current understanding and directions for future research. The book is in three sections; the first covers the historical context of cerebral microbleeds, and technical aspects relating to their detection, definition and mapping in the brain. The second considers the mechanisms underlying microbleeds from histopathological studies, epidemiological studies and imaging. The third, and largest, section, discusses microbleeds in the context of different populations and disease groups, and also covers specific clinical settings and questions including cognitive impairment, and the use of antithrombotic medications. The book has been designed to be of interest to all clinical researchers and physicians in the fields of stroke and cognitive impairment, including neurologists, stroke physicians, neuroradiologists, neuropsychologists and vascular scientists. It should provide a useful synthesis of what is currently known about cerebral microbleeds, but more importantly, it will show how many fascinating and clinically important questions remain, and stimulate further research.

David Werring
London, September 2010

Terminology

This book is about radiological lesions corresponding to small areas of bleeding in the brain, commonly referred to as microbleeds. The term microbleed was first coined in 1996 [1], but in subsequent years many different terms have been applied to what seem to be the same thing. These include petechial hemorrhages, silent microbleeds, asymptomatic microbleeds, multifocal signal loss lesions, dot-like hemosiderin spots, brain microbleeds, cerebral microbleeds, microhemorrhages and microsusceptibility changes. In the interests of consistency, a single term, *cerebral microbleeds* (CMBs), the most frequently used term, has been used throughout this book. The term "microbleed" is not often applied to lesions outside the central nervous system, but it nevertheless seems appropriate to make clear that the lesions being discussed are in the brain. Although a few recent studies have preferred to use the term brain microbleeds (BMBs) [2], these are in the minority. Cerebral (French *cérébral*, "pertaining to the brain," derived from the Latin *cerebrum*, "the brain") has the advantages of already being widely used and is consistent with much of the other terminology used in hemorrhagic disorders affecting the brain, including intracerebral hemorrhage and cerebral amyloid angiopathy.

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