Hughes Syndrome

Second Edition

M. A. Khamashta (Ed.)

Hughes Syndrome

Antiphospholipid Syndrome

Second Edition

With 80 Figures

Springer

M. A. Khamashta, MD, FRCP, PhD
Deputy Head, Lupus Research Unit, St Thomas' Hospital, London, UK

Artwork marked with 🕮 symbol throughout the book is original to the 1st edition (Khamashta MA. Hughes Syndrome: Antiphospholipid Syndrome. Springer-Verlag London Ltd. 2000) and is being republished in this 2nd edition.

A catalogue record for this book is available from the British Library

Library of Congress Control Number: 2005926817

ISBN-10:1-85233-873-3 Printed on acid-free paper
ISBN-13:978-1-85233-873-2

ISBN 1-85233-232-8 1st edition

First published 2000
Second edition 2006

Printed in Singapore (EXP/KYO)

9 8 7 6 5 4 3 2 1

Springer Science+Business Media
springeronline.com

To my parents, Andrawes and Azizeh,
who have supported me throughout my life
and continue to inspire me to achieve.

Foreword to the Second Edition

The studies and discussions presented in the second edition of the *Hughes Syndrome* text had their beginning with a 1983 *British Medical Journal* publication entitled "Thrombosis, abortion, cerebral disease and the lupus anticoagulant." In the mid-20th-century, it was recognized that some patients with systemic lupus erythematosus had biological false positive serological tests for syphilis, often coincident with the presence of an anticoagulant in plasma and the some of these patients (particularly ones with somewhat atypical of patterns of lupus) paradoxically manifested an increased incidence of procoagulant complications. Nothing much was made of these associations, however, until Graham Hughes, author of the above citation, applied his talents of astute bedside observation, knowledge of disease mechanisms, imagination, and a "bloodhound" instinct for following relevant clues. Graham and his colleagues early-on documented vasculopathy as basis for the diffuse (variable) pathology characteristic of the syndrome; evidence that procoagulant features were mediated by antiphospholipid autoantibodies (aPL) followed. Over the past two decades, investigators around the world have turned their attention to the study of the Hughes syndrome. (Contributors to this text include 83 clinicians and/or scientists from 13 countries in Europe, the Americas, Near East, and Asia. They represent more than a dozen clinical subspecialties and several basic science disciplines; professionals and students in these fields will need access to this book, whether in institutional libraries or personal collections – good news for the publisher.)

Truly rational treatment and/or prevention of the Hughes syndrome will await more precise knowledge of its pathogenesis but the recognition in the 1980s that ischemic and necrotic lesions in affected organs are secondary to thrombosis rather than to inflammation played a significant role in improved management of the illness and avoidance of inappropriate therapy. Beyond anticoagulation, there is enormous potential for discovery of more specific (and potentially more effective) therapies based on better definition of the complex humoral and/or cellular events activated by aPL. For example, studies by Giradi and Salmon (described in Chapter 31) demonstrated that blockade of the complement system prevented fetal loss and thrombosis in an animal model of the Hughes syndrome, extrapolation to clinical trials of complement blockade should be forthcoming.

I would like to address the issue of terminology for this illness, herein designated the "Hughes syndrome." I have already referred to the historical role Graham Hughes played in describing the syndrome, the recognition of

clinical-pathological associations, and the relationship to aPL (reviewed in more detail by Munther Khamashta in Chapter 1). This alone, in my judgment, justifies acceptance of the eponym "Hughes syndrome" rather than "antiphospholipid syndrome." There are other rationales for that recommendation: (1) the precise molecular target of aPL remains a subject of study (beta 2 glycoprotein-1 versus phospholipids), (2) in some patients the illness and presence of aPL are disassociated over time, and (3) the longstanding use of eponyms for other vasculopathies (e.g., Wegener, Churg-Strauss, Kawasaki, Henoch-Schöenlein, Behçet, Takayasu) have utility in recognizing individual clinical and pathological patterns of disease and management objectives.

Finally, I would like to draw attention to a short chapter at the end of the book, "The Future of Hughes Syndrome." In this chapter, Michael D. Lockshin summarizes recent progress in our understanding of the problem and, more importantly, identifies areas of ignorance and special opportunities for study. It is an exciting time for seeking new insights regarding the pathogenesis and management of the Hughes syndrome; this revised reference text will be an invaluable resource for anyone engaged in such inquiries.

Charles L. Christian, MD
Department of Medicine
University of Florida
Jacksonville, Florida
USA

Foreword to the First Edition

I am very happy to be asked by Dr. Munther Khamashta to write a Foreword to this first comprehensive description of the many facets of the antiphospholipid syndrome (APS). Although I have been an interested and long-time participant in studies to elucidate the nature of some human diseases associated with immunological abnormalities, I have not had a personal involvement with work on the APS. I have however watched with great fascination the evolution of this field from initial observations of clinical symptoms to studies defining the pathophysiological abnormalities.

The APS began with reports in 1983, 1984 and 1985 (see Khamashta: Hughes Syndrome, A History) on a number of clinical symptoms which appeared to have an underlying common pathogenic mechanism – vascular thrombotic episodes. These included peripheral vascular thromboses, cerebral vascular infarctions, livedo reticularis, spontaneous abortions and portal and pulmonary hypertension. A striking feature of this unfolding story was that already in 1983, suspicion was cast on the likely association of anti-cardiolipin/phospholipid antibodies with the clinical syndromes. Continuing studies on the pathophysiology have helped to fine-tune the immunological abnormalities. Most investigators believe that proteins complexed to phospholipids such as β-2–glycoprotein-1 are the primary targets of the autoantibodies but there appears to be continuing evidence that phospholipids themselves are also target antigens. The argument here may hinge on the fact that the immunogen itself might be a complex of phospholipid and protein and the humoral immune response is directed at different component parts of this complex, depending on the "immunogenicity" of different components to a genetically susceptible host. In fact, many autoantigens in lupus and other autoimmune diseases are complexes of nucleic acids and proteins, a classical example being the Sm antigens comprising complexes of small nuclear RNAs and small nuclear ribonucleoproteins.

In autoimmune diseases like lupus, we have advanced the notion that the humoral antibody responses are antigen-driven and that the antigens are self proteins rendered immunogenic due to a variety of reasons, including overexpression, ectopic localization and structural alterations of various kinds such as mutagenesis or complexing with foreign materials. An interesting aspect of the APS story is the diverse nature of clinical symptoms which involve totally different organ systems but rarely involve more than one organ system at a time. This is in contrast to lupus which is also a multi-system disease, but the individual patient often has multiple organ

system involvement. It is possible that the APS might fall into the following mechanistic scenario:

Different inciting agents ➔ ➔ ➔ Thrombosis in different organ systems ➔ ➔ ➔ antigenic modification of procoagulant phospholipid-protein ➔ ➔ ➔ humoral antibody responses ➔ ➔ ➔ in-situ antigen-antibody complex formation ➔ ➔ ➔ inflammation, further thrombosis, recruitment of cellular immune infiltrates ➔ ➔ ➔ perpetuation of repeated cycles of thrombosis, inflammation and immune responses.

The diversity of the APS could be explained on the uniqueness of the initial inciting event leading to pro-coagulation occurring in specific organ systems and thus would not have to invoke aberrant immune responses manifesting the great variety of clinical syndromes. One of the challenges in the future would be to explain or identify the different inciting agents for the different syndromes encountered.

One of the issues which has been raised is that the anti-phospholipid syndrome is a misnomer since the major target antigen appears to be the protein or the lipoprotein complex. Many investigators are inclined towards keeping the original moniker of the APS because of both historical and common usage reasons. The history of clinical medicine and biomedical research is replete with examples where original designations have been retained in spite of subsequent studies showing that the designation was not totally correct. The important thing is that the essence of the original observations in the APS was correct.

It is rare that an investigator and his colleagues have the opportunity to open up a new field in clinical medicine and biomedical research. This has happened with the anti-phospholipid syndrome. Graham Hughes and his colleagues deserve enormous kudos for recognizing that a number of clinical syndromes shared a common feature of vascular thrombosis and for carrying this into consolidation of the clinical observations with laboratory analysis. Much clinical and basic research by many investigators worldwide have resulted from these beginnings. This volume stands as a tribute to Hughes and his colleagues.

Eng M. Tan, MD
The Scripps Research Institute
La Jolla, California 92037
USA

Prologue to the First Edition

Memory loss, migraine, strokes, accelerated atheroma, recurrent miscarriages – some of the features which make the antiphospholipid syndrome (APS) so important to patients and clinicians worldwide.

The finding that simple and reproducible assays can identify patients at risk both for venous and arterial thrombosis has opened up new avenues for treatment across many specialities.

From the early days in the late 1970's and early 1980's, I had felt strongly that the syndrome would one day outstrip lupus in frequency. Indeed my colleagues and I were often impatient at the seemingly slow acceptance of the syndrome by the medical (and obstetric) community in the early years. All that has changed. The number of papers and meetings relating to the syndrome has become a flood, and there is widespread realisation that this may, in fact be one of the most common and important auto-immune diseases.

My grateful thanks to my colleagues, mentors and friends, especially Dr Tan and Charles Christian, whose guidance I have always valued, and to Nigel Harris and Aziz Gharavi, who not only worked with me in the early days of the syndrome, but have become world leaders in APS research.

Most of all, my grateful thanks to Munther Khamashta, my colleague and friend for a decade.

His reputation in this field is truly international. It is a testimony to his personal qualities that he has been able to persuade the world leaders in APS to contribute to this volume.

Graham Hughes

Prologue to the Second Edition

"*There are two 'new' diseases of the late twentieth century, AIDS and APS*"
Miquel Vilardell, Dean of Medicine of the University of Barcelona

Munther Khamashta deserves plaudits for his contributions to this corner of medicine. He has not only published numerous original papers on the syndrome, notably in the field of recurrent pregnancy loss, but he has also brought together colleagues with clinical and research expertise. The first edition of his book was a triumph – an example of clinically-based research which has had a major direct impact on medical practice.

In the 5 years since the first edition, there has been a dawning realisation of the extent of the impact of the antiphospholipid syndrome in so many branches of medical practice – in Alzheimer's, in multiple sclerosis, myocardial infarction, movement disorders, leg ulcers, infertility, renal and cardiac transplantation, avascular necrosis, ischaemic fractures – and even more so with the original pillars of the syndrome – stroke, TIA, DVT, pulmonary hypertension, and recurrent pregnancy loss.

Many of us working in this field have felt frustration at the seemingly slow recognition of its importance. However, things are changing. The number of research publications, reviews and conferences is increasing. In our own clinic, the number of referrals of patients with Hughes Syndrome now promises to overtake those with lupus.

In the original description of the clinical syndrome back in 1983, I wrote…. "For those of us hardened into nihilism by years of study of various autoantibodies in SLE there is a rare sense of excitement at the implications of the associations now being reported".

Twenty-two years later, this sense of clinical excitement has not waned.

Graham Hughes
Head, Lupus Unit

Contents

Contributors

Olga Amengual, MD, PhD
Department of Medicine II,
Hokkaido University Graduate School
of Medicine, Sapporo, Japan

Paul R. J. Ames, MD
Academic Department of
Rheumatology, Leeds University
Teaching Hospitals, Leeds, UK

Mary-Carmen Amigo, MD, FACP
Department of Rheumatology,
Instituto Nacional de Cardiología
Ignacio Chávez
Mexico City, Mexico

Eduardo Anglés–Cano, MD, DSc
Institut National de la Santé et de la
Recherche Médicale, CHU Bichat-
Claude Bernard, Paris, France

Jef M. M. C. Arnout, PhD
Centre for Molecular and Vascular
Biology, Faculty of Medicine,
University of Leuven, Leuven, Belgium

Tatsuya Atsumi, MD, PhD
Department of Medicine II,
Hokkaido University Graduate School
of Medicine, Sapporo, Japan

Tiziano Barbui, MD
Division of Haematology, Ospedali
Riuniti, Bergamo, Italy

Carlos A. Battagliotti
Department of Internal Medicine and
Therapeutics, National University of
Rosario, Rosario, Argentina

H. Michael Belmont, MD
Department of Rheumatology,
Hospital for Joint Diseases, New York
University School of Medicine,
New York, NY, USA

Maria Laura Bertolaccini, MD, PhD
Lupus Research Unit, The Rayne
Institute, St Thomas' Hospital, London,
UK

Susan Bewley, MBBS, MA, MD
Department of Obstetrics, Guy's and
St. Thomas' Hospitals NHS Trust,
London, UK

Miri Blank, PhD
Department of Internal Medicine and
Center for Autoimmune Diseases,
Sheba Medical Center, Tel-Hashomer,
Ramat-Gan, Israel

Maria Orietta Borghi, PhD
Department of Internal Medicine,
IRCCS Istituto Auxologico Italiano,
University of Milan, Milan, Italy

D. Ware Branch, MD
Department Obstetrics and Gynecology,
Division of Maternal and Fetal
Medicine, University of Utah Health
Services Center, Salt Lake City, UT,
USA

Robin L. Brey, MD
Department of Medicine, University of
Texas Health Science Center,
San Antonio, TX, USA