

## Cerebral Amyloid Angiopathy in Alzheimer's Disease and Related Disorders

# Cerebral Amyloid Angiopathy in Alzheimer's Disease and Related Disorders

*Edited by*

**Marcel M. Verbeek**

*Departments of Neurology and Pathology,  
University Medical Center St. Radboud,  
Nijmegen, The Netherlands*

**Robert M.W. de Waal**

*Department of Pathology,  
University Medical Center St. Radboud,  
Nijmegen, The Netherlands*

and

**Harry V. Vinters**

*UCLA Medical Center,  
Los Angeles, CA, U.S.A.*



**SPRINGER-SCIENCE+BUSINESS MEDIA, B.V.**

A C.I.P. Catalogue record for this book is available from the Library of Congress.

ISBN 978-90-481-5480-7

ISBN 978-94-017-1007-7 (eBook)

DOI 10.1007/978-94-017-1007-7

---

*Printed on acid-free paper*

All Rights Reserved

© 2000 Springer Science+Business Media Dordrecht

Originally published by Kluwer Academic Publishers in 2000

No part of the material protected by this copyright notice may be reproduced or utilized in any form or by any means, electronic or mechanical, including photocopying, recording or by any information storage and retrieval system, without written permission from the copyright owner.

# Contents

<b>Contributors</b>	ix
<b>Preface</b>	xvii
<b>SECTION I: CLINICAL ASPECTS OF CAA AND CAA-RELATED HEMORRHAGE</b>	
<b>Chapter 1</b>	3
<b>Clinical aspects and diagnostic criteria of sporadic CAA-related hemorrhage</b>	
<i>Steven M. Greenberg</i>	
<b>Chapter 2</b>	21
<b>Diagnosis of CAA during life. Neuroimaging of CAA</b>	
<i>Ulrich Bickel</i>	
<b>Chapter 3</b>	43
<b>Vascular risk factors for Alzheimer's disease. An epidemiologic perspective</b>	
<i>Monique M.B. Breteler</i>	
<b>Chapter 4</b>	59
<b>Cerebral microvascular and macrovascular disease in the aging brain; similarities and differences</b>	
<i>Harry V. Vinters</i>	

## SECTION II: GENETICS OF CAA

- Chapter 5** 81  
**ApoE genotype in relation to sporadic and Alzheimer-related CAA**  
*Mark O. McCarron and James A.R. Nicoll*
- Chapter 6** 103  
**Clinical and genetic aspects of hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D)**  
*Marjolijn Bornebroek, Joost Haan, Egbert Bakker and Raymund A.C. Roos*
- Chapter 7** 121  
**Genetics and neuropathology of hereditary cystatin C amyloid angiopathy (HCCAA)**  
*Ísleifur Ólafsson and Leifur Thorsteinsson*

## SECTION III: CELLULAR AND MOLECULAR PATHOLOGY OF CAA

- Chapter 8** 137  
**Neuropathologic features and grading of Alzheimer-related and sporadic CAA**  
*Harry V. Vinters and Jean-Paul G. Vonsattel*
- Chapter 9** 157  
**Chemical analysis of amyloid  $\beta$  protein in CAA**  
*Alex E. Roher, Yu-Min Kuo, Alexander A. Roher, Mark R. Emmerling and Warren J. Goux*
- Chapter 10** 179  
**Immunohistochemical analysis of amyloid  $\beta$  protein isoforms in CAA**  
*Haruyasu Yamaguchi and Marion L.C. Maat-Schieman*
- Chapter 11** 189  
**Blood Brain Barrier dysfunction and cerebrovascular degeneration in Alzheimer's disease**  
*Raj N. Kalaria*
- Chapter 12** 207  
**A $\beta$ -associated proteins in cerebral amyloid angiopathy**  
*Robert M.W de Waal and Marcel M. Verbeek*

**Chapter 13** 223

**Neuropathology of hereditary cerebral hemorrhage with amyloidosis-Dutch type**

*Marion L.C. Maat-Schieman, Sjoerd G. Van Duinen, Remco Natté and Raymund A.C. Roos*

**Chapter 14** 237

**Neuropathology and genetics of prion protein and British cerebral amyloid angiopathies**

*Bernardino Ghetti, Pedro Piccardo, Blas Frangione, Rubén Vidal and Jorge Ghiso*

SECTION IV: *IN VITRO* AND ANIMAL MODELS OF CAA

**Chapter 15** 251

**Amyloid  $\beta$  protein internalization and production by canine smooth muscle cells**

*Reinhard Prior and Britta Urmoneit*

**Chapter 16** 265

**Degeneration of human cerebrovascular smooth muscle cells and pericytes caused by amyloid  $\beta$  protein.**

*Marcel M. Verbeek, William E. Van Nostrand and Robert M.W. de Waal*

**Chapter 17** 281

**Vasoactivity of amyloid  $\beta$  peptides**

*Daniel Paris, Terrence Town and Michael Mullan*

**Chapter 18** 295

**CAA in transgenic mouse models of Alzheimer's disease. What can we learn from APP transgenic mouse models?**

*Greg M. Cole and Fusheng Yang*

**Chapter 19** 313

**Cerebral amyloid angiopathy in aged dogs and nonhuman primates**

*Lary C. Walker*

**Chapter 20** 325

**Vascular transport of Alzheimer's amyloid  $\beta$  peptides and apolipoproteins**

*Berislav V. Zlokovic, Jorge Ghiso and Blas Frangione*

**Index** 347

## **Contributors**

**Egbert Bakker**

*Department of Neurology and Clinical Genetics, Leiden University Medical Center,  
Leiden, The Netherlands*

**Ulrich Bickel**

*Institute of Pharmacology and Toxicology, Philipps University, Marburg,  
Germany*

**Marjolijn Bornebroek**

*Department of Neurology and Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands*

**Monique M.B. Breteler**

*Department of Epidemiology & Biostatistics, Erasmus Medical Center  
Rotterdam*

**Greg M. Cole**

*Department of Medicine and Neurology, UCLA and Sepulveda VAMC,  
North Hills, CA, USA*

**Mark R. Emmerling**

*Department of Neuroscience and Therapeutics, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, MI, USA*

**Blas Frangione**

*New York University School of Medicine, New York, NY, USA*

**Bernardino Ghetti**

*Indiana University School of Medicine, Indianapolis, IN, USA*

**Jorge Ghiso**

*New York University School of Medicine, New York, NY, USA*

**Warren J. Goux**

*Department of Chemistry, University of Texas at Dallas, Richardson, TX, USA*

**Steven M. Greenberg**

*Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA*

**Joost Haan**

*Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands*

**Raj N. Kalaria**

*Institute for Health of the Elderly, Newcastle General Hospital, Westgate Road, and Department of Psychiatry, University of Newcastle, Newcastle upon Tyne, United Kingdom*

**Yu-Min Kuo**

*Haldeman Laboratory for Alzheimer Disease Research, Sun Health Research Institute, Sun City, AZ, USA*

**Marion L.C. Maat-Schieman**

*Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands*

**Mark O. McCarron**

*University of Glasgow Department of Neuropathology, Institute of Neurological Sciences, Southern General Hospital, Glasgow, Scotland, UK*

**Michael Mullan**

*Roskamp Institute, University of South Florida, Tampa, FL, USA*



**Remco Natté**

*Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands*

**James A.R. Nicoll**

*University of Glasgow Department of Neuropathology, Institute of Neurological Sciences, Southern General Hospital, Glasgow, Scotland, UK*

**Ísleifur Ólafsson**

*Department of Clinical Biochemistry, Reykjavík Hospital and deCODE Genetics Inc., Reykjavík, Iceland*

**Daniel Paris**

*Roskamp Institute, University of South Florida, Tampa, FL, USA*

**P. Piccardo**

*Indiana University School of Medicine, Indianapolis, IN, USA,*

**Reinhard Prior**

*Department of Neurology, University of Duesseldorf, Duesseldorf, Germany*

**Alexander A. Roher**

*Haldeman Laboratory for Alzheimer Disease Research, Sun Health Research Institute, Sun City, AZ, USA*

**Alex E. Roher**

*Haldeman Laboratory for Alzheimer Disease Research, Sun Health Research Institute, Sun City, AZ, USA*

**Raymund A.C. Roos**

*Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands*

**Dennis J. Selkoe**

*Harvard Medical School and Center for Neurologic Diseases, Brigham & Women's Hospital, Boston, MA, USA*

**Leifur Thorsteinnsson**

*Department of Clinical Biochemistry, Reykjavik Hospital and deCODE Genetics Inc., Reykjavik, Iceland*

**Terrence Town**

*Roskamp Institute, University of South Florida, Tampa, FL, USA*

**Britta Urmoneit**

*Department of Neurology, University of Duesseldorf, Duesseldorf, Germany*

**Sjoerd G. Van Duinen**

*Department of Pathology, Leiden University Medical Center Leiden, The Netherlands*

**William E. Van Nostrand**

*Departments of Medicine and Pathology, Health Sciences Center, State University of New York, Stony Brook, NY, USA*

**Marcel M. Verbeek**

*Departments of Pathology and Neurology, University Medical Center St. Radboud, Nijmegen, The Netherlands*

**R. Vidal**

*New York University School of Medicine, New York, NY, USA*

**Harry V. Vinters**

*Department of Pathology & Laboratory Medicine, Section of Neuropathology, Brain Research Institute & Neuropsychiatric Institute, UCLA Medical Center, Los Angeles, CA, USA*

**Jean-Paul G. Vonsattel**

*Department of Pathology and Neuroscience Center, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, USA*

**Robert M.W. de Waal**

*Department of Pathology, University Medical Center St. Radboud, Nijmegen, The Netherlands*

**Larry C. Walker**

*Neuropathology Laboratory, Neuroscience Therapeutics, Parke-Davis Pharmaceutical Research Division, Warner-Lambert, Ann Arbor, MI, USA*

**Haruyasu Yamaguchi**

*Gunma University School of Health Sciences, Maebashi 371-8514, Japan*

**Fusheng Yang**

*Dept. Medicine and Neurology, UCLA and Sepulveda VAMC, North Hills, CA, USA*

**Berislav V. Zlokovic**

*Department of Neurological Surgery, USC School of Medicine, Los Angeles, CA, USA*

## **Dedication**

Dedicated to the late dr. George Glenner, dr. Henryk Wisniewski and dr. Thaddeus Mandybur, pioneers in research on amyloid in the nervous system, including its blood vessels.

## Preface

Since at least the time of Scholz, students of Alzheimer's disease have been grappling with the role of microvascular pathology in the cause and mechanism of this complex and devastating disorder. A number of historical milestones in the elucidation of Alzheimer's disease have derived directly from scientists' desire to understand the whys and wherefores of the striking cerebrovascular amyloidosis that accompanies the disorder. Perhaps the most notable example of this connection is the original discovery by George Glenner of the amyloid beta protein. Glenner was understandably fascinated by the parallels between Alzheimer's disease and other human amyloidoses, and he purposely focused on the high prevalence of meningovascular amyloid deposition in approaching AD, both conceptually and experimentally. While neurobiologists were generally more interested in the neurofibrillary tangles and senile plaques that filled the cerebral cortex, Glenner correctly surmised that understanding the biochemical nature of meningovascular amyloid would provide a simpler and more tractable route to understanding Alzheimer's disease. Applying the methods that had been well-developed by pathologists and biochemists studying other human amyloidoses, Glenner and Wong successfully purified and partially sequenced the subunit of the meningovascular amyloid deposit of both Alzheimer's disease and Down's syndrome. What Glenner instinctively knew quickly became apparent to others: that deciphering the microvascular amyloid would be an excellent first step in unraveling the pathogenesis of Alzheimer's. We now know that his instincts were prescient.

It is both timely and compelling that Marcel Verbeek, Harry Vinters and Rob de Waal and their many talented co-authors have now decided to weave together the many threads of knowledge about cerebrovascular amyloidosis

in Alzheimer's disease and related disorders. As I have examined the brains of Alzheimer victims under the microscope over the years, I have been impressed by the striking relationship of beta-amyloidosis to the cerebral microvasculature. In a series of brains of patients dying with Alzheimer's disease, Cathy Joachim and I observed the invariant occurrence of at least some and often many meningeal and intracortical microvessels bearing amyloid  $\beta$ -protein deposits. Not infrequently, the immediately surrounding brain tissue showed a neuritic and gliotic response that closely resembled that found in senile plaques. Numerous investigators have pointed to the potential importance of vascular basement membrane constituents as a substrate for  $\beta$ -amyloidosis in the brain. While it has been exceedingly difficult to confirm unequivocally a seminal pathogenetic role for microvessel constituents, there can be no doubt that a full understanding of Alzheimer's disease will require a detailed knowledge of the contribution of altered vascular form and function. The comprehensive review of current information about many aspects of this subject provided by this volume will no doubt serve as a highly useful resource to investigators seeking to make further progress.

The attention devoted to the genetics and clinicopathology of hereditary cerebral hemorrhage with amyloidosis (HCHWA) of the Dutch type in this volume seems particularly appropriate. Those of us working in the field of Alzheimer pathogenesis sometimes forget that the first specific genetic abnormality that could be credibly linked to the Alzheimer phenotype was the missense mutation in the beta-amyloid precursor protein causing the "Dutch disease." This discovery made it highly likely that APP would turn out to be the site of missense mutations in conventional Alzheimer's disease, a prediction that was soon shown to be true. HCHWA-D epitomizes the intimate relationship between vascular and parenchymal  $\beta$ -amyloidosis in the human brain that has fascinated neuropathologists for so long.

The current volume cogently places the Dutch disorder into the broader context of "sporadic" cerebral amyloid angiopathy, a syndrome which we now know occurs more frequently and with more disastrous consequences than was once believed. Thus, the old and new information brought together in one place by dr. Verbeek, Vinters and de Waal and their colleagues is meaningful not just for those concerned about Alzheimer's disease but for basic and applied biologists interested in understanding how the cerebral microvasculature works. I commend the editors and authors for taking on this important task and believe that you, the reader, will find their efforts to be both highly informative and useful to your own work.

*Dennis J. Selkoe,*

*Professor of Neurology and Neuroscience,*

*Harvard Medical School,*

*Director of Center for Neurologic Diseases,*

*Brigham & Women's Hospital,*

*Boston, MA, USA*