INTERNATIONAL REVIEW OF CHILD NEUROLOGY SERIES

TUBEROUS SCLEROSIS COMPLEX

Edited by
Paolo Curatolo
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From Basic Science to Clinical Phenotypes

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FOREWORD

The International Child Neurology Association (ICNA) was founded in 1973 with the aim of improving the quality of care of children with neurological disorders. One of the methods it uses to further this aim is the publishing of the International Review of Child Neurology, a series of books on specific child neurology subjects. The series has an international audience and has drawn its authors from many parts of the globe. This book is no exception, with a multinational authorship which is quite apt for a volume on tuberous sclerosis as the disorder was almost simultaneously described by Bourneville from France and Hartdegen from Germany.

ICNA is committed to continue publication of this series to fulfil its stated aim.

Peter G Procopis
Senior Editor
PREFACE

Harvey B Sarnat

Tuberous sclerosis complex (TSC) is the prototype of a category of malformations uniquely characterized by disturbances in cellular differentiation and growth. Other diseases are also now recognized under the rubric of “disturbances of cellular lineage” involving multiple organ systems and tissues, but particularly the nervous system. These include Proteus syndrome and hemimegalencephaly, both the isolated and the syndromic forms of the latter. TSC is the most frequent and the most studied amongst these cytological disorders. My own personal studies of both surgical and autopsy brain tissue in children with tuberous sclerosis are highly consistent with the concept of a primary disorder of cellular lineage and mixed expression of neuronal and glial proteins in the same cells, which I reported in a previous study and have corroborated in several additional patients I have subsequently studied. Other authors have published similar results, discussed in the excellent chapter on neuropathology by Mizuguchi and Hino in this monograph. These findings have resulted in a reclassification of tuberous sclerosis as a “disorder of cellular lineage” in new schemes of CNS malformations that integrate molecular genetic with morphological criteria.

Despite the classical text of Manuel Gomez, including the third edition published as recently as 1999, a fountainhead of new molecular and genetic data has emerged that alone justifies another monograph on the topic. Clinical advances in recognition, imaging, including functional imaging, and neuropsychological studies, as well as the genetic and the histopathological cell markers of maturation and of lineage, also require a review at this time to summarize the wealth of literature in diverse medical specialties on TSC and to update patient care. Professor Paolo Curatolo, a foremost world authority on TSC, with both experience and insight of patients with this disease, has met the challenge well in this new monograph. He has called upon colleagues in various disciplines most capable of assisting him with focused chapters that describe the most recent findings and interpretations; these are the very individuals whose original contributions other authors would almost certainly cite in writing a review. The scope ranges from highly clinical studies of cognitive and linguistic functions to the animal model of TSC, the Eker rat. Even the rich historical aspects of the disease are chronologically described in a highly interesting presentation.

TSC is an important disease not only because it is a relatively common hereditary neurological disease with great morbidity, but because it has conceptual
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Implications in many areas in which it forms a borderland with other pathological processes: dysplasia and neoplasia; hamartoma formation and other disturbances in morphogenic processes such as neuroblast migration and synaptogenesis; relationships between neurons and glial cells. It also raises important issues about the timing of the formation of the hamartomas and cytological dysgenesis. Do cortical hamartomas in humans develop after the migration of normal or abnormal neuroblasts, and how do they arrive at the cortex if the radial glial cells in the same subventricular zone from which they arise are also abnormal? Why are cortical tubers so much rarer in the Eker rat than in the human, whereas subependymal hamartomatous nodules are frequent in both species? Can this difference be related to the shorter time during which neuroblast migration proceeds to completion in the rat?

This present monograph is clearly the most authoritative and contemporary statement of current knowledge about TSC yet published. It is the first monograph to make a meaningful correlation between the fountainhead of new genetic and basic science data and the clinical presentation of the disease. It provides, furthermore, a guide to future research strategies by discussing unresolved issues. Whereas one cannot speak of the first volume of any book as a "classic", at least not until much time has passed, it nevertheless has the potential to become a classic, which will be realized in multiple future updates. I regard it a great honour to be invited to write the Foreword to the first edition of Tuberous Sclerosis Complex, with many future editions anticipated for the digestion and interpretation of research yet to be done in this fascinating and complex disease.
EDITOR’S PREFACE

Paolo Curatolo

My interest in tuberous sclerosis began in the early 1980s. At that time I worked in the Department of Child Neurology and Psychiatry in the University of Rome, and I was dedicating my time to children with early-onset and intractable seizures in which tuberous sclerosis represented one of the most frequent aetiologies. As a child neurologist, I was particularly intrigued by the special association in these children of different neurological phenotypes caused by tuberous sclerosis, including seizures, cognitive impairments and autism, and the puzzling interrelation between these three symptoms. The arrival of the first MRI instrument in Rome in 1984 gave me the opportunity to study in detail the localization of the cortical tubers in different lobes, and allowed me to investigate the relationship between EEG foci, the MRI localization of cortical tubers, and the cognitive and behavioural phenotypes.

In those years I also had the opportunity to meet for the first time Manuel Gomez, who has dedicated his life to the study of TSC, and to discuss with him issues relating to this complex and fascinating disease, a meeting which has been of great stimulus for my future clinical research. Manuel Gomez’s monograph appeared in three different editions, the last of which was published in 1999. It was widely regarded as a milestone by all clinicians and researchers in the field.

Recent advances in the field of tuberous sclerosis and new discoveries from molecular genetics and biology are actually progressing at a rate of about 500 papers published each year. This is the reason that our clinical practice necessitates a continuous upgrading. With this book I seek to encapsulate in a single text modern knowledge about current research, ideas and practice on tuberous sclerosis, from basic neuroscience to clinical phenotypes.

The first part of the book is designed to provide the reader with a review of the historical background and current criteria for diagnosis. The next part of the book is intended to provide readers with detailed descriptions of the clinical manifestations of this protean disease. Special emphasis has been placed on the neurological phenotypes of the cortical tubers, including seizures, cognitive impairments and autism. A large part of the book deals with the recent significant advances in the fields of neuropathology, molecular genetics and neurobiology, which allow a better understanding of the pathogenesis of the disease. To cover this vast and complex subject I have enlisted a panel of experts in their respective fields.

No book is an individual enterprise. This book has benefited greatly from the co-operation, assistance, wisdom and generosity of many people: my editor, academic
EDITOR'S PREFACE

mentor, researchers, colleagues and family. Important material for many chapters in this book was pulled together by my researchers Drs Magda Verdecchia and Roberta Bombardieri, whose assistance proved fundamental to my writing. I would also like to give a special thank you to all the people with TSC and their families who put their trust in me, giving me constant energy and motivation to continue my efforts and research in the field. Finally, I am indebted to Mac Keith Press for their great patience, understanding and professional assistance in producing the book.

Scientific books reflect the continuous and dynamic process of knowledge acquisition, and are therefore never complete. It is my hope that this book will consolidate what is known about TSC in a single source, making it easier to apply this new information to the cure of individual patients, and perhaps stimulating scientific research on some of the remaining questions about this devastating disease.